

## Seminar

## Intravascular-catheter-related infections

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Intravascular catheters are essential in complex medical and surgical interventions such as bone-marrow and organ transplantations, haemodialysis, cancer therapies, and abdominal, cardiothoracic, and trauma surgery. More than 150 million intravascular catheters are purchased annually by clinics and hospitals in the USA,<sup>1</sup> including more than five million central-venous and pulmonary-artery catheters. Given these figures, and the reported frequency of bloodstream infections associated with various types of intravascular catheters, my colleagues and I have estimated that at least 400 000 episodes of vascular-catheter-related bloodstream infections (CRBSI) occur in the USA per year.<sup>2</sup> The estimated cost of treating one episode of CRBSI ranged from US\$8000 in 1988 to more than \$28 000 for patients in intensive-care units in 1994.<sup>3,4</sup>

As with other diseases, successful management of CRBSI, including early diagnosis, cost-effective prevention, and effective treatment, depends on a thorough understanding of the pathogenesis of the infection. This review discusses novel diagnostic, preventive, and therapeutic strategies in the light of current understanding of the pathogenesis of CRBSI.

### Pathogenesis

Micro-organisms on catheter surfaces take two forms: the sessile form whereby organisms are embedded in a biofilm; and the planktonic free-floating form in which organisms disseminate over the catheter surface. Studies by transmission and scanning electron microscopy have shown that almost all indwelling vascular catheters, even those for which quantitative catheter cultures are negative, are colonised by micro-organisms. These micro-organisms are usually embedded in a biofilm layer. By measuring the uptake of compounds uniformly labelled with carbon-14, Costerton and colleagues<sup>5</sup> showed that the bacteria in a biofilm were metabolically active. Confocal scanning laser microscopy confirms that biofilm bacteria are viable.<sup>6</sup> Microbial colonisation, and biofilm formation on catheter surfaces, can occur as little as 24 h after insertion.

There is a link between the number of organisms retrieved by semiquantitative or quantitative cultures from a catheter surface and the risk of infection associated with these catheters. The sonication and quantitative catheter-culture technique was used by

Sherertz and colleagues<sup>7</sup> to study 161 central-venous catheters. The study found a high correlation between the numbers of colonies retrieved from these catheters and the frequency of CRBSI. Similarly, Maki and colleagues<sup>8</sup> found that the risk of venous CRBSI was directly proportional to the number of organisms counted by the roll-plate technique. Although all catheters are colonised with organisms embedded in biofilm, only a few of these organisms cause bloodstream infection. Infection depends on whether the organisms on the catheter surface, particularly those in a planktonic free-floating phase, exceed a certain quantitative threshold.

The adherence of micro-organisms to the catheter surface depends on the physical characteristics of the catheter surface, the surface characteristics of adherent bacteria, the presence of host-derived proteins, and the intrinsic phenotypic changes of adherent bacteria that form the biofilm (figure 1). Adherence results from interaction of physical characteristics of catheters, such as surface irregularities and charge differences, and the surface characteristics of bacteria, such as hydrophobicity. Hydrophobic staphylococcal organisms adhere better to polyvinyl chloride, silicone, and polyethylene surfaces than to polyurethane or Teflon polymers.<sup>9,10</sup>

Host-derived proteins are deposited on indwelling catheter surfaces. *Staphylococcus aureus* adheres tightly to proteins such as fibronectin, fibrinogen, and, to a lesser extent, laminin. In contrast, *Staphylococcus epidermidis* adheres only to fibronectin, and does not adhere to other host-derived protein receptors.

Adherence to catheter surfaces and biofilm formation are byproducts of intrinsic phenotypic changes of the colonising bacteria (figure 2). These phenotypic changes trigger the expression of several enzymes that catalyse the production of exopolysaccharide, thus causing biofilm to form. Deretic and colleagues<sup>11</sup> suggest that free-floating bacteria become biofilm-adherent organisms through an  $\alpha$ -factor-directed phenotypic change that results in adherence, biofilm formation, and resistance to antibacterial agents. Biofilm bacteria are resistant to antibiotics, especially glycopeptides, and are also resistant to host defence agents such as phagocytes and antibodies.

Organisms causing CRBSI generally enter the bloodstream from the skin insertion site or through the hub of the catheter device.<sup>12</sup> Haematogenous seeding and contamination of the infused fluid are rare causes of catheter colonisation and infection.<sup>1</sup> The skin insertion site is the most common source of colonisation and infection for vascular catheters in place for less than 10

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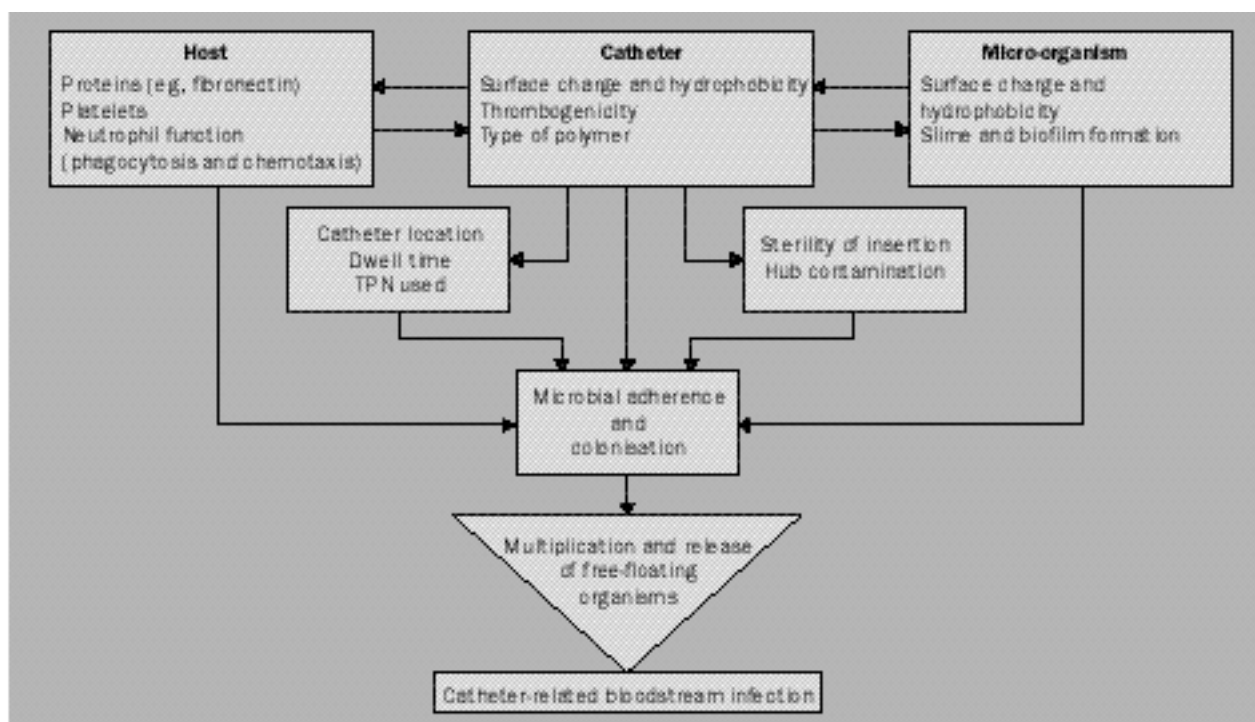


Figure 1: **Pathogenesis of vascular-catheter-related colonisation and infection**

TPN=total parenteral nutrition.

days.<sup>13,14</sup> Skin organisms migrate from the skin insertion site along the external surface of the catheter, colonising the distal intravascular tip of the catheter, and ultimately causing bloodstream infection.<sup>1</sup> Hub contamination is more common in long-term catheters in place for more than 10 days, because such catheters often have to be intercepted and manipulated.<sup>12</sup> Organisms are usually introduced into the hub from the hands of medical personnel. These organisms migrate along the internal surface of the catheter, leading to luminal colonisation and bloodstream infection.

The microbiology of CRBSI shows a predominance of skin organisms such as *S epidermidis*, *S aureus*, *Bacillus* species, and *Corynebacterium* species, and organisms that contaminate the hands of medical personnel, such as *Pseudomonas aeruginosa*, *Acinetobacter* species, *Stenotrophomonas maltophilia*, *Candida albicans*, and *Candida parapsilosis*.<sup>1,2,7,8</sup> Organisms emerging as pathogens such as species of *Micrococcus* and *Achromobacter*, rapidly growing mycobacteria such as *Mycobacterium fortuitum* and *M chelonae*, and fungal organisms such as *Malassezia furfur*, *Rhodotorula* species, *Fusarium* species, *Trichosporon* species, and *Hansenula anomala*, have also caused catheter infections.<sup>2,15,16</sup>

### Diagnostic applications

A single positive culture of blood drawn through the vascular catheter can indicate either intraluminal catheter colonisation or hub contamination, rather than a bloodstream infection, because samples taken through the catheter inevitably retrieve organisms from the catheter lumen. Paired quantitative blood cultures should be used to diagnose CRBSI. The diagnosis is suggested when the number of colonies isolated from the cultures of blood taken through the vascular catheter is at least five times greater than that seen in culture of a concurrent peripheral-blood sample. The paired blood

culture method is probably most helpful when the suspected infection is related to a long-dwelling silicone catheter, in which setting luminal colonisation is predominant.<sup>2,7</sup>

The roll-plate semiquantitative culture method is the

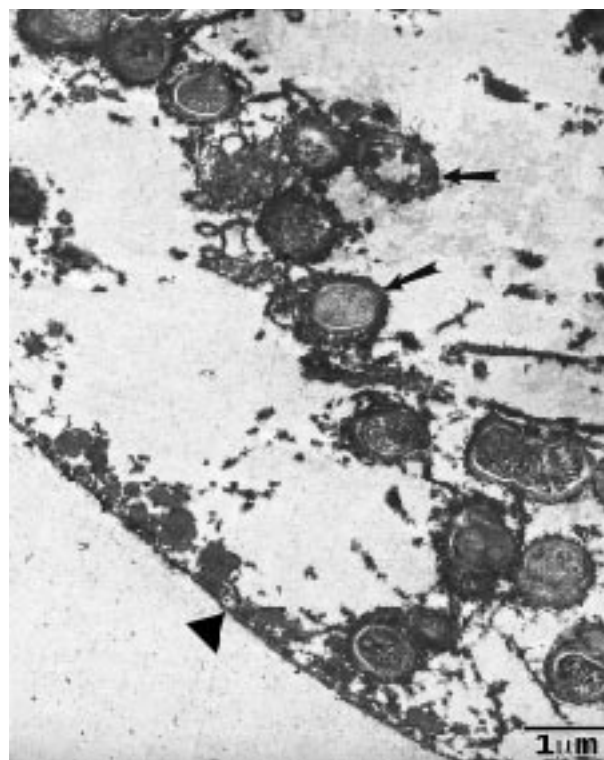


Figure 2: **Transmission electron micrograph showing colony of cocci embedded in biofilm layer on surface of vascular catheter**

Arrowhead points to wall of biofilm; arrows point to cocci embedded in exopolysaccharide slime of biofilm.

## Measures to decrease risk of colonisation of central-venous catheters

### Short-term placement ( $\leq 10$ days)

To prevent colonisation of external surface of catheter:

Maximum sterile barrier (handwashing, sterile gloves, large drape, sterile gown, mask, and cap)

Infusion therapy team

Cutaneous antimicrobial or antiseptic agents (mupirocin, chlorhexidine)

Subcutaneous silver cuff

Antimicrobial coating of catheter

### Long-term placement ( $>10$ days)

To prevent colonisation of catheter lumen:

Maximum sterile barrier (handwashing, sterile gloves, large drape, sterile gown, mask, and cap)

Infusion therapy team

Antimicrobial flush or lock

Tunnelling

Antiseptic hub

most common way of taking culture samples from vascular catheters.<sup>8</sup> However, this method is limited, in that it can take samples only from the external surfaces of catheters, and may not retrieve organisms that are strongly held in the biofilm layer. Therefore, the roll-plate method is less useful for examination of long-dwelling silicone catheters, which have predominant luminal colonisation. Quantitative culture techniques, including the sonication and vortexing methods, have the advantages of isolating organisms from the external and internal surfaces of the catheters and possibly releasing organisms embedded within the biofilm layer. Thus, quantitative culture methods are more useful with long-dwelling silicone catheters.<sup>7</sup>

The main limitation of the roll plate, sonication, and vortexing methods is that the central-venous catheter must be removed for a culture sample to be taken. New diagnostic culture techniques, such as the endoluminal brush technique acridine orange leucocyte cyto-spin, allow samples to be taken with the central-venous catheter in situ. In patients receiving total parenteral nutrition, the endoluminal brush method had sensitivity of 95% and specificity of 84% in diagnosis of CRBSI without catheter removal. The endoluminal brush technique also improves the diagnostic yield from subsequent acridine orange leucocyte cyto-spin tests on blood drawn through the central-venous catheter. However, the endoluminal brush does induce transient bacteraemia in 6% of patients.

## Preventive strategies

Understanding of the pathogenesis of catheter infections is necessary so that effective strategies can be developed to prevent CRBSI (panel). There are several preventive measures that decrease the rate of CRBSI in clinical studies.

### Infusion therapy team

Establishment of an experienced infusion therapy team to insert and maintain catheters decreases the rate of CRBSI by up to eight times.<sup>18,19</sup> An infusion therapy team is also cost-effective, particularly in medical centres with high rates of catheter-related infection.

### Maximum sterile barriers

The routine procedure for insertion of a central-venous

catheter is to wear gloves and use a small drape. However, we recommend that a larger sterile barrier is created by use of sterile gloves, mask, gown, and cap, as well as a large drape all to be done after careful handwashing. Use of these precautions has been linked to a four-fold decrease in the rate of bacteraemia related to pulmonary-artery catheters,<sup>13</sup> and to a more than six-fold decrease in the rate of sepsis related to central-venous catheters.<sup>20</sup>

### Cutaneous antimicrobials and antiseptics

The microbial burden at the skin insertion site can be lowered. Although the application of polyvidone-iodine ointment at the insertion site does not significantly decrease the rate of CRBSI, the use of a topical polyantibiotic regimen (polymyxin  $\beta$ , neomycin, bacitracin) is associated with a significantly lower rate of CRBSI.<sup>21</sup> However, the overall protective effect of the topical antibiotic regimen is offset by a higher risk of fungal (candida) colonisation and infection. A randomised controlled trial of mupirocin, a topical antibiotic with high antistaphylococcal activity, showed a five-fold decrease in the risk of colonisation of central-venous catheters inserted in the internal jugular vein.<sup>22</sup> In a three-group trial that compared the efficacy of treatment with 70% alcohol, with 10% polyvidone-iodine, and with 2% chlorhexidine gluconate, the rate of catheter-related bacteraemia was almost four times lower in the group of patients who received chlorhexidine than in the other two groups.<sup>23</sup>

### Tunnelling

Two prospective randomised studies have investigated the effect of catheter tunnelling (placing the proximal segment of the catheter under the skin at a distance from the point of entry to the vein) on catheter-related infections.<sup>24,25</sup> The first study looked at long-dwelling central-venous catheters, mostly silicone catheters, placed in immunocompromised patients. The risk of catheter-related bacteraemia was 2% with tunnelled and 5% with non-tunnelled catheters.<sup>24</sup> The difference in risk was not significant, probably because of the relatively small number of patients in each group (107 and 105 patients). In the second study, in which short-dwelling polyurethane catheters were placed in the internal jugular vein in critically ill patients, tunnelled catheters showed a significantly lower rate of catheter-related bacteraemia than non-tunnelled catheters.<sup>25</sup> Tunnelling of central-venous catheters may decrease the risk of CRBSI, but more data are required to support this observation, especially for long-term silicone catheters. However, tunnelling does incur significant additional costs that may not be justified, given the marginal infection-control benefits described in these two studies.

### Ionic silver cuffs

A silver-impregnated subcutaneous collagen cuff is both an antimicrobial deterrent (through the effect of silver ions) and a physical barrier to the migration of bacteria. The cuff reduced the rate of infection in critically ill patients with central-venous catheters placed for between 5.6 and 9.1 days.<sup>3</sup> The anti-infective effect is short-lived, however, because the collagen to which the silver ions are chelated is biodegraded. The cuff does

not prevent infection of long-dwelling central-venous catheters.

#### *Intraluminal antibiotic locks*

Schwartz and colleagues,<sup>26</sup> in a study of catheter-related bacteraemia caused by vancomycin-resistant gram-positive organisms, found that flushing of tunnelled central-venous catheters with heparin plus vancomycin was associated with a significantly lower rate of bacteraemia than flushing with heparin alone. By contrast, Rackoff and colleagues' randomised trial<sup>27</sup> found no effect of vancomycin plus heparin on the risk of bacteraemia. Moreover, the use of such a catheter-flush solution could lead to the emergence of vancomycin-resistant gram-positive organisms, which is highly undesirable because vancomycin is the only drug available for the treatment of infections due to methicillin-resistant staphylococci and penicillin-resistant enterococci. However, there is an alternative catheter flush containing minocycline and edetic acid, which has been successfully used to prevent recurrent catheter infection in several high-risk patients.<sup>28</sup>

#### *Antiseptic hubs*

A new hub model, designed to protect against hub colonisation, showed a four-fold decrease in catheter-related sepsis in patients at high risk of hub-related sepsis.<sup>29</sup> The major limitation of this model is that it protects only against organisms migrating through the hub along the internal surface of the catheter. It does not prevent the migration of skin organisms along the external surface of the catheter.

#### *Antimicrobial coating of catheters*

A prospective, randomised study by Maki and colleagues<sup>14</sup> showed that central-venous catheters that are coated on the external surface with chlorhexidine plus sulphadiazine silver were nearly 50% less likely to be colonised with micro-organisms and at least four times less likely to produce bacteraemia than uncoated catheters. Another approach uses minocycline and rifampicin to coat the external and internal surfaces of catheters. Coating of catheters with this combination gives a broad-spectrum in-vitro inhibition of gram-positive bacteria, gram-negative bacteria, and *C albicans*.<sup>30</sup> In a prospective, randomised, multicentre study, central-venous catheters with minocycline and rifampicin lowered the rate of catheter colonisation three-fold and prevented catheter-related septicaemia, compared with uncoated catheters.<sup>31</sup> This study also found no antibiotic resistance among bacteria recovered from patients managed with coated central-venous catheters. Studies in vitro and in animals, as well as a randomised clinical trial, have shown that catheters coated with minocycline and rifampicin have significantly better antimicrobial activity than catheters coated with chlorhexidine and sulphadiazine silver.<sup>30,32</sup>

### **Therapeutic directives**

#### *Coagulase-negative staphylococcus*

The best duration of treatment for coagulase-negative staphylococcus has not been defined. However, if the patient responds in 48–72 h, a 7-day course of treatment should be adequate.<sup>33</sup> Glycopeptide antibiotics are suitable for treating methicillin-resistant

coagulase-negative staphylococcal bloodstream infections. Although catheter removal was once thought essential, rates of acute catheter-related bacteraemia, caused by coagulase-negative staphylococci and treated with vancomycin, are not affected by catheter removal.<sup>33</sup> However, if the central-venous catheter is not removed, there is still a 20% chance that the bacteraemia will recur, compared with only a 3% risk of recurrence if the catheter is removed ( $p < 0.005$ ).<sup>33</sup> Of course, immediate removal of surgically implanted central-venous catheters might not be practicable for a patient with poor venous access or thrombocytopenia. Nonetheless, there is a 20% risk of bacteraemia recurrence if the catheter remains in place, especially for longer than 3 weeks after the initial bacteraemia episode.

#### *Staphylococcus aureus*

Serious infectious complications can arise in catheter-related *S aureus* bacteraemia. Complications include septic thrombosis, fatal sepsis, and deep-seated infections such as endocarditis, osteomyelitis, septic emboli, and abscesses.<sup>34</sup> Retention of the catheter can lead to persistence of *S aureus* bacteraemia, to relapse, and to increased mortality.<sup>35</sup> The duration of treatment with parenteral antibiotic—2 weeks (short course) or at least 4 weeks (long course)—remains controversial. The two largest retrospective trials, each of 55 uncomplicated *S aureus* CRBSI, showed no recurrence after catheter removal, followed by a short course of intravenous antibiotics over at least 10 days.<sup>34,36</sup> Treatment of uncomplicated *S aureus* CRBSI for less than 10 days was associated with a significantly higher rate of relapse. This treatment was therefore judged unacceptable. A 2-week course of parenteral antibiotics may be given to patients with uncomplicated *S aureus* CRBSI, who have no underlying cardiac valvular disease, and who respond within 3 days to antibiotics and catheter removal.<sup>34</sup> Patients with *S aureus* CRBSI complicated by septic thrombosis, endocarditis, and similar disorders, should be treated with at least a 4-week course of intravenous antibiotics.

#### *Candida species*

Systemic antifungal therapy is necessary in all cases of vascular-catheter-related candidaemia. Rose<sup>37</sup> reviewed 26 patients with catheter-associated candidaemia, who were treated by catheter removal without antifungal therapy. Four patients developed endophthalmitis caused by candida, and three had significant loss of vision. In a prospective randomised study of 206 non-neutropenic patients with candidaemia (judged to be catheter-related in 72%), fluconazole 400 mg daily for at least 14 days was as effective as amphotericin B 0.5 mg/kg daily for 14 days, but fluconazole was less toxic.<sup>38</sup> Fluconazole may be used even in neutropenic patients, unless the candidaemia is caused by fluconazole-resistant organisms, such as *C glabrata* or *C krusei*. Removal of the vascular catheter is recommended, since catheter retention allows the candidaemia to persist.<sup>38,39</sup> Multivariate analysis has shown that vascular catheter retention is an independent risk factor for the persistence of candidaemia and mortality.<sup>39</sup> Early removal of the catheter should be considered for a patient with suspected catheter-related candidaemia, in the absence of another apparent source of bloodstream infection.

### Gram-positive bacilli

Vancomycin remains the antibiotic of choice in the treatment of CRBSI caused by gram-positive bacilli such as *Corynebacterium jeikeium* and *Bacillus* species. Removal of the catheter is recommended for the successful management of such infections, although additional prospective studies are necessary to examine the effect of catheter removal on the treatment of these infections.

### Gram-negative bacilli

Enteric gram-negative bacilli, such as *Escherichia coli* and *Klebsiella pneumoniae*, rarely cause catheter-related sepsis. Elting and Bodey reported 149 episodes of bloodstream infection caused by *Stenotrophomonas maltophilia* and non-aeruginosa *Pseudomonas* species,<sup>40</sup> in which the central-venous catheter was the most common source of the bacteraemia. Failure to remove the catheter resulted in significantly higher rates of treatment failure and bacteraemia recurrence. Moreover, antibiotic therapy alone does not generally cure catheter-related infections

caused by *Pseudomonas* species, and removal of the catheter is recommended. CRBSI caused by organisms such as *Pseudomonas* species, *Acinetobacter* species, and *Stenotrophomonas maltophilia*, that are often acquired for the hospital environment, should be managed by removal of the catheter and a 1-week course of appropriate broad-spectrum antibacterial parenteral antibiotics.

### Conclusion

In conclusion, the management of CRBSI, including early and accurate diagnosis, effective preventive strategies, and therapeutic clinical decisions related to catheter removal, must be guided by current understanding of the pathogenesis of catheter infections. Micro-organisms that colonise catheter surfaces are often embedded in a layer of biofilm, and are resistant to antimicrobial agents. Clinicians should take care to prevent such challenging, and often complicated, infections.

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