Device-Associated Infections: A Macroproblem that Starts with Microadherence

Rabih O. Darouiche
Infectious Disease Section and Center for Prostheses Infection, Veterans Affairs Medical Center and Baylor College of Medicine, Houston

Medical devices are responsible for a large portion of nosocomial infections, particularly in critically ill patients. Device-associated infections can cause major medical and economic sequelae. Bacterial colonization of the indwelling device can be a prelude to both infection and malfunction of the device. The pathogenesis of device-associated infection centers around the multifaceted interaction among the bacteria, the device, and the host. Bacterial factors are probably the most important in pathogenesis of infection, whereas device factors are the most amenable to modification with the objective of preventing infection. Some, but not all, of the studied bacterial receptors satisfy the proposed “adherence/infection” version of Koch’s postulates. Traditional surface-modifying preventive approaches have largely focused on antimicrobial coating of devices and resulted in variable clinical success in preventing device-associated infections. The potential protective role of newer innovative approaches, such as biofilm modification and bacterial interference, ought to be further investigated.

American medicine has made great strides during the past several years, owing to enhanced medical knowledge and advanced technology. The more extensive use of medical devices has affected mostly critically ill patients, which has resulted in longer survival of patients who are at even higher risk for infection. Most cases of infection in critically ill patients are associated with medical devices. In this population of patients, 95% of cases of urinary tract infection are catheter related, 87% of cases of bloodstream infection originate from an indwelling vascular catheter, and 86% of cases of pneumonia are associated with mechanical ventilation [1]. The objectives of this article are to (1) assess the magnitude of the general problem of device-associated infections; (2) address the potential impact of bacterial colonization on device function; (3) discuss the bacterial, device, and host factors that contribute to the pathogenesis of device-associated infections; (4) propose an “adherence/infection” version of Koch’s postulates and examine them with regard to some bacterial adhesins; and (5) conclude with a perspective on the potential role of some innovative surface-modifying approaches for prevention of bacterial colonization and biofilm formation around the indwelling device.
least 6-fold, and the overall rate of catheter-related urinary tract infection is higher than that of bloodstream infection associated with central venous catheters [2]. However, the vast majority of cases of catheter-related urinary tract infection involve only the lower urinary tract and have a low attributable mortality rate (<5%), whereas 5%–25% (moderate mortality) of patients, particularly the critically ill [3], may not survive an episode of vascular catheter–related bloodstream infection. Differences also exist within the same group of medical devices. Although fracture fixation devices are more commonly inserted and are more likely to become infected (open fractures lead to infection more than do closed fractures, and external fixation pins become infected more than do intramedullary nails) than are joint prostheses [4], infection of the latter is more difficult and expensive to manage. Infections of all intravascularly placed medical devices, including vascular grafts [5], cardiac pacemakers [6], mechanical heart valves [7], and left-ventricular assist devices [8] are considered life-threatening, with prosthetic valve endocarditis causing the highest risk of mortality (≥25%) [7].

Although the mortality rate attributed to infections associated with certain devices is low, such infections can result in major morbidity. For instance, infections of medical devices implanted in sexual organs, including mammary [9] and penile [10] implants, can cause major disfigurement and serious psychological trauma but rarely result in death. The morbidity of device-associated infections may also differ among infections with similar attributable mortality. For example, the medical and economic sequelae of infection are far more serious in association with a joint prosthesis than with a bladder catheter, although both infections have a low attributable mortality rate.

The rates of device-associated infections listed in table 1 generally refer to first-time insertion of medical devices, with cases of infection documented by appropriate diagnostic cultures. However, the true rates of device-associated infection may be higher than those listed in table 1 for 5 reasons. (1) The rate of infection associated with reimplanted devices exceeds that of first-time implants by several-fold. For example, the rate of infection increases from 1%–3%, for first-time placement of penile implants, [10] to 18%, after reimplantation [11]. (2) The rates of device-associated infection are also usually higher in patients in whom the infected implants have been only partially explanted, as is the case with infected pacemaker systems [12]. (3) Physicians who care for patients with surgically implanted devices may rely on cultures with relatively low yield,

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**Figure 1.** The pathogenesis of device-associated infections centers around the multifaceted interaction of bacterial, device, and host factors.
such as cultures of aspirates of hip joints instead of intraoperative samples [13]. (4) The failure of currently used microbiological techniques to consistently culture organisms located in the biofilm may result in an underestimation of the true rate of infection associated with devices. (5) Antibiotics are often administered before the appropriate diagnostic cultures are obtained, thereby possibly yielding false-negative results.

**BACTERIAL COLONIZATION AND DEVICE FUNCTION**

Not only does bacterial colonization of the medical device precede clinical infection, but it also can adversely affect the function of the indwelling device. For example, capsular contraction, the most common reason for the removal of mammary implants, is etiologically related to bacterial colonization of the implant, usually by coagulase-negative staphylococci, without clinical evidence of infection [14]. Ultrastructural examination of the biofilm that usually blocks biliary stents and requires their removal within few months of insertion regularly demonstrates the presence of bacteria [15]. Although loosening of joint prostheses often occurs because of solely mechanical reasons, this complication may also be caused by bacterial colonization of the prosthesis [16]. Biofilm formation can also result in failure of dental implants [17]. Furthermore, vascular occlusion is associated with colonization of the indwelling central venous catheters [18].

**PATHOGENESIS OF DEVICE-RELATED INFECTION**

Device-related infection results from the multifaceted interaction of bacterial, device, and host factors (figure 1). Of these 3 factors, bacterial factors are probably the most important in the pathogenesis of device-associated infection, whereas device factors are the most amenable to modification with the objective of preventing infection.

**Bacterial Factors**

Different bacteria use different adhesins to colonize medical devices. In the present article, I will briefly discuss the adherence properties of common pathogens, including *Staphylococcus aureus* and *Staphylococcus epidermidis* (the 2 most common causes of infection of intravascular, orthopedic, and penile devices), as well as *Providencia stuartii* and *Escherichia coli*, which commonly cause infection of urological devices and biliary stents.

**S. epidermidis.** Adherence of *S. epidermidis* to the surface of the device is not a one-time phenomenon but rather an evolving process. Initially, there is a rapid attachment of bacteria to the surface of the device that is mediated either by nonspecific factors (such as surface tension, hydrophobicity, and electrostatic forces) or by specific adhesins (including the proteinaceous autolysin encoded by the *atlE* gene and the capsular polysaccharide intercellular adhesin [PSA] probably encoded by the *ica* operon) [19]. This initial phase of *S. epidermidis* adherence is followed by an accumulative phase during which bacteria adhere to each other and form a biofilm, a process that is mediated by the polysaccharide intercellular adhesin (PIA) encoded by the *ica* operon [20].

**S. aureus.** Unlike *S. epidermidis*, which uses well-defined adhesins on the bacterial surface to adhere to one another and to the device, adherence of *S. aureus* appears to be more dependent on the presence of host-tissue ligands, including fibrinectin, fibrinogen, and collagen. *S. aureus* adheres to such host-tissue ligands via genetically defined microbial surface proteins, commonly referred to as “microbial surface components recognizing adhesive matrix molecules” (MSCRAMM) [16, 21]. The most important MSCRAMMs include FnbpA and FnbpB, which bind to fibronectin; clumping factor, which binds to fibrinogen; and collagen adhesin, which binds to collagen [16, 21]. The role of MSCRAMM in the pathogenesis of device-associated infections, however, is not clear, and at least in the case of orthopaedic device infection, has been a bit controversial. On one hand, a mutant strain of *S. aureus* deficient in fibronectin-binding protein was found in a rabbit model of hematogenously acquired septic arthritis to be less virulent than was the wild strain [21]. On the other hand, a *S. aureus* mutant strain deficient in fibronectin-, fibrinogen-, and collagen-binding proteins was as virulent as the MSCRAMM-possessing bacterial strain in a rabbit model of locally acquired septic arthritis and osteomyelitis [16]. It is possible, however, that such variations in the contribution of MSCRAMM to bacterial virulence in the 2 animal studies that used isogenic (with the exception of fibronectin-, fibrinogen-, and collagen-binding proteins) strains of *S. aureus* could be model dependent. Theoretically, it may be more difficult to demonstrate differences in virulence between the MSCRAMM-positive and the MSCRAMM-negative bacterial strains when high bacterial inocula are placed directly on the surface of the implanted device in the animal scenario of locally acquired infection [16].

**P. stuartii.** In general, we know much less about the adherence of gram-negative bacilli than gram-positive cocci to medical devices. *P. stuartii* is more prevalent in the urinary tract of patients with long-term bladder catheters than it is in catheter-free patients. Persistent adherence of *P. stuartii* to urinary catheters is thought to be mediated by type 3 fimbriae on the basis of the following observations: (1) bacterial isolates that caused long-term (≥12 weeks) bacteriuria expressed type 3 fimbriae more than did isolates that caused short-term (≤1 week) bacteriuria (74% vs. 26%, respectively) in catheter-dependent patients; (2) bacterial isolates that expressed type 3 fimbriae bound in higher numbers to catheters than did isolates
that did not express type 3 fimbriae; and (3) bacterial isolates that expressed type 3 fimbriae bound less to Tomm Harsfall protein (an inhibitory urinary protein) than did bacterial isolates that did not express type 3 fimbriae [22].

**E. coli.** Despite the plethora of data on the adherence of *E. coli* to the uroepithelium, relatively little is known about adherence of this organism to urological devices. *E. coli* isolates that caused long-term (≈12 weeks) bacteriuria expressed type 1 fimbriae more than did isolates that caused short-term (=1 week) bacteriuria (92% vs. 59%, respectively) [23]. Although expression of P fimbriae in that same study did not correlate with persistence in the urinary tract, another study demonstrated that *E. coli* strains with P fimbriae adhere to ureteral stents more avidly than do strains that lack P fimbriae [24]. These observations suggest that adherence of *E. coli* to urological devices and local predominance of certain bacterial strains, given that *E. coli* strains that express type 1 fimbriae prevail in the bladder, whereas *E. coli* strains that express P fimbriae usually infect the kidneys.

### Device Factors

The presence of the device can, in and of itself, enhance bacterial virulence. For instance, a study of rats with occluded biliary tracts demonstrated ultrastructural evidence of bacterial colonization and biofilm formation on the mucosal biliary surfaces only in animals that had indwelling biliary implants [25].

Careful analysis of the data on bacterial adherence and surface modification of the device yields the following 5 major principles: (1) different bacteria may adhere differently to the same device material; (2) the same bacteria may adhere differently to different device materials; (3) the same bacteria may adhere differently to the same device material placed under different circumstances, including the medium in which the device is placed (hydrophobic vs. hydrophilic medium), type of flow (dynamic vs. stationary), and temperature; (4) in vitro inhibition of bacterial colonization of the device does not ensure anti-infective efficacy in vivo; and (5) the clinical benefit of a particular surface-modifying approach may vary from one application to another. Notwithstanding these 5 major principles, there are a number of device-related factors that can affect bacterial adherence to the device, including the source of device material, surface of the device, and shape of the device (table 2).

### Host Factors

These factors can be divided into 2 groups: (1) host factors that can affect bacterial adherence of bacteria to the device, including tissue ligands that mediate adherence of the MSCRAMM-positive bacteria to a variety of medical devices; and (2) host factors that can either promote or inhibit the persistence of already adherent bacteria on the surface of the device. Studies have indicated that *S. aureus* binds more to the surfaces of vascular catheters and *E. coli* binds more to biliary stents that had been explanted from patients or animals (and, therefore, contain host-tissue ligands on the device surface, particularly fibronectin) than to unused devices. The contribution of host-tissue ligands to bacterial adherence was further supported by the demonstration that *S. aureus* binds more to catheters coated with fibronectin or fibrogen than to uncoated catheters.

Immune-mediated phenomena that promote bacterial persistence are illustrated by the reduced complement-mediated opsonic activity and the decreased bactericidal activity of WBCs in tissues surrounding the implanted device [26]. The most studied immune mediator that can inhibit persistence of already adherent bacteria on the surface of the device is IFN-γ. This immune mediator reduces the intracellular persistence of *S. epidermidis* in macrophages around catheters subcutaneously implanted in mice and inhibits catheter colonization [27]. IFN-γ may exert this protective antibacterial effect by inducing major histocompatibility complex class II proteins on phagocytic cells, activating mononuclear phagocytes, and regulating humoral immune response.

### Table 2. Device-related factors that may favor bacterial adherence.

<table>
<thead>
<tr>
<th>Type of device material</th>
<th>Device-related factors that may favor bacterial adherence</th>
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<tbody>
<tr>
<td>Polyvinyl chloride</td>
<td>favors bacterial adherence more than does teflon</td>
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<tr>
<td>Polyethylene</td>
<td>favors bacterial adherence more than does polyurethane</td>
</tr>
<tr>
<td>Latex</td>
<td>favors bacterial adherence more than does silicone</td>
</tr>
<tr>
<td>Silicone</td>
<td>favors bacterial adherence more than does polyltetrafluoroethylene</td>
</tr>
<tr>
<td>Stainless steel</td>
<td>favors bacterial adherence more than does titanium</td>
</tr>
<tr>
<td>Source of device material: synthetic</td>
<td>favors bacterial adherence more than does biomaterial</td>
</tr>
<tr>
<td>Surface of device</td>
<td></td>
</tr>
<tr>
<td>Irregular</td>
<td>favors bacterial adherence more than does regular</td>
</tr>
<tr>
<td>Textured</td>
<td>favors bacterial adherence more than does smooth</td>
</tr>
<tr>
<td>Hydrophobic</td>
<td>favors bacterial adherence more than does hydrophilic</td>
</tr>
<tr>
<td>Shape of device:</td>
<td></td>
</tr>
<tr>
<td>Polymeric tubing</td>
<td>favors bacterial adherence more than does wire mesh</td>
</tr>
</tbody>
</table>

**Koch’s Postulates for Bacterial Adherence/Infection**

Because Koch’s postulates were originally conceived almost 2 centuries ago for identification of the bacterial causes of epidemic diseases, modified versions, such as the “molecular version” of Koch’s postulates, have been constructed and applied...
for other aspects of medical diseases [28]. With the vast increase in our knowledge of the molecular and physiochemical properties of bacterial adhesins, it is only proper that we attempt to construct an “adherence/infection” version of Koch’s postulates (table 3). Because *S. epidermidis* is generally the most common cause of device-associated infections and also possesses some of the most defined adhesins, I will examine whether 2 of this organism’s adhesins, including the PIA and the capsular PSA, satisfy the adherence/infection version of Koch’s postulates.

*S. epidermidis* and PIA. The PIA satisfies, so far, only 2 of the 3 adherence/infection Koch’s postulates: (1) the *ica* operon that encodes PIA is more prevalent in *S. epidermidis* strains that infect catheters [29] and joint prostheses [20] than it is in strains that do not cause infection; (2) when inoculated onto subcutaneously implanted catheters in mice, the PIA-negative mutant strain of *S. epidermidis* 1457 was less likely than was the wild strain to adhere to catheters, cause subcutaneous abscesses, and resist eradication by host defense [19]; and (3) although antibodies to purified PIA protect against colonization in vitro, there are no reported data yet on protection in vivo.

*S. epidermidis* and PSA. This adhesin satisfies all 3 adherence/infection Koch’s postulates: (1) the *ica* operon that probably encodes the PSA is more prevalent in *S. epidermidis* strains that infect catheters [29]; (2) PSA-negative mutant strains of *S. epidermidis* are avirulent in a rabbit model of endocarditis [30]; and (3) antibodies to purified PSA protect against catheter-related bacteremia and endocarditis in a rabbit model [31].

**CONCLUSION: PERSPECTIVE ON INNOVATIVE SURFACE-MODIFYING APPROACHES FOR POTENTIAL CONTROL OF PATHOGENIC BIOFILMS**

The serious medical consequences and soaring economic sequelae of device-associated infections underscore the importance of prevention. At the present time, the most commonly used preventive approach is surface modification of the device with the objective of inhibiting bacterial presence in the biofilm and, one hopes, preventing device-associated infections. The surface of the device can be modified either with or without the use of antimicrobial agents. The antimicrobial-use approach for surface modification has had variable clinical success, with differences in the degree of protection attributed to the location of the device, concentration, type of infecting pathogens, type of antimicrobial agents used for coating the device, concentration of antimicrobial agents on the surface of the coated device, and degree of leaching of the antimicrobial agent off the coated surface to produce a zone of inhibition. Some in vitro and animal studies have indicated that bacteria may adhere more to devices with unmodified surfaces than to devices whose surfaces have been coated with nonantimicrobial agents, including catheters and intraocular lenses coated with nonsteroidal anti-inflammatory agents, stainless steel wire coated with fibrinolytic agents, hydroxyapatite-coated fracture fixation devices, gelatin-coated grafts, urinary catheters or biliary stents coated with hydrophilic polymers, and surfactant-coated surfaces. However, there have been no well-conducted prospective randomized clinical trials that have assessed the clinical benefit of nonantimicrobial modification of the surface of the device.

A recent in vitro report indicated that interference with the *Pseudomonas aeruginosa* cell-to-cell quorum signaling results in a flat undifferentiated biofilm that may more amenable to antimicrobial therapy [32]. Recent preliminary data also suggested that naturally existing substances, such as furanones, can prevent formation of biofilm around oil pipes placed in deep water. Although such an outcome may be ideal, it is still too early to predict whether this approach can be applied safely and effectively in clinical medicine.

Because biofilm is so ubiquitous in nature, it may not be feasible to eliminate it. Instead, it is probably more feasible to use the approach of bacterial interference to replace biofilms that are a result of pathogenic bacteria with biofilms that are a result of less pathogenic or nonpathogenic bacteria. In other words, bacterial adherence may be used to circumvent rather than enhance clinical infection. Earlier in vitro studies indicated that coating of polymers with *Lactobacillus acidophilus* decreases the adherence of *S. epidermidis* and *E. coli* to the modified surfaces [33]. A recent report indicated that bladder catheters coated with a nonpathogenic strain of *E. coli* 83972 reduce the adherence of *Enterococcus faecalis* to the catheter in vitro [34]. Although a pilot open-label clinical trial has indicated that deliberate bladder inoculation with *E. coli* 83972 protects against the development of symptomatic urinary tract infection in patients who have spinal cord injury [35], the clinical efficacy of inserting bladder catheters coated with this nonpathogenic organism has yet to be examined. Because the introduction of nonpathogenic bacterial strains into the human body has a potential, although unlikely, risk of causing symptomatic in-

**Table 3.** The adherence/infection version of Koch’s postulates.

<table>
<thead>
<tr>
<th>Postulate</th>
<th>Adherence or infection version</th>
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<tbody>
<tr>
<td>1</td>
<td>The gene(s) responsible for an adhesin is (are) more prevalent in clinical strains that cause device-associated infection than in strains that do not cause infection.</td>
</tr>
<tr>
<td>2</td>
<td>Deletion or inactivation of the gene(s) responsible for an adhesin results in reduced pathogenicity in animal models.</td>
</tr>
<tr>
<td>3</td>
<td>Antibodies to adhesins protect against device-associated infections in vivo.</td>
</tr>
</tbody>
</table>
fection, the clinical success of this approach of bacterial interference is currently being examined.

References


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