

# Intravascular catheter-related infections: advances in diagnosis, prevention, and management

Issam Raad, Hend Hanna, Dennis Maki

Indwelling vascular catheters are a leading source of bloodstream infections in critically ill patients and cancer patients. Because clinical diagnostic criteria are either insensitive or non-specific, such infections are often overdiagnosed, resulting in unnecessary and wasteful removal of the catheter. Catheter-sparing diagnostic methods, such as differential quantitative blood cultures and time to positivity have emerged as reliable diagnostic techniques. Novel preventive strategies include cutaneous antisepsis, maximum sterile barrier, use of antimicrobial catheters, and antimicrobial catheter lock solution. Management of catheter-related bloodstream infections involves deciding on catheter removal, antimicrobial catheter lock solution, and the type and duration of systemic antimicrobial therapy. Such decisions depend on the identity of the organism causing the bloodstream infection, the clinical and radiographical manifestations suggesting a complicated course, the underlying condition of the host (neutropenia, thrombocytopenia), and the availability of other vascular access sites.

## Introduction

The use of vascular catheters is essential for the care of critically ill and chronically ill cancer and haemodialysis patients.<sup>1,2</sup> However, vascular catheter-related bloodstream infections (CRBSIs) have become a leading cause of health-care-associated bloodstream infections and are associated with substantial morbidity and mortality.<sup>3-6</sup> More than 250 000 vascular catheter-related bacteraemias and fungaemias occur annually in the USA with an attributable mortality ranging from 12% to 25% in critically ill patients,<sup>7,8</sup> with an added cost ranging from US\$3000 to \$56 167.<sup>9,10</sup>

Over the past decade, new knowledge in the epidemiology and pathogenesis of CRBSIs has led to advances in the diagnosis, prevention, and management of such infections. This Review will highlight these recent developments and outline the evidence supporting novel approaches, methods, and technologies for the control of CRBSIs.

## Types of intravascular devices

In addition to the pulmonary artery catheters, midline catheters, and peripheral vascular catheters (venous and arterial), there are a number of different central venous catheters (CVC) available with varying insertion techniques, sizes, and catheter materials. CVCs can be single, double, or triple-lumen.

### Non-tunnelled and tunnelled CVCs

Non-tunnelled CVCs may be made of polyurethane or silicone materials and they are inserted into either the peripheral venous system (subclavian vein) or the neck (jugular vein) through a percutaneous stick, where the catheter tip is advanced until it rests into the superior vena cava. These short-term catheters can be placed in outpatient non-surgical settings and can be exchanged over a guidewire.

By contrast, tunnelled CVCs are long-term catheters tunnelled surgically under the skin for several inches to the cannulated vein. The proximal end exits via a

subcutaneous tunnel from the lower anterior chest wall. A felt Dacron cuff is used to anchor the catheter in place subcutaneously, where eventually it becomes enmeshed with fibrous tissues. The catheter is therefore securely anchored, making it more stable and less likely to be pulled out accidentally. The cuff also creates a tissue interface that acts as a barrier against the migration of microorganisms. A further modification of these tunnelled catheters led to the development of the Groshong catheter, which unlike the traditional open-ended catheters has a rounded closed tip, with an adjacent two-slit valve that remains closed unless the catheter is in use, hence reducing the risk of intraluminal blood clotting or infusion of air when the catheter is not in use. The valve also eliminates the need for routine clamping of the catheter.

### Implantable ports

Ports are implantable vascular access devices that are made of plastic or titanium material and inserted completely beneath the skin, connected to the catheter tube. Ports are surgically placed as either a central subclavian port in the subcutaneous pocket of the upper chest wall, or as a peripheral port in the antecubital fossa of the arm. Ports are available as single or double-lumen catheters, with or without the Groshong valve.

### Peripherally inserted CVCs

The use of peripherally inserted CVCs has gained acceptance as a method for long-term venous access (6 weeks to 6 months). This type of catheter is made of silicone or polyurethane material and may or may not have the Groshong valve. The catheter is inserted peripherally at or above the antecubital space into the cephalic, basilic, medial cephalic, or medial basilic vein, after which it is advanced into the superior vena cava above the right atrium. A peripherally inserted CVC is usually placed in a non-surgical outpatient setting, under local anaesthesia, and it can be placed by a skilled and trained infusion therapy nurse.

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Department of Infectious Diseases, Infection Control and Employee Health, University of Texas MD Anderson Cancer Center, Houston, TX, USA (Prof I Raad MD, H Hanna MD); and Section of Infectious Diseases, University of Wisconsin Center for Medical Sciences, Madison, WI, USA (D Maki MD)

Correspondence to: Prof Issam Raad, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blv, Houston, TX 77030, USA. Tel +1 713 792 7943; fax +1 713 792 8233; iraad@mdanderson.org



Figure 1: Drained infusion port pocket abscess with evidence of intravascular device-related inflammation

### Clinical manifestations and definitions

The clinical manifestations of catheter-related infections can be systemic, which include CRBSIs, or local, where the clinical manifestations of the infection occur at the insertion site or tunnel track.<sup>11</sup>

### Local catheter infections

Local catheter infections are defined as an exit site infection, tunnel infection, or pocket infection. As shown in figure 1, local catheter infections are often characterised by inflammatory manifestations, including induration, erythema, warmth, and pain or tenderness at or around the catheter exit site.<sup>11</sup> Local catheter infections can be

associated with CRBSIs; however, on their own, they cannot be relied on to identify or predict a CRBSI,<sup>12</sup> and could exist independently of a systemic infection.<sup>13</sup>

### Systemic catheter infections

CRBSI should be considered when a patient with a CVC presents with bacteraemia or fungaemia in the presence of signs and symptoms of systemic infection, such as fever, chills, and hypotension in the absence of hypovolaemia or a cardiac event. Hence, probable CRBSI can be diagnosed by one or more positive blood cultures obtained from a peripheral vein, when there is no apparent source for the bloodstream infection except the catheter. In addition to the above, the Infectious Diseases Society of America (IDSA)<sup>11</sup> has suggested one of the following microbiological methods to confirm diagnosis of CRBSI: (1) positive semiquantitative or quantitative culture of the catheter; (2) simultaneous quantitative blood cultures drawn through the CVC and peripheral vein with a ratio of 5:1 or more (CVC versus peripheral); or (3) differential time to positivity.

### Diagnosis: quantitative methods

The diagnosis of CRBSI remains a major challenge. Fever and chills that are often associated with CRBSI are not specific and local catheter site inflammation is associated with sensitivity of 3% or less.<sup>11,12</sup> Furthermore, local catheter inflammation and phlebitis could exist in the absence of CRBSI or even a local infection, as has been reported with peripherally inserted central catheters.<sup>13</sup> Therefore, microbiological evidence implicating the catheter as a source of the bloodstream

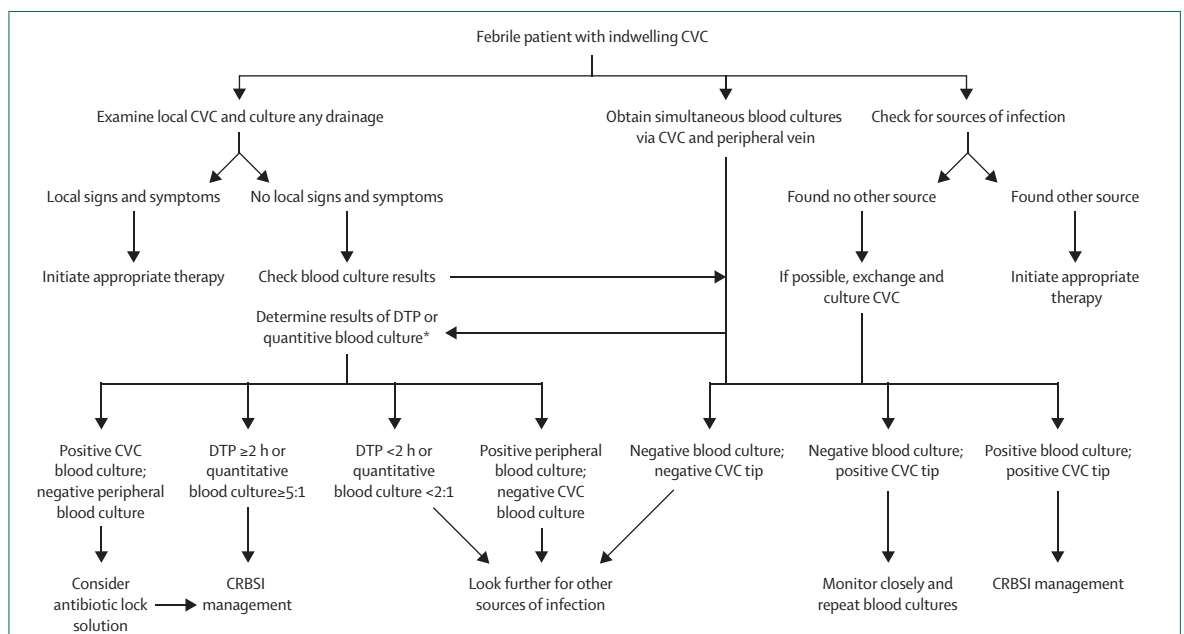


Figure 2: Diagnosis of acute febrile episode in a patient with central venous catheter

CVC=central venous catheter. DTP=differential time to positivity. \*A blood culture is considered positive if the ratio of colony forming units growing from simultaneously drawn central and peripheral blood is  $\geq 5:1$  or the DTP is  $\geq 2$  h (central blood culture turns positive before simultaneously drawn peripheral blood culture).

	Diagnostic criteria	Accuracy		Disadvantages
		Sensitivity	Specificity	
<b>Techniques without CVC removal</b>				
Simultaneous quantitative blood cultures	Quantitative blood culture drawn through CVC yields CFU count five-fold higher or more than CFU count from simultaneously drawn blood from peripheral vein	93% <sup>22</sup>	97–100% <sup>22</sup>	Labour intensive, costly
Differential time to positivity	Blood culture drawn from CVC becomes positive $\geq 2$ h before simultaneously drawn blood culture from peripheral vein	89–90% <sup>22</sup>	72–87% <sup>22</sup>	Hard to interpret when patient is taking antibiotics through the CVC
CVC-drawn quantitative blood culture	Quantitative blood culture from CVC is $\geq 100$ CFU/mL	81–86% <sup>22</sup>	85–96% <sup>22</sup>	Cannot differentiate between CRBSI and high-grade bacteraemia
Acridine orange leucocyte cytospin	Presence of any bacteria	87% <sup>23</sup> (96% if followed by Gram stain <sup>24</sup> )	94% <sup>23</sup> (92% if followed by Gram stain <sup>24</sup> )	Not widely tested or used
Endoluminal brush	Quantitative culture with $>100$ CFU/mL	95% <sup>25</sup>	84% <sup>25</sup>	May induce bacteraemia, arrhythmia, embolisation
<b>Techniques requiring CVC removal</b>				
Semiquantitative CVC tip culture, roll plate	$\geq 15$ CFU/mL from CVC tip	45–84% <sup>22,26,27</sup>	85% <sup>22,26,27</sup>	Unable to culture organisms embedded intraluminally
Quantitative CVC culture: centrifugation, vortexing, sonication	$\geq 103$ CFU from CVC tip	82–83% <sup>22</sup>	89–97% <sup>22</sup>	The cut-off point of $\geq 103$ CFU vs $\geq 102$ CFU is not well defined
Microscopy of stained CVC: Gram stain and acridine orange staining	Direct visualisation of the microorganisms	84–100% <sup>28,29</sup>	97–100% <sup>28,29</sup>	Labour intensive, impractical

CVC=central venous catheter. CFU=colony forming units. CRBSI=catheter-related bloodstream infection.

**Table: Microbiological diagnostic methods of catheter-related bloodstream infections**

infection is necessary for establishing a diagnosis of CRBSI (figure 2). Several older qualitative culture methods involving the catheter segment or blood drawn through the catheter have been studied, but have been found to be associated with limited sensitivity and specificity.<sup>14–16</sup> Similarly, other quantitative culture methods of the insertion site or catheter hub have been associated with a limited specificity and positive predictive value.<sup>17–21</sup> The methods outlined below have been studied the most during the past decade and most of them have shown promising results (table). These diagnostic approaches can be divided into two major groups: those that necessitate catheter removal and those that can be done without the removal of the catheter.

### Catheter-sparing diagnostic methods

#### Simultaneous quantitative blood cultures

The first method involves obtaining paired blood cultures drawn simultaneously from the CVC and the peripheral vein. Although several quantitative blood culture methods are available, one of the most widely used techniques sees a 10 mL blood sample placed in an isolator tube (Isolator 10, Wampole, Granbury, NJ, USA) for quantitative culturing by lysis centrifugation.<sup>30</sup> When the quantitative blood culture drawn through the CVC yields a colony count that is several-fold higher than that obtained from simultaneously drawn blood of the peripheral vein, the result is considered to be predictive of CRBSI. Since studies have reported different cut-off points for a positive

diagnosis ranging from two-fold to ten-fold,<sup>31–36</sup> the IDSA accepted a midpoint level whereby a colony count that is five-fold or greater from blood culture drawn through the CVC versus peripheral vein is indicative of CRBSI (figure 2). Simultaneous quantitative blood culture was found to be the most accurate test for diagnosis of CRBSI in a meta-analysis<sup>22</sup> of studies of diagnostic tests (pooled sensitivity and specificity for short-term catheters 75% and 97%, respectively, and for long-term catheters 93% and 100%, respectively), particularly when compared with a gold standard involving quantitative catheter culture methods. However, the use of the simultaneous quantitative blood culture technique has been limited because it is labour intensive and expensive.

#### Differential time to positivity

Differential time to positivity is a simple technique and involves simultaneous qualitative blood cultures drawn through the catheter and a peripheral vein.<sup>37–43</sup> Regular blood cultures are routinely placed in an automatic culture detector that records culture positivity every 15 min according to changes in fluorescence related to microbial growth. Several studies indicated that definite diagnosis of CRBSI is established when the blood culture drawn from the CVC becomes positive at least 2 h earlier than the blood culture drawn from the peripheral vein.<sup>37,38,43</sup> A meta-analysis found the pooled sensitivity and specificity for this method of diagnosing CRBSI in short-term catheters to be 89% and 87%, respectively,

compared with 90% and 72%, respectively, for long-term catheters.<sup>22</sup> In view of the wide use of automated radiometric blood culture systems, in which blood cultures are continuously monitored for microbiological growth, it would be easy to include the assessment of differential time to positivity, with no added cost or labour. However, the interpretation of this diagnostic method could be compromised if antibiotics are given intraluminally at the time of drawing blood through the catheter, in which case colonised catheters may become falsely negative.<sup>43</sup>

#### *Catheter-drawn quantitative blood cultures*

A single quantitative blood culture drawn through the CVC without an accompanying peripheral blood culture can also be used to diagnose CRBSI. The threshold required for a positive diagnosis is at least 100 colony-forming units (CFU)/mL.<sup>33,44</sup> However, this method cannot distinguish between CRBSI and high-grade bacteraemia, particularly in immunocompromised patients who have serious sepsis. Further studies are required to verify this method.

#### *Acridine orange leucocyte cytospin*

Acridine orange leucocyte cytospin (AOLC) is a rapid diagnostic microscopy method, requiring 30 min. 1 mL of blood is drawn through the CVC and subsequently centrifuged, placed on slides, and stained with acridine orange before examination of the slides under ultraviolet microscopy.<sup>23,24,45-47</sup> The presence of any bacteria indicates a positive diagnosis. The sensitivity and specificity of this test have been reported to be 87% and 94%, respectively.<sup>23</sup> AOLC followed by a Gram stain can facilitate the initial morphological distinction of the pathogens, increasing sensitivity to 96%.<sup>24</sup> Although cost-efficient and simple, this test has not been widely used and has only been tested by a small group of investigators.

#### *Endoluminal brush*

A tapered nylon brush on a steel wire is passed through the catheter hub and lumen, withdrawn, and immediately placed in a buffered container. This container undergoes sonication and vortexing after which the solution is cultured onto blood agar plates. Counts of greater than 100 CFU/mL are deemed positive.<sup>25</sup> This technique is based on the fact that bacteria adhere to the fibrin sheath on the inner surface of the CVC and fibrin becomes enmeshed in the brush's bristles. Kite and colleagues<sup>25</sup> reported a sensitivity for the test of 95% and a specificity of 84%. However, this method has been criticised as being impractical and risky, sometimes producing several side-effects, including arrhythmias, embolisation, and induced bacteraemia related to the disruption of existing biofilm.<sup>22,48,49</sup> The endoluminal brush method has not been widely used and further studies assessing its adverse effects are required.

### **Diagnostic methods requiring catheter removal**

#### *Semiquantitative roll-plate catheter culture*

In one of the most frequently studied diagnostic techniques, the distal segment of the CVC is cut and rolled against a blood agar plate at least four times before the plate is incubated overnight.<sup>22,49</sup> Upon examination of the plate, a colony count of 15 CFU/mL or more can suggest catheter colonisation.<sup>50</sup> Diagnosis of CRBSI is only confirmed if catheter colonisation is associated with a positive peripheral blood culture revealing the same organism.<sup>26,51-57</sup> The limitation of this method is that it only detects colonisation of the external surface of the catheter rather than intraluminal colonisation. This concern is augmented in long-term catheters in which luminal colonisation more frequently leads to bloodstream infections and in first generation antiseptic catheters where only the external surface of the CVC is impregnated. Hence, the sensitivity of this method for diagnosing CRBSI in long-term CVCs (>30 days of dwell time) was found to range from 45% to 75%.<sup>26,27</sup> Notably, the original study describing this method showed a correlation between short-term peripheral venous catheter colonisation and exit site infections.<sup>50</sup> However, pooled sensitivity and specificity for roll-plate catheter culture in 14 trials involving short-term CVCs were calculated to be 84% and 85%, respectively.<sup>22</sup> Bouza and colleagues<sup>58</sup> calculated acceptable sensitivity and specificity values for this technique of more than 90% for both short-term and long-term CVCs. However, long-term CVCs in this study were defined as those with only 7 days of dwell time or more.

#### *Quantitative catheter segment cultures*

Several methods such as centrifugation,<sup>59</sup> vortexing,<sup>60</sup> and sonication<sup>27,55,61</sup> have been used to retrieve organisms from both the external and internal surfaces of the catheter. The sonication method involves placing a 5 cm catheter segment in a 10 mL broth container and then sonicating the container for 1 min followed by vortexing for 15 s. 0.1 mL of the sonicated/vortexed broth and 0.1 mL of a 1:100 dilution of the broth are subsequently streaked on blood agar plates and incubated at 35°C. The numbers of colonies are counted after accounting for the dilution and a count of more than 100 CFU per catheter segment is deemed positive. The advantage of sonication or vortexing is that these methods help release organisms from both the external and internal surfaces of the CVC. The disadvantage is that these methods release biofilm organisms that might not be clinically relevant, whereas relevant planktonic organisms might be killed. The sonication and vortexing methods have been shown to have similar sensitivity and specificity to the roll-plate method in diagnosing CRBSI in patients with short-term CVCs;<sup>58,62</sup> however, for long-term CVCs, the sonication method was found to have higher sensitivity than the roll-plate method.<sup>27</sup> The pooled sensitivity and specificity of quantitative catheter segment culture for short-term

catheters were 82% and 89%, respectively, and 83% and 97% for long-term catheters, respectively.<sup>22</sup>

#### Microscopy of stained catheters

Several microbial staining methods, including Gram stain or acridine orange stain, with subsequent microscopy, have been developed. Cooper and Hopkins<sup>28</sup> explored the use of direct Gram staining and reported a 100% sensitivity and 97% specificity with predictive values of 84% or more. Another trial showed less promising results.<sup>63</sup> Acridine orange staining has been used for diagnosis where fluorescence is indicative of positivity, achieving a sensitivity of 84% and specificity of 99%.<sup>29</sup> In general, microscopy techniques have not been widely used and are thought labour intensive and impractical.<sup>22,49</sup>

### Novel preventive strategies

Traditional measures for the prevention of catheter-related infection, recommended by the Healthcare Infection Control Practices Advisory Committee (HICPAC) guidelines, include education of health-care workers on proper catheter insertion and maintenance, routine monitoring of institutional rates of CRBSI, hand hygiene, the use of a dedicated infusion therapy team, use of sterile semipermeable dressings, evidence of femoral insertion, and removing the vascular catheter as soon as possible.<sup>64</sup> Other interventions associated with limited use or supporting evidence include attachable silver-impregnated cuff, inline filters, antimicrobial hubs and connectors, and topical antibiotics at the insertion site.<sup>65,66</sup> In this section, we will outline novel aseptic techniques that have either been strongly recommended for implementation by HICPAC<sup>64</sup> or supported in the literature by at least five well-designed prospective randomised studies. Of the strategies outlined below, the cutaneous antiseptic techniques, maximum sterile barriers, and chlorhexidine sponges protect against the colonisation of the external surface of the CVC, antimicrobial lock minimises the risk of luminal colonisation, and antimicrobial catheters protect against external and internal surface colonisation.

#### Cutaneous antiseptics

Povidone-iodine is the most frequently used antiseptic for local catheter insertion sites in the USA.<sup>64</sup> At least three studies evaluating the chlorhexidine-containing cutaneous antiseptic regimen in comparison with either povidone-iodine or alcohol for the care of an intravascular catheter insertion site have shown lower rates of CRBSI associated with the chlorhexidine preparation.<sup>67-69</sup> However, the efficacy of cutaneous antiseptics with chlorhexidine gluconate might be related to the concentration of chlorhexidine. A study evaluating tincture of chlorhexidine 0.5% showed that it is no more effective in preventing CRBSI or CVC colonisation than 10% povidone-iodine.<sup>70</sup> By contrast, Maki and colleagues<sup>67</sup>

showed that 2% aqueous chlorhexidine gluconate tended to decrease CRBSI compared with 10% povidone-iodine or 70% alcohol. The HICPAC guidelines have, therefore, strongly recommended cutaneous antiseptics with a 2% chlorhexidine-based preparation.<sup>64</sup> In a prospective randomised trial, Parienti and co-workers<sup>71</sup> showed that skin insertion antiseptics consisting of 5% povidone-iodine solution in 70% ethanol was associated with a substantial reduction of CVC-related colonisation and infection compared with 10% povidone-iodine.<sup>71</sup>

#### Maximum sterile barrier

Maximum sterile barrier precautions require wearing a sterile gown, gloves, and cap, and using a large sterile drape during the insertion of the CVC, similar to the drapes used in the operating room. In a prospective randomised study, maximum sterile barrier during the insertion of non-tunnelled long-term silicone CVCs and peripherally inserted central catheters was associated with an almost significant reduction in CRBSI ( $p=0.06$ ).<sup>72</sup> The use of maximum sterile barrier precautions also decreased the risk of CRBSI associated with pulmonary artery catheter placement compared with limited precautions that included only the use of sterile gloves and a small drape.<sup>73</sup> By contrast, maximum sterile barrier precautions failed to reduce the risk of colonisation or bloodstream infections associated with the insertion of arterial catheters in a recent prospective randomised study.<sup>74</sup> However, in that study the risk of arterial catheter exit site infection in patients who underwent maximum sterile barrier precautions was at least four-fold lower than in patients randomised to the minimum barrier precautions arm. The HICPAC guidelines strongly recommend the use of maximum sterile barrier precautions during the insertion of CVCs and pulmonary artery catheters.<sup>64</sup>

#### Chlorhexidine-impregnated sponge

A commercially available chlorhexidine-impregnated sponge, about 2.5 cm in diameter, can be placed over the CVC insertion site and covered with transparent polyurethane. In a prospective randomised study, use of the chlorhexidine sponge led to a three-fold reduction in CRBSI.<sup>75</sup> However, other paediatric studies showed a pronounced decrease in CVC colonisation but not CRBSI,<sup>76,77</sup> and another smaller randomised trial failed to show a decrease in either CVC colonisation or CRBSI.<sup>78</sup> A meta-analysis including eight randomised controlled trials showed that chlorhexidine-impregnated sponges are associated with a trend towards reduction of vascular and epidural catheter infection.<sup>79</sup> However, the number of sponges needed to prevent one episode of CRBSI was 142 with an estimated cost of \$532.50.<sup>79</sup> The latest guidelines for the prevention of intravascular catheter-related infections<sup>64</sup> made no recommendation regarding the chlorhexidine sponge dressings and their usefulness is considered to be an unresolved issue.

### Antimicrobial catheters

Impregnation or coating of the catheter polymer surface with antimicrobial agents might prevent or minimise the adherence of microbial organisms.<sup>80</sup> Antiseptic, antibiotic-coated, and silver-impregnated catheters have all been approved in the USA for use in patients. The HICPAC guidelines strongly recommend the use of antiseptic or antibiotic-coated CVCs in patients whose catheter is expected to remain in place for more than 5 days, combined with a comprehensive strategy that aims to reduce CRBSI through education, maximum sterile barrier, and 2% chlorhexidine skin antiseptics during CVC insertion.<sup>64</sup>

#### Antiseptic catheters

Antiseptic catheters are polyurethane CVCs coated with chlorhexidine and sulfadiazine silver (ArrowGard and ArrowGard Plus; Arrow International Inc, Reading, PA, USA). At least 16 prospective randomised trials<sup>81–96</sup> have evaluated the first-generation antiseptic catheters, most of which showed a reduction in catheter colonisation, with only two trials reporting a significant reduction in CRBSI ( $p < 0.05$ ).<sup>86,92</sup>

Second-generation chlorhexidine/sulfadiazine silver catheters impregnated on both the external and internal surfaces have also been developed. Three multicentre studies evaluated these catheters in prospective randomised trials and all failed to show a significant decrease in CRBSI, which may be related to a lack of power in the studies' design to detect a difference if it existed.<sup>97–99</sup> However, a significant decrease in catheter colonisation, which could be considered a prelude for CRBSI, was shown.

Clinical resistance associated with the chlorhexidine/sulfadiazine silver catheters has not been reported, even though chlorhexidine resistance has been shown to occur among Gram-negative isolates, including *Pseudomonas stutzeri*.<sup>100</sup>

#### Antibiotic-coated catheters

The only antibiotic-coated catheter that is FDA-approved and available for use in the USA is one coated with minocycline and rifampicin. In-vitro, ex-vivo, and animal studies have shown that minocycline/rifampicin-coated CVCs have superior and more prolonged activity against staphylococci compared with first-generation chlorhexidine/sulfadiazine silver catheters.<sup>101,102</sup> Subsequently, five prospective randomised clinical trials have shown that CVCs coated with minocycline/rifampicin also substantially decrease the risk of CRBSI.<sup>103–107</sup> Several factors could have contributed to the superiority of the antibiotic-coated catheter, including the fact that minocycline/rifampicin catheters are impregnated on both the external and internal surfaces, whereas first-generation chlorhexidine/sulfadiazine silver catheters are coated on the external surface only.<sup>65,66</sup>

Investigators are concerned that bacterial resistance may develop to either minocycline or rifampicin with the prolonged use of these antibiotic-coated catheters.<sup>108</sup>

In-vitro studies have shown that resistance might occur if either antibiotic (particularly rifampicin) is used alone, but resistance to a combination of the antibiotics is very unlikely.<sup>108,109</sup> Furthermore, four of the prospective randomised studies evaluated the skin at the catheter insertion site before and after the insertion of the antibiotic-coated catheters and failed to detect any emergence of resistance.<sup>103–106</sup>

#### Silver-impregnated catheters

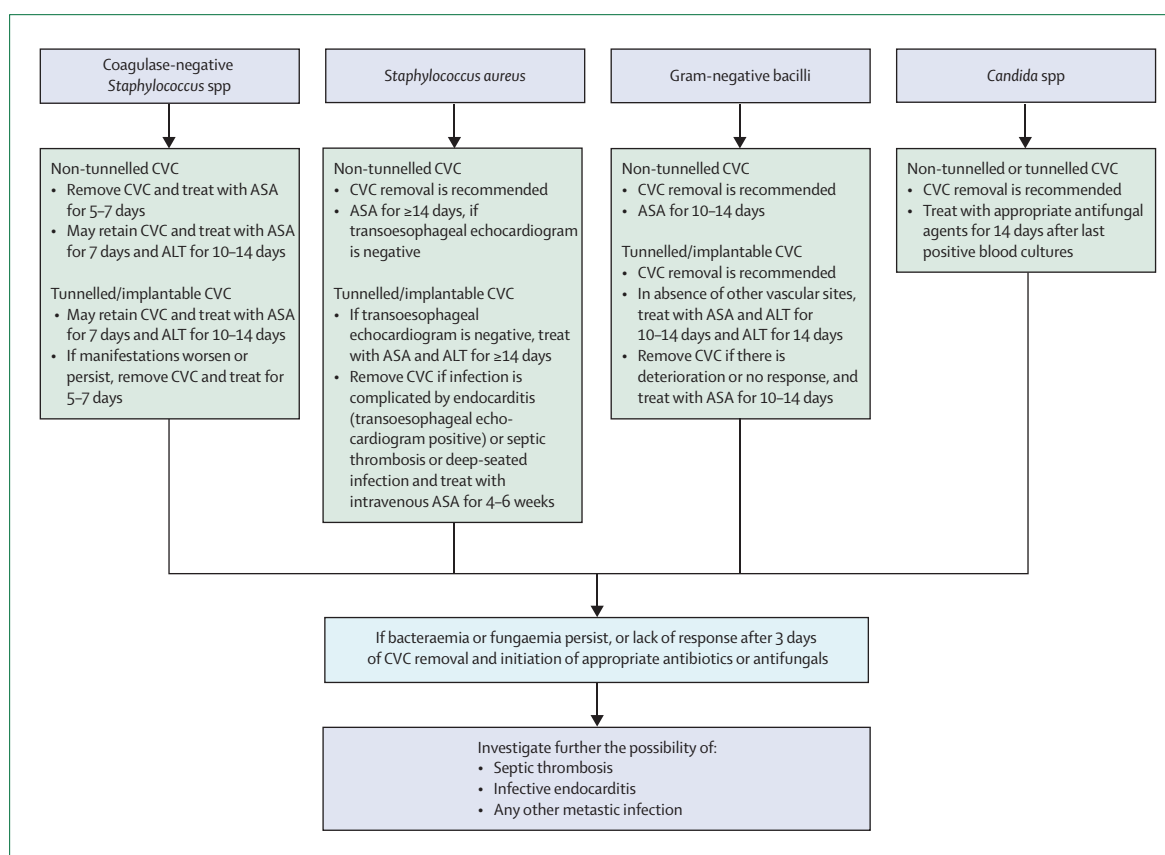
The only available silver-impregnated catheter in the USA uses oligodynamic iontophoresis, in which silver, platinum, and carbon are incorporated into the catheter, allowing topical silver ion release (Vantex CVC with Oligon, Edwards Life Sciences, Irvine, CA, USA). Several randomised clinical trials have shown that silver, platinum, and carbon catheters are associated with a significant decrease in catheter colonisation.<sup>110,111</sup> However, two prospective randomised controlled trials failed to show any benefit of the novel silver/platinum-impregnated catheters in reducing catheter colonisation and CRBSI.<sup>112,113</sup>

### Antimicrobial catheter lock

Heparin catheter lock has become widely used as an antithrombotic agent in catheters, as a result of studies published between 1979 and 1996 that showed heparin infusion and bonding effectively reduces catheter-related thrombus formation and may reduce catheter infection.<sup>114</sup> However, it has been shown that saline is as effective as heparin in maintaining catheter patency and preventing phlebitis of peripheral intravenous catheters.<sup>115</sup> Shanks and colleagues<sup>116</sup> showed that heparin, and to a lesser extent saline, enhances staphylococcal biofilm formation. Several prospective randomised studies have shown that an antimicrobial catheter lock is superior to heparin alone as a lock solution in preventing catheter infection.<sup>117–121</sup>

Antimicrobial lock solution consists of 2 mL of an antimicrobial drug, often mixed with an anticoagulant, which is used to fill the lumen of the catheter. A few studies have independently shown a significant reduction of CRBSI associated with the use of vancomycin and heparin lock solution,<sup>119,120</sup> although others failed to show significant benefit.<sup>122,123</sup> A meta-analysis of seven randomised controlled trials showed that the use of vancomycin lock solution in mostly cancer patients with long-term CVCs reduced the risk of CRBSI (risk ratio [RR] 0.49, 95% CI 0.26–0.95;  $p = 0.03$ ), but the test of heterogeneity was significant.<sup>117</sup> In view of the limited activity of vancomycin against staphylococci embedded in biofilm,<sup>124</sup> further data derived from large prospective studies are required to address concerns regarding vancomycin resistance associated with vancomycin-containing catheter lock solutions.

Chelators such as EDTA (edetic acid) or citrate have an anticoagulant activity similar to heparin and have been found to enhance the activity of antimicrobial drugs against organisms embedded in biofilm.<sup>118,121,125,126</sup>



**Figure 3: Management of catheter-related bloodstream infections**

CRBSI=catheter-related bloodstream infection. CVC=central venous catheter. ASA=appropriate systemic antibiotic. ALT=antibiotic lock therapy.

Other catheter lock solutions that may reduce catheter infection are minocycline and EDTA,<sup>121,125–127</sup> taurolidine,<sup>128</sup> or ethanol (at a concentration ranging between 25% and 40%).<sup>129,130</sup>

### Antiseptic practice versus novel technology

A large multicentre trial in 108 intensive care units (ICUs) in Michigan, USA, included 375 757 catheter-days and five antiseptic techniques highly recommended by the US Centers for Disease Control and Prevention (CDC) guidelines,<sup>64</sup> including emphasis on appropriate hand hygiene, use of chlorhexidine for skin preparation, use of maximum sterile barrier precautions during insertion of the CVC, use of the subclavian vein as the preferred insertion site, and the removal of unnecessary CVCs.<sup>131</sup> The investigators reported a decrease in the mean rate of CRBSIs from 7.7 bloodstream infections per 1000 catheter-days at baseline to 1.4 infections at 16–18 months follow-up ( $p < 0.002$ ). A regression model analysis in this study showed a persistent reduction in the incidence rate of CRBSIs from the baseline at 0–3 months after implementation to 16–18 months later. Although this study is unique in terms of the number of ICUs and CVCs involved, there were several concerns in evaluating the data, including the cross-over design,<sup>132</sup> the

definition of CRBSI, which could have included patients with false-positive blood cultures related to coagulase-negative colonisation of the CVC or contamination, and lack of information on the compliance of specific ICUs in implementing the interventions. Hence, the decrease in CRBSI could be related to the Hawthorne effect of being involved in an observational study.<sup>133</sup> Indeed, Gastmeier and colleagues<sup>134</sup> have shown a significant decrease in CRBSIs among ICU patients involved in a multicentre observational surveillance study without any intervention (RR 0.8, 0.72–0.09).

Bhutta and colleagues<sup>135</sup> have shown a significant decrease in CRBSI associated with the implementation of the antiseptic techniques outlined above as well as novel technology that included antibiotic-coated catheters. Hence, if the target is to decrease the risk of CRBSI to zero, it would take a coordinated effort of implementing both a policy of strict adherence to antiseptic techniques and the introduction of novel technology, such as antimicrobial catheters and antimicrobial lock solutions in high-risk patients.

### Management: a multifaceted approach

The management of CRBSI involves making decisions related to: (1) whether the CVC should be removed or

retained with antibiotic catheter lock therapy; (2) the type of antimicrobial therapy, based on the type of organism and its resistance pattern; and (3) the duration of antimicrobial therapy (figure 3).

Since the CVC is an identifiable, removable source of the infection, there is a tendency to assume that all patients with a CVC and a concurrent bloodstream infection must have a catheter-related infection. Indiscriminate removal of the CVC in this situation would result in an unnecessary, wasteful, and highly expensive practice. Furthermore, in a subset of patients, the indwelling catheter and vascular access site could be salvaged through antimicrobial catheter lock. Decisions as to whether the CVC should be removed or retained, with antibiotic catheter lock, and the duration and type of therapy depend on the type of organism causing the CRBSI.

#### Coagulase-negative *Staphylococcus* spp

Since coagulase-negative *Staphylococcus* spp, which include *Staphylococcus epidermidis*, are usually skin organisms, they are the leading cause of CRBSIs as well as contaminated blood cultures. Costa and co-workers<sup>136,137</sup> have suggested that the nasal mucosa rather than the CVC skin insertion site is the major source of coagulase-negative staphylococcal bacteraemia. However, their study included only 11 episodes of true coagulase-negative bacteraemia (defined as two or more positive blood cultures of the same species and antibiogram with symptoms of clinical sepsis and no other primary source of infection) with no catheter hub or tip culture, or subsequent molecular typing of organisms isolated from these important sites.<sup>137</sup>

To ascertain the diagnosis of bacteraemia, at least two positive blood cultures, including one drawn from a peripheral vein, are necessary. When quantitative blood cultures were evaluated, a colony count of more than 15 CFU of coagulase-negative staphylococci isolated from a blood sample drawn through the CVC was highly suggestive of true bacteraemia.<sup>138</sup>

Although catheter removal was once thought to be necessary, almost 80% of the CRBSIs caused by coagulase-negative staphylococci can be treated with glycopeptide antibiotics, such as vancomycin, without catheter removal. However, if the CVC is not removed, there is a 20% chance that the bacteraemia will recur.<sup>139</sup> According to IDSA guidelines,<sup>11</sup> if the CVC is to be retained, a longer duration of therapy consisting of 10–14 days (rather than 5–7 days if the CVC is removed) is to be considered with antibiotic catheter lock therapy.<sup>11</sup> If the bacteraemia is persistent, particularly after the CVC is removed, then other sources for the bacteraemia (including endocarditis and septic phlebitis) should be contemplated.

Vancomycin is the most frequently used anti-staphylococcal antibiotic for systemic and local catheter lock therapy.<sup>11</sup> However, glycopeptide antimicrobial drugs, including vancomycin, have previously been reported to have limited activity against staphylococci embedded in biofilm on catheter surfaces.<sup>124,125,140</sup>

Alternative lock therapy consists of minocycline and EDTA, ethanol, or the triple combination of minocycline and EDTA in 25% ethanol.<sup>141–143</sup> Dalbavancin, a long-acting investigational glycopeptide given once per week, has recently been shown to be superior to vancomycin in the systemic treatment of CRBSI caused by coagulase-negative staphylococci and *Staphylococcus aureus*.<sup>144</sup> Another alternative antibiotic for systemic therapy with added activity against vancomycin-resistant organisms is daptomycin.<sup>145</sup> Although linezolid is active against methicillin-resistant staphylococci, a prospective randomised trial on the treatment of catheter-related Gram-positive bacteraemia showed linezolid to be associated with higher mortality compared with other agents (vancomycin, oxacillin, and dicloxacillin).<sup>146</sup>

#### *Staphylococcus aureus*

*S aureus* is associated with a high rate of deep-seated metastatic infections, including septic thrombosis and endocarditis.<sup>147</sup> Three observational prospective studies have shown that removal of the CVC in *S aureus* CRBSI (including the uncomplicated cases) is associated with a more rapid response to therapy and a lower relapse rate.<sup>147–149</sup>

In a subset of patients with a surgically implantable catheter with no other available vascular access or with profound thrombocytopenia, consideration should be given to catheter salvage and antibiotic lock therapy.<sup>1</sup> Vancomycin and heparin or minocycline and EDTA are two combinations to be considered.<sup>119,141</sup> However, vancomycin catheter lock therapy in dialysis patients with CRBSI caused by *S aureus* was associated with a 60% failure rate.<sup>150</sup> Interest in ethanol lock therapy has also emerged, particularly after its safety was reported.<sup>129,142</sup> However, an animal study reported the failure of 50% ethanol catheter lock solution to treat methicillin-resistant *S aureus* (MRSA) catheter infection in rabbits.<sup>151</sup> The combination of minocycline and EDTA in 25% ethanol is highly active in eradicating *S aureus* in biofilm within 60 min of dwell time.<sup>143</sup>

The type of antibiotics used should be based on the susceptibility of *S aureus*. For methicillin-sensitive *S aureus* a semisynthetic antistaphylococcal penicillin, or first-generation cephalosporin is the first choice.<sup>11</sup> For MRSA, several options can be considered, including vancomycin, daptomycin, or even dalbavancin.<sup>144,145</sup> However, dalbavancin is not yet available in US or European markets.

The duration of therapy should be based on the likelihood of deep-seated complications. For uncomplicated *S aureus* CRBSI, a 10–14 day course of intravenous therapy is necessary if the CVC is removed.<sup>11</sup> The strongest predictor of complicated *S aureus* bacteraemia is the persistence of fever and/or bacteraemia for more than 72 h after catheter removal and initiation of antibiotics.<sup>152,153</sup> The leading complication of catheter-related *S aureus* bacteraemia in cancer patients is septic thrombosis of large veins.<sup>154</sup> This



complication mainly occurs in patients with an underlying solid tumour. However, CVC-related thrombosis has been reported in patients with underlying haematological malignancy and an inherited prothrombotic abnormality.<sup>155</sup>

In patients with *S aureus* CRBSI and persisting fever or bacteraemia, transoesophageal echocardiogram should be used to rule out endocarditis and the treatment duration should be expanded to at least 4 weeks of intravenous therapy with an active agent.<sup>11,153</sup>

### Gram-negative bacilli

Gram-negative bacillary bacteraemia usually emerges from a non-catheter-related source, such as nosocomial urinary tract infection, nosocomial pneumonia, or intra-abdominal infection. However, Gram-negative bacillary CRBSI caused by organisms such as *Klebsiella pneumoniae*, *Enterobacter* spp, *Pseudomonas* spp, *Acinetobacter* spp, and *Stenotrophomonas maltophilia* have been reported.<sup>156,157</sup> Elting and Bodey<sup>156</sup> reported on 149 episodes of bacteraemias caused by *S maltophilia* and other non-aeruginosa *Pseudomonas* species in which the CVC was the most common source of the bloodstream infection. Failure to remove the catheter was associated with a significantly higher rate of treatment failure and bacteraemia recurrence ( $p < 0.001$ ). Hanna and colleagues<sup>157</sup> showed that documented CRBSIs caused by Gram-negative bacilli were associated with a high frequency of relapse if the CVC was retained, whereas CVC removal was associated with only 1% risk of relapse ( $p < 0.001$ ). Antibiotic catheter lock therapy with compounds with activity against Gram-negative bacteria, such as gentamicin, amikacin, or ceftazidime, has been successfully used but data are anecdotal and limited.<sup>11</sup> Therefore, if the Gram-negative bacillary bacteraemia is judged to be a CRBSI, then it is prudent to remove the CVC and treat with a 1-week course of appropriate broad-spectrum antibacillary antibiotics.

### Candida species

Five prospective studies have shown that CVC removal is associated with improved outcome in patients with candidaemia.<sup>158–162</sup> These included large prospective studies in which catheter retention proved to be a significant factor for the persistence of candidaemia or was associated with higher mortality. Nucci and co-workers<sup>159</sup> prospectively analysed the risk factors for death in 145 patients with nosocomial candidaemia. Catheter retention was found to be an independent variable for increased risk of death in multivariate analysis, independent of persistent neutropenia. In a retrospective study involving 404 patients with candidaemia and an indwelling CVC, multivariate analysis showed that CVC retention for more than 72 h was associated with a poorer outcome (decreased response to antifungal agents, morbidity, and mortality).<sup>163</sup> In the study, CVC removal did not have any effect on improving outcome in patients

### Search strategy and selection criteria

We searched the Medline database (1966 to June 30, 2007) and PubMed (1966 to June 30, 2007) by using the search terms "intravascular device", "vascular catheter", "bloodstream infection", "primary bacteremia", "candidiasis", "blood cultures", and combinations of these terms. Abstracts of meetings of the InterScience Conference on Antimicrobial Agents and Chemotherapy, the American Society of Microbiology, The Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, and the Association for Professionals in Infection Control were also reviewed. We excluded non-English-language articles.

with non-catheter-related secondary candidaemia. The CVC should, therefore, be removed within 72 h in patients with suspected or documented catheter-related candidaemia. There are limited data on the efficacy of antifungal catheter lock solution and further clinical studies are required in the setting of catheter-related candidaemia.<sup>11</sup>

Fluconazole has similar efficacy to amphotericin B in the treatment of candidaemia, although fluconazole has a better safety profile.<sup>158,161</sup> Echinocandin (caspofungin and micafungin) have been shown to be equivalent to amphotericin B or liposomal amphotericin B in the treatment of candidaemia, with a superior safety profile.<sup>164,165</sup> A recent multicentre study has shown that anidulafungin (another echinocandin) is equivalent and possibly superior to fluconazole in the treatment of invasive candidiasis.<sup>166</sup> Therefore, in patients with catheter-related candidaemia, fluconazole or an echinocandin should be considered as an efficacious and safer alternative to amphotericin B, although in centres where there are higher rates of fluconazole-resistant *Candida glabrata* and *Candida krusei*, an echinocandin should be used. According to IDSA guidelines, the duration of therapy for uncomplicated catheter-related candidaemia should be 2 weeks from the last positive blood culture.<sup>11</sup>

### Conclusions

Although advances in diagnosing, preventing, and managing intravascular catheter-related infections have been demonstrated, this frequent clinical problem could still benefit from future breakthroughs. Accurate diagnostic techniques, especially while the suspected indwelling catheter is still in situ, can identify CVCs that should be removed while sparing others. Novel preventive measures should combine antiseptic techniques and novel technology and ought to prolong infection-free catheter dwell time safely, without breeding resistant microorganisms. A successful approach to managing CRBSI requires making an appropriate decision regarding the removal or sparing of the CVC and the use of efficacious antimicrobial therapy for the optimum duration of treatment.

**Conflicts of interest**

IR is a co-inventor on two patents associated with devices coated with minocycline and rifampicin. These patents are the property of the University of Texas MD Anderson Cancer Center and Baylor College of Medicine. Both patents were licensed to Cook Critical Care, American Medical Systems, Biomet, and TyRx with royalty rights to the institutions and inventors involved. IR is also a co-inventor of patents associated with minocycline and EDTA catheter flush solution. These patents are the property of the University of Texas MD Anderson Cancer Center, Baylor College of Medicine, and Wake Forest University. One of these patents has been licensed to Akorn. IR is also on the speakers' bureau for, and has received grants from, Cook Inc. DM has received research support from Tyco Labs. HH is a co-inventor on patents involving novel antiseptic (Gendine) for the impregnation of catheters (licensed to Cook).

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