Received October 2006; accepted in revised form August 2007

REVIEW

Catheter-Related Infections, a Diagnostic Problem

S van der Geest

Department of Intensive Care, University Hospital Maastricht, The Netherlands

Abstract. In critically ill patients, catheter-related bloodstream infections (CRBSIs) are associated with increased mortality, length of stay in the ICU and extra costs. The relative risk of infection can be best determined by analyzing rates of catheter-related bloodstream infections per 1000 catheter-days. Coagulase-negative staphylococci, *Staphylococcus aureus* and *Candida* spp are the pathogens found most commonly both on catheter tips and in blood. The commonly used definitions of intravascular catheter-related infections are summarized in this review. Clinical signs of catheter-related infections are unreliable because of their poor sensitivity and specificity. Therefore diagnosis is mainly dependent on microbiological techniques. The available diagnostic tests can be classified as methods requiring removal of the central venous catheter and methods not requiring removal of the catheter. The reliability of the various methods is described; none of the described methods has a 100% sensitivity and specificity, and therefore diagnosing CRBSI is still problematic. Finally a diagnostic approach to catheter-related infection is proposed.

Introduction

Intravascular catheters are indispensable in intensive care units, yet their use exposes patients to the risk of infectious complications. The incidence of local or bloodstream infections (BSIs) due to the use of peripheral venous catheters is usually low. Bloodstream infections are mainly caused by central venous catheters (CVCs). More than 90% of catheter-related bloodstream infections (CRBSIs) are associated with CVCs[1,2].

In critically ill patients nosocomial infections are a leading cause of morbidity and mortality. The attributable mortality for CRBSIs in hospitals is an estimated 12 to 25% per infection[3]. The attributable costs per CRBSI vary in different studies from $ 3,517 to $ 56,167, whereas the length of stay in ICU increases by 6.5 to 20 days[4]. Therefore strategies should be implemented to reduce the incidence of these infections[5].

This review will deal with the problems in diagnosing CVC-related infections.

Epidemiology, pathogenesis and microbiology

Hospitals in the USA have been collecting data on the incidence and aetiologies of hospital-acquired infections, including CRBSIs and central line-associated BSIs, since 1970.

The distinction between CRBSI and central line-associated BSI is described in the Definitions section of this paper. The National Nosocomial Infection Surveillance (NNIS) System, instituted by the Centers for Diseases Control (CDC), has been collecting data on hospital-acquired infections from nearly 300 hospitals in the United States. These data probably correspond to the data from European hospitals. The relative risk of infection is best determined by analyzing rates of CRBSIs/catheter-associated BSIs per 1000 catheter-days and/or CRBSIs/catheter-associated BSIs per 100 catheters[3]. Data of the NNIS can be used as a benchmark for individual ICUs. As a form of quality control, the incidence of central line-associated BSIs on individual ICUs can be compared with the incidence of central line-associated BSIs in ICUs participating in the NNIS. Data collected by the NNIS for well over 12 years with more than two million central catheter days, reveal a central line-associated BSI rate between a mean of 2.7 per 1000 central line-days in cardiothoracic ICUs and 7.4 per 1000 central line-days in trauma ICUs. High rates are also seen in burn and paediatric ICUs, 7.0 and 6.6/1000 days respectively[6].

The pathogenesis of CVC infection is predominantly related to extraluminal colonization of the catheter, especially in short-term catheters. In a prospective study, 45% of CVC-related BSIs were extraluminally acquired from the contiguous skin flora, 26% were of intraluminal origin (infected hub and/or contaminated fluid aspirated from the catheter), and in 29%, the mechanism of infection was indeterminate. However, the successful suppression of cutaneous colonization by cutaneous antisepsis, showed CRBSIs were much more likely to be intraluminal (60%) or indeterminate (30%) in origin[7]. Inserting a catheter into the femoral vein[8] or internal jugular vein[9] rather than the subclavian vein, carries a higher risk of CRBSI, probably because of higher rates of cutaneous colonization at the insertion sites. A CVC may also be contaminated haematogenously from distant infected sites.

To diagnose CRBSI, the determination of colonization of the catheter is essential. In a European study, 151 hospitals from 26 countries participated in a 1-day point-prevalence survey performed by microbiology laboratories. A total of 168 micro-organisms were recovered from catheter tip cultures, semiquantitative or quantitative techniques determined that 23.7% of catheter tips were considered positive. Gram-positive bacteria represented 70.7%, gram-negative bacteria 22.2%, and yeasts 7.2% of all isolates. Overall, 19% of the cultures were polymicrobial. The incidence of various micro-organisms from significant catheter tip cultures is depicted in Table 1[10]. The CRBSI occurrence was analyzed in another European study from the same group (Table 1)[11]. Coagulase-negative staphylococci, *S. aureus* and *Candida* spp were the most commonly found pathogens both from catheter tips and blood. Although coagulase-negative staphylococci in CRBSI were the pathogens isolated most commonly in EU countries, *S. aureus* was predominant in non-EU countries (39% vs 13%; p 0.01)[11]. Data from the NNIS correspond to these data from Europe[12].

Correspondence:

S. van der Geest
E-mail: sge@sint.azm.nl

Table 1. Organisms isolated from catheter tip samples and blood [10,11]

	Total N = 168	Total N = 105
Organism	**Catheter tip %**	**CRBSI* %**
CNS**	49.1	34
S. aureus	11.9	17
Candida spp	7.2	9
Enterococcus spp	5.9	6
Pseudomonas spp	4.9	6
Acinetobacter spp	4.2	
Enterobacter spp	4.2	9
Klebsiella spp	3.6	6
Proteus spp	2.4	
Corynebacterium spp	2.4	
E. coli	1.8	
Others	3.6	

*CRBSI: catheter-related bloodstream infection, most frequently cultured micro-organisms
**CNS: coagulase-negative staphylococci

Definitions

The Infectious Diseases Society of America (IDSA), the American College of Critical Care Medicine (for the Society of Critical Care Medicine) and the Society for Healthcare Epidemiology of America have formulated guidelines for the management of intravascular catheter-related infections. These guidelines assess the commonly used definitions of intravascular catheter-related infections[13]:

1. Catheter colonization

Significant growth of a micro-organism in a quantitative or semi-quantitative culture of the catheter tip, subcutaneous catheter segment, or catheter hub.

2. Phlebitis

Induration or erythema, warmth and pain or tenderness around catheter exit site.

3. Exit-site infection

- *Microbiological*
  Exudate at catheter exit site yields a micro-organism with or without concomitant bloodstream infection.
- *Clinical*
  Erythema, induration and/or tenderness within 2 cm of the catheter exit site; may be associated with other signs and symptoms of infection, such as fever or pus emerging from the exit site, with or without concomitant bloodstream infection.

4. Tunnel infection

Tenderness, erythema and/or induration > 2 cm from the catheter exit site, along the subcutaneous tract of a tunnelled catheter (e.g. Hickman or Broviac catheter), with or without concomitant bloodstream infection.

5. Pocket infection

Infected fluid in the subcutaneous pocket of a totally implanted intravascular device; often associated with tenderness, erythema and/or induration over the pocket; spontaneous rupture and drainage or necrosis of the overlying skin, with or without concomitant bloodstream infection, may also occur.

6. Bloodstream infection

- *Infusate related*
  Concordant growth of the same organism from infusate and cultures of percutaneously obtained blood samples with no other identifiable source of infection.
- *Catheter related*
  Bacteraemia or fungaemia in a patient who has an intravascular device and ≥ 1 positive result of culture of blood samples obtained from a peripheral vein, clinical manifestations of infection (e.g. fever, chills and/or hypotension) and no apparent source for bloodstream infection (with the exception of the catheter). One of the following should be present: a positive result of semiquantitative (≥ 15 cfu per catheter segment) or quantitative (≥ 10^2 cfu per catheter segment) catheter culture, whereby the same organism (species and antibiogram) is isolated from a catheter segment and a peripheral blood sample; simultaneously quantitative cultures of blood samples with a ratio of ≥ 5:1 (CVC vs peripheral); differential time to positivity (i.e., a positive result of culture from a CVC is obtained at least 2 h earlier than is a positive result of culture from peripheral blood).
- *Catheter- associated*
  This includes all BSIs that occur in patients with CVCs, when other sites of infection have been excluded. It is a surveillance definition and not a clinical definition and overestimates the true incidence of CRBSI because not all BSIs originate from a catheter[14].

Diagnosis

Clinical diagnosis

Because of their poor sensitivity and specificity, clinical signs are unreliable in diagnosing CRBSI. Inflammation or purulence around the CVC have a good specificity but poor sensitivity, while the most sensitive clinical findings like fever with or without chills have poor specificity [15]. For instance inflammation at the catheter site is absent in approximately 70% of CRBSIs[16]. Because of the unreliability of clinical symptoms, 80% or more of catheters removed for suspected CRBSI is not infected[17-19]. The clinical probability of CRBSI however is increased in the following situations:

- positive peripheral blood cultures with coagulase-negative staphylococci, *S. aureus* or *Candida* spp, in the absence of another source of infection[13] (see Table 1).
- a catheter has been in place ≥ 7 days, and in particular if a catheter has been longstanding (e.g. in place ≥ 21 days) or has been placed using non-sterile technique[20].
- hypotension upon flushing the catheter. Although a rare occurrence, this is a strong sign of an infected catheter[20].
- local signs of infection at the exit site in increasing order of specificity: erythema or induration extending ≥ 2 cm of the catheter exit site, cellulitis along the subcutaneous tract of the catheter, and pus at the catheter entry site[20].

Over the past decades, semiquantitative (e.g. the roll-plate method) and quantitative (e.g. sonication) culture techniques of catheters together with blood cultures have been used to establish the diagnosis of CRBSI [21,22]. Maki's semiquantitative technique has been considered the reference standard for determining catheter tip colonization for over 25 years[21]. However both methods require the removal of the catheter. To avoid unnecessary removal of the CVC – especially because approximately 80% of the catheters is not infected – CVC-sparing diagnostic methods have been sought for. In a meta-analysis, methods for diagnosing intravascular device-related bloodstream infection have been analyzed to identify the most accurate methods. The eight diagnostic tests that are most frequently used in clinical practice were studied. In total, 51 studies published from 1966 to 2004 were used; the Standards for Reporting of Diag-

nostic Accuracy statement and other published criteria were used to assess study quality[23]. No studies were reviewed that included catheters coated with anti-infective agents. Definitions of colonization and CRBSI of these catheters may need to be modified because the coatings may lead to false negative culture results.
Available diagnostic tests can be categorized as methods that require removal of the CVC and those that do not require removal of the CVC.

Diagnostic methods requiring removal of the intravascular device

1. ***Qualitative catheter segment culture[24].***
   The result of the qualitative culture of the catheter segment (any growth) is concordant with the result of the concomitant blood culture for diagnosing CRBSI.
   The overall sensitivity amounted to 90%, and specificity to 72%. This method revealed a high sensitivity but poor specificity.
2. ***Semi-quantitative catheter segment culture (roll-plate method)[21].***
   The result of the semi-quantitative culture of the catheter segment (≥ 15 cfu) is concordant with the result of the concomitant blood culture.
   The overall sensitivity was 85%, and specificity was 82%.
3. ***Quantitative catheter segment culture[22,25,26].***
   The result of the quantitative culture of the catheter segment (≥ 1000 cfu) is concordant with the result of the concomitant blood culture.
   This test had an overall sensitivity of 83%, and specificity of 87%.

Diagnostic methods sparing the intravascular device

1. ***Paired quantitative blood cultures[27-29].***
   Blood for concomitant quantitative cultures is drawn through the device and percutaneously. Cultures are positive from both sites and the concentration of micro-organisms in the culture from the device is 3- to 5-fold greater than in the percutaneously drawn culture. The overall sensitivity was 87%, and specificity 98%. This was the most accurate of the tests studied.
2. ***Quantitative blood culture through the intravascular device[30,31].***
   Blood for culture is drawn through the device, growth ≥ 100 cfu/ml.
   The overall sensitivity was 77%, and specificity 90%.
3. ***Acridine orange leukocyte cytospin test[32].***
   Approximately 1 ml of blood is aspirated from the catheter; the cells are lysed with sterile water, and the specimen is centrifuged, stained with acridine orange, and examined microscopically. Visualization of any micro-organisms signifies a positive test. This test offers rapid diagnosis of CRBSI. The overall sensitivity and specificity were 72% and 91% respectively.
4. ***Qualitative blood culture through the intravascular device[33].***
   One or more conventional blood cultures are drawn through the device. Any growth means a positive test. The overall sensitivity was 87%, and specificity 83%.
5. ***Differential time to positivity (DTP)[34,35]***
   Concomitant conventional blood cultures are drawn through the device and percutaneously and are monitored continuously. The test is positive if both blood cultures are positive with the same micro-organism and the catheter-drawn blood culture turns positive ≥ 2 h earlier than the peripherally drawn culture. The overall sensitivity amounted to 85%, and specificity to 81%.

Two diagnostic methods were not included in this meta-analysis:
1. Endoluminal brushing[32,36].
A brush is introduced into the lumen of the catheter. The brush is then removed for culture. A growth ≥ 100 cfu/ml is considered positive. There were too few studies suitable for inclusion in the meta-analysis, and four of the five studies were performed by the same group of investigators.
2. Catheter insertion site or hub culture.
These studies were excluded because of methodological differences among the studies and a wide range of cut-off-points for positivity.

The results of these tests are hampered by the use of different gold standards to determine CRBSI in the various studies. Also these results can be influenced by the duration of placement of the CVC. During the first 10 days after CVC insertion, extraluminal infections predominate, therefore quantitative catheter tip culture should be used because it accurately detects both intraluminal and extraluminal routes of infection[37]. In long-term catheters, intraluminal colonization becomes more important and therefore the most accurate test, the paired quantitative blood culture, is the gold standard[37]. This advice is in agreement with the results from the meta-analysis[23]. In short-term catheters, quantitative or semi-quantitative culture of the catheter combined with blood cultures will allow accurate diagnosis of intravascular device-related bloodstream infection whereas in long-term intravascular devices, paired quantitative blood culture is the most accurate diagnostic method. However paired conventional (qualitative) blood cultures using DTP provides comparable sensitivity and acceptable specificity at no increased cost.

One should realize that none of the above described diagnostic methods for CRBSI have a 100% sensitivity and specificity, which means that a negative test does not definitely rule out a CRBSI , and a positive test does not always signify a CRBSI. The meta-analysis demonstrates that paired quantitative blood culture is the most accurate test for diagnosis of CRBSI. The least accurate of the tests studied was the qualitative culture of the catheter segment. This test should no longer be used because of its poor specificity (28% of tests false positive)[23].

So why, as it is accurate and as there is no need to remove the catheter, is the **paired quantitative blood culture test** not used in all ICUs ? There are several reasons for this: quantitative blood cultures are difficult to perform, are time-consuming[38], and expensive[30]; frequently it is impossible to obtain blood from the appropriate lumen. In one study, 26% of lumens could not be sampled [39]. There are no comprehensive data about the influence of antimicrobial therapy on sensitivity and specificity and sampling of blood from only one lumen in multilumen CVCs causing CRBSI has a 40% chance of missing significant colonization[40]. For reliable results, it is essential to draw blood for cultures within 10 minutes of one another, similar volumes of blood have to be taken, and blood must be obtained before empirical anti-infective therapy begins. For all the above reasons this method is not suitable for routine use.

The **difference in time to positivity test** is a practical alternative for the paired quantitative blood culture method considering the fact that only qualitative blood cultures are needed. It provides similar sensitivity and acceptable specificity compared with the paired quantitative blood culture method. A number of remarks should be made

about this test. Two sets of blood cultures from the catheter hub of the CVC and from a peripheral vein have to be obtained at the same time, immediately taken to the microbiology laboratory – outside business hours too –, and placed in an automatic culture detector, which records culture positivity at least once every 15 minutes. As with the paired quantitative blood culture test, it is frequently impossible to draw blood from the CVC[39], and in multilumen CVCs, colonization from the lumens not cultured will be missed[40]. Many IC patients receive antibiotics. In one study antibiotic use decreased the specificity dramatically from 88 to 29%, although sensitivity remained high (91%)[41]. In another study DTP test yielded poor results in IC patients, perhaps caused by the high percentage of patients receiving antibiotic therapy[42]. In *C. albicans* CRBSI one must realize that with the slower growth of *Candida*, DTP will increase[43].

In most ICUs the **semi-quantitative catheter segment culture method** is routinely used to diagnose CRBSI. It has been considered the reference standard for nearly 30 years[21]. The method is simple and cheap. Quantitative methods of sonication and vortexing for the detection of colonization of intravascular catheter tips and CRBSIs are not superior to Maki's semi-quantitative technique. The greater simplicity of Maki's technique makes it therefore the procedure of choice for routine work in the microbiology laboratory[44]. The only disadvantage of this test is the necessity to remove the catheter, although exchanging the catheter over a guidewire for another CVC is an accepted method with hardly any morbidity[45]. However the semi-quantitative catheter segment culture method is less accurate than the paired quantitative blood culture test.

Diagnostic approach catheter-related infection

In many ICUs central venous catheter tips are routinely cultured on removal. Nearly 25% of catheters is colonized, most frequently with coagulase-negative staphylococci (Table 1)[10]. Often antibiotics will be given in this situation, even if there is no clinical suspicion of catheter-related infection (CRI) or documented bloodstream infection. This increases the unnecessary use of vancomycin and other broad-spectrum antibiotics[46]. Therefore central venous catheters and other vascular catheters should not be cultured routinely, unless local inflammation is present at the insertion site or the patient has clinical signs suggestive of bacteraemia or candidaemia.

With a surplus of methods available what policy should be followed to diagnose CRI?

If **localized CRI** (exit-site infection) is suspected a swab culture of the exit site of the catheter is taken to identify the causative microorganism. A negative culture almost rules out a localised CRI because of the high negative predictive value of this procedure. Positive cultures with *S. aureus*, *Candida* spp and gram-negative bacteria are suggestive of localized CRI. Care should be taken if a culture reveals coagulase-negative staphylococci as this may reflect the presence of normal skin flora not associated with infection.

Analysis to determine **CRBSI** will be done only if there is a clinical suspicion of catheter-related sepsis (see above: clinical diagnosis). In patients who are haemodynamically stable, have no proven bacteraemia, no insertion site infection, and no intravascular foreign body, one may consider taking two peripheral blood cultures, and following watch and see policy for five days. In one study, removal of CVC was reduced by 62%[47]. In nearly all cases the CVC can be exchanged over a guidewire. A semiquantitative, or if facilities are available in the microbiology laboratory , a quantitative culture of the CVC tip may be performed concomitant with two peripheral blood cultures. Two blood cultures are drawn, because if a CNS is found in one blood culture, contamination is possible. If CRBSI is diagnosed or the CVC is significantly colonized (≥ 15 cfu) the replacement CVC should be removed and a new catheter should be placed in a new site[48]. CVC should be removed without exchange over a guidewire in case of an exit site infection or if hypotension occurs upon flushing the catheter. A negative (semiquantitative) culture of the exit site makes a CRBSI unlikely[49].

Sometimes exchange over a guidewire is not feasible. Long-term Hickman or Broviac catheters are tunnelled and therefore hardly suitable for exchange over a guidewire. If the CVC is a life-line and CVC removal is the last resort, ideally paired quantitative blood cultures should be taken. However, most microbiology laboratories are not able to deliver this service. In this situation a good second alternative is the differential time to positivity method. A prerequisite for a reliable result of these tests is no antibiotic use at the time of drawing the blood cultures.

Last but not least, one must realize that none of the diagnostic methods have a 100% sensitivity and specificity. Therefore diagnosing catheter-related infections is still troublesome.

Abbreviations

BSI:	bloodstream infection
cfu:	colony forming units
CRBSI:	catheter-related bloodstream infection
CRI:	catheter-related infection
CVC:	central venous catheter
DTP	differential time to positivity
NNIS :	National Nosocomial Infection Surveillance

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