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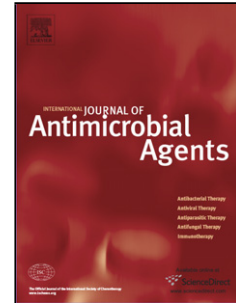
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Catheter-related bloodstream infections: catheter
management according to pathogen

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Abstract

Central-line access is an essential part of modern healthcare practice; however, catheter-related bloodstream infection is a major problem that causes substantial morbidity and mortality, and excess length of stay and cost. The risk of infection depends on the type of device, the site of insertion, the underlying conditions and the appropriate prevention measures taken during catheter insertion. Management of catheter-related bloodstream infection involves deciding on catheter removal, antimicrobial catheter lock solution and the type and duration of systemic antimicrobial therapy. Systemic antimicrobial use is essential but, although generally effective in controlling sepsis, it often fails to sterilize the line, increasing the incidence of complications or recurrence. The decision regarding whether the catheter should be removed or retained is therefore crucial. One of the major factors to be considered is the type of organism involved in the catheter-related infection. This review outlines the epidemiology, pathogenesis, diagnosis, microbiology and management of catheter-related infections, mainly focusing on the management of the intravascular device according to the pathogen.

Keywords:

Catheter-related infections

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1. Introduction

Intravascular catheters are indispensable in current medical practice, particularly in intensive care units, but are no longer restricted to hospital inpatients. The central venous catheter (CVC) has become a lifeline for many critically ill patients, as well as chronically ill patients who have cancer or are undergoing haemodialysis.

Although such catheters provide necessary vascular access, their use puts patients at risk of local and systemic infectious complications. These devices are increasingly associated with sepsis and are the most common cause of all bloodstream infections (BSI), which have significant morbidity and mortality. Recently, the Infectious Diseases Society of America (IDSA) updated the guidelines for the diagnosis and management of intravenous catheter-related BSIs (CRBSIs).

2. Epidemiology

In Europe, >60% of nosocomial infections are catheter-related, the majority of these being CVCs [1]. Since 1970 the Centers for Disease Control's (CDC) National Nosocomial Infection Surveillance System has been collecting data on the incidence and aetiology of hospital-acquired infections, including CVC-associated BSI, in a group of nearly 300 US hospitals. The data show that BSI rates are substantially higher among patients with CVCs than those without

[2]. Rates of CVC-associated BSI vary considerably by hospital size, hospital service/unit and type of CVC.

In the USA, approximately 80 000 cases of CVC-associated BSI occur in intensive care units each year, and 15 million CVC days (the total number of days of exposure to CVCs by all patients in the selected population during the selected time period) are reported in intensive care units annually. Although the consequences of these infections in terms of mortality rate remain uncertain, with a wide estimated range of 3–25% [2–4], it is clear that they increase the duration of intensive care unit stay and add a substantial burden to the cost of intensive care. The attributable cost per infection is an estimated \$34 508–56 000 [5]. A total of 250 000 cases of CVC-associated BSI have been estimated to occur annually if entire hospitals are assessed rather than intensive care units [6]. In this case, attributable mortality is an estimated 12–25% for each infection and the marginal cost to the healthcare system is \$25 000 per episode.

3. Types of catheter and associated mortality

Peripheral venous catheters are the devices most frequently used for vascular access. Although the incidence of infection associated with peripheral venous catheters is usually low, serious infectious complications produce considerable annual morbidity because of the frequency with which such catheters are used [7]. However, most

serious CRBSIs are associated with non-tunnelled CVCs percutaneously inserted into central veins, especially those placed in patients in intensive care units. The daily infection risk with CVCs is about 20 times that with peripheral catheters [8].

Short-term catheters (<14 days) are the most commonly used CVCs and account for most CRBSIs. Long-term CVCs that are surgically implanted (e.g. Hickman, Broviac or Groshong catheters) appear to have one-quarter the daily risk associated with percutaneous CVCs, but still pose a much higher risk than peripheral catheters.

Peripherally inserted central catheters seem to have a similar risk of infection to CVCs in intensive care units, whereas midline catheters are associated with lower rates of infection. A lower rate of infection is also detected with totally implantable devices (ports or reservoirs) compared with CVCs. Peripheral arterial catheters, commonly used to determine blood gas levels in critically ill patients and in pressure monitoring systems, are both associated with epidemic and endemic nosocomial BSIs. Pulmonary artery catheters appear to have rates of BSI similar to those with CVCs. The highest rates of infection are reported for short-term non-cuffed and non-tunnelled haemodialysis catheters (8.0%, 4.8 per 1000 device-days), intra-aortic balloon pumps (3.0%, 7.3 per 1000 device-days) and left ventricular assist devices (21.6%, 2.1 per 1000 device-days) [9].

Apart from the type of intravascular device, factors that partially account for the marked differences in daily infection risk rates are the experience and education of the staff, the duration of catheter placement and the clinical state of the patient [10]. Total parenteral nutrition, triple-lumen catheters and certain catheter insertion sites (jugular and femoral) seem to be independent risk factors [11]. Other factors are prolonged hospitalization before catheterization, heavy microbial colonization at the insertion site or the catheter hub, and the presence of neutropenia.

4. Microbiology

The microbes that colonize catheter hubs and the skin surrounding the insertion site are the source of most CRBSIs [6–8]. Migration of skin organisms from the insertion site into the cutaneous catheter tract, with colonization of the catheter tip, is the most common route of infection for peripherally inserted short-term catheters [21,22]. Contamination of the catheter hub contributes substantially to intraluminal colonization of long-term catheters [12,13]. Other routes of infection are haematogenous seeding from a distant infection or, rarely, contaminated infusate. Approximately 65% of catheter-related infections originate from the skin flora, 30% from the contaminated hub and 5% through other pathways [14].

Scanning and transmission electron microscopy have shown that virtually all indwelling CVCs are colonized by microorganisms

embedded in a biofilm matrix [15]. The organisms most commonly isolated from catheter biofilms are *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Candida albicans*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Enterococcus faecalis* [16].

The nature of the fluid administered through CVCs may affect microbial growth. Gram-positive organisms (*S. epidermidis*, *S. aureus*) did not grow well in intravenous fluids, whereas the Gram-negative aquatic organisms (e.g. *P. aeruginosa*, *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp. and *Pantoea* spp.) sustained growth [16]. The number of organisms on the catheter tip is related to the occurrence of BSI, supporting the concept of a critical level for biofilm development, above which substantial cell detachment and embolism occur [16].

The early stages of biofilm formation in devices involve the adherence of bacteria to cellular or matrix surfaces [17]. Further biofilm organization into complex structures is regulated by the exchange of chemical signals between bacterial cells in a process known as quorum sensing [18,19]. The multicellular bacterial arrangement is associated with increased resistance to antibiotics. A critical pathogenic step is the adherence of *S. aureus* to host cells or polymer surfaces and the subsequent accumulation of toxin-producing bacteria that promote attachment to host proteins such as laminin and fibronectin. Coagulase-negative staphylococci adhere to polymer surfaces more readily than other pathogens and certain

strains produce an extracellular polysaccharide referred to as 'slime', which acts as a barrier against polymorphonuclear cells and binds antimicrobial agents, preventing their contact with the organism cell wall [20].

Candida albicans remains the fungal species most commonly associated with biofilm formation [21,22], and the increase in *Candida* infections in recent decades has almost paralleled the increase and widespread use of a broad range of implanted medical devices. Different strains of *C. albicans* and different *Candida* spp. differ in their capacity to form biofilms [23]. Mature *Candida* biofilms exhibit a complex three-dimensional structure and display extensive spatial heterogeneity [21,23,24]. The overall architecture of the biofilm may vary depending on the substrate on which it is formed and its growth conditions [25]. *Candida* biofilms have been shown to be resistant to the action of clinically important antifungal agents, including amphotericin B and fluconazole [26].

P. aeruginosa is considered to be a model organism for the study of the diverse bacterial and molecular mechanisms that cause the switch from planktonic growth to a biofilm phenotype and contribute to bacterial persistence. Recent studies show interactions between *C. albicans* and *P. aeruginosa* in which *P. aeruginosa* forms a dense biofilm on *C. albicans* filaments and kills the fungus, but neither binds to nor kills yeast forms of *C. albicans* [27]. Furthermore, a *P. aeruginosa* quorum-sensing molecule (N-(3-oxododecanoyl)

homoserine lactone) and structurally related compounds have been shown to be capable of suppressing filamentation in *C. albicans* cells [28].

A recent European study found that the microorganisms most often isolated from intravascular catheters are coagulase-negative staphylococci (30–51.5%), followed by *Candida* spp., *S. aureus*, *Enterococcus* spp. and *Pseudomonas* spp. [14,16,29]. *Acinetobacter* spp. [30], *Enterobacter* spp., *K. pneumoniae* and other bacteria have been identified less frequently [14]. Another recent European study of intravascular catheter-related infections found that fungi (mainly *C. albicans*) are the third leading cause of catheter-related infections, representing the second highest colonization-to-infection rate and the highest overall crude mortality [31]. Gram-negative bacilli accounted for 19% of catheter-associated BSIs during 1986–1989 [32], compared with 14% during 1992–1999 [33]. An increasing percentage of intensive care unit-related isolates are extended-spectrum β -lactamase-producing Enterobacteriaceae, particularly *Klebsiella pneumoniae* [34].

A recent report describing the frequency of select antimicrobial resistance patterns among pathogens reported to the CDC National Healthcare Safety Network from January 2006 to October 2007 gave the rate of occurrence among device-related infections of the following resistant isolates: methicillin-resistant *S. aureus* (MRSA; 56% of *S. aureus*); vancomycin-resistant enterococci (80% of *E.*

faecium, 7% of *E. faecalis*); *P. aeruginosa* resistant to ceftazidime and quinolones, or piperacillin, or carbapenems (30%, 17% and 25%, respectively). In the same report the rates of carbapenem-resistant *A. baumannii* and *K. pneumoniae* were 29% and 10%, respectively [35].

5. Diagnosis

The diagnosis of CVC-associated infection traditionally relies on clinical features, quantitative cultivation, Gram staining and acridine-orange leucocyte cytospin testing of blood samples [3–5], or on methods that can only be applied following CVC removal [14,36,37]. The international reference diagnostic method is Maki's semi-quantitative method, which is based on removing the catheter and rolling the distal tip back and forth on an agar plate [38]. The growth of 14 colony-forming units (CFU) defines an insertion site infection. Growth of 10^5 CFU from a 5 cm segment of the catheter tip by semi-quantitative (roll-plate) culture, or growth of 10^2 CFU from a catheter by quantitative (sonication) broth culture, reflects catheter colonization. Definitive diagnosis of CRBSI requires that the same organism grows from at least one percutaneous blood culture and from a culture of the catheter tip.

The CDC recommends one of two blood culture techniques for diagnosing CRBSI when retention of the catheter is desirable – paired quantitative blood cultures or paired qualitative blood

cultures observing a differential time to positivity. For quantitative blood cultures, CRBSI is best defined by a colony count of microbes grown from blood obtained through the catheter hub that is at least threefold greater than the colony count from blood obtained from a peripheral vein [39]. Using differential time to positivity, CRBSI is best defined by growth of microbes from a blood sample drawn from a catheter hub at least 2 h before microbial growth in a blood sample obtained from a peripheral vein. If a blood sample cannot be drawn from a peripheral vein it is recommended that two blood samples should be drawn through different catheter lumens.

Alternatively, two quantitative blood cultures of samples obtained through two catheter lumens in which the colony count for the blood sample drawn through the first lumen is at least threefold greater than that obtained from the second lumen should be considered to indicate possible CRBSI [39].

6. Management

The management of CRBSI involves making decisions about retaining or removing the catheter and the type and duration of the antimicrobial therapy. Determining whether the catheter should be removed or retained in place with antibiotic lock therapy (see below) in patients with CRBSI should take at least three factors into consideration: the type of CVC (whether it is short-term, arterial, long-term or port), the status of the host and the type and microbiology of the infection.

Peripheral intravenous catheters with associated pain, induration, erythema, or exudate should be removed [39]. For a patient suspected of having short-term CVC infection or arterial catheter infection the catheter should be removed if the patient has unexplained sepsis or erythema overlying the catheter insertion site, or purulence at the catheter insertion site, or the CRBSI is associated with either suppurative thrombophlebitis, endocarditis or osteomyelitis.

Long-term central catheters or ports should be removed from patients with CRBSI associated with any of the following conditions: severe sepsis; suppurative thrombophlebitis; endocarditis; bloodstream infection that continues despite 72 h of antimicrobial therapy to which the infecting microbes are susceptible; or if a port abscess is diagnosed [39]. In uncomplicated cases, given the limited access in many patients who require long-term intravascular access for survival (e.g. haemodialysis), salvage of the catheter can be attempted. Both systemic and antimicrobial lock therapy should be used, repeated blood cultures obtained and the catheter removed if blood cultures remain positive for a microorganism when drawn 72 h after initiation of appropriate therapy.

Antibiotic lock therapy for CRBSIs is often used in conjunction with systemic antibiotic therapy and involves instilling into the catheter lumen a high concentration of an antibiotic to which the causative pathogen is susceptible [14]. Antibiotic solutions that contain the

desired antimicrobial agent in a concentration of 1–5 mg/mL are usually mixed with 50–100 U of heparin in sufficient volume to fill the catheter lumen (usually 2–5 mL) and are instilled or 'locked' into the catheter lumen during periods when it is not being used (e.g. for a 12 h period each night). Several open trials of antibiotic lock therapy for tunnelled catheter-related bacteraemia, with or without concomitant parenteral therapy, have reported response and catheter salvage without relapse in 138 (82.6%) of 167 episodes [14,40,41].

While awaiting blood culture results, empirical therapy to cover staphylococci and Gram-negative bacilli is the best initial treatment. In addition, for suspected CRBSI involving femoral catheters in critically ill patients, empirical therapy should include coverage for *Candida* spp. [39]. The regimen may be modified once the pathogen is identified. The type of pathogen causing the CRBSI is an important factor in the choice of the type and duration of therapy. Decisions as to whether the CVC should be removed or retained, the use of antibiotic lock therapy and the duration and type of therapy depend on the type of organism causing the CRBSI.

7. Specific organisms

7.1. Coagulase-negative *Staphylococcus* spp.

Coagulase-negative staphylococci (e.g. *S. epidermidis*) are the most common pathogens in CRBSIs, possibly because they appear to

have the best adherence to inert surfaces. If a catheterized patient has a single positive blood culture that grows a coagulase-negative *Staphylococcus* sp., then additional cultures obtained through the suspected catheter and from a peripheral vein should be performed to be certain that the patient has true BSI and that the catheter is the likely source [42]. To ascertain the diagnosis of bacteraemia, at least two positive blood cultures, including one drawn from a peripheral vein, are necessary.

As coagulase-negative staphylococci are organisms of low virulence, removal of the line may be sufficient to resolve the infection but the patient should usually be treated with 1 week of intravenous antibiotics. Alternatively, patients with uncomplicated CRBSI can be observed without antibiotics if they have no intravascular or orthopaedic prostheses, the catheter is removed and additional blood cultures are obtained after catheter withdrawal to confirm the absence of bacteraemia [39]. According to IDSA guidelines, 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 lock therapy. This may control the infection in 80% of cases; however, if bacteraemia or fever persists despite appropriate antimicrobial therapy, the catheter must be removed [42]. In some cases of outpatient management of CRBSI with coagulase-negative staphylococci, when blood cultures have become negative and signs of sepsis have resolved, an oral

antibiotic (e.g. a fluoroquinolone or linezolid) and an antibiotic lock left in place for 24–48 h have been successfully used [43].

Vancomycin is the most frequently used antistaphylococcal antibiotic for systemic and local catheter lock therapy in healthcare settings with an increased prevalence of MRSA; for institutions with a preponderance of MRSA isolates that have vancomycin minimum inhibitory concentration values $>1 \mu\text{g/mL}$, alternative agents such as daptomycin should be used [39]. An open-label, randomized trial that compared linezolid to vancomycin, oxacillin or dicloxacillin in the treatment of seriously ill patients with CRBSIs showed that patients treated with linezolid had a higher chance of death than patients treated with any comparator antibiotic [44]. The difference was found to be due to the inferiority of linezolid in the treatment of mixed Gram-negative/Gram-positive infections. In participants whose infection was caused by Gram-positive bacteria alone, linezolid was as safe and effective as vancomycin [45]. In light of these results the US Food and Drug Administration issued an alert for linezolid, which has not been recommended for empirical therapy in the recent guidelines.

Catheter-related bloodstream infection due to *Staphylococcus lugdunensis*, an uncommon cause of catheter-related infection, can cause endocarditis and metastatic infections similar to those caused by *S. aureus* [46] and are managed accordingly.

7.2. Staphylococcus aureus

An increased risk for *S. aureus* infection of CVC has been described for several patient groups. Patients with end-stage renal disease requiring haemodialysis or peritoneal dialysis are at higher risk of *S. aureus* catheter infections, especially those who are nasal carriers [47].

If a non-tunnelled CVC is suspected to be the source of *S. aureus* bacteraemia, the device should be removed and a new catheter inserted at a different site. Similarly, tunnelled CVCs should be removed if there is evidence of tunnel or exit-site infection. Patients with uncomplicated CRBSIs or septicaemia caused by *S. aureus* should be treated for a minimum of 10–14 days after catheter removal [39]. 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 [48–50].

In a subset of patients with a surgically implantable catheter and no other available vascular access, or with profound thrombocytopenia, consideration should be given to catheter salvage and antibiotic lock therapy for at least 14 days [48]. Catheter guidewire exchange should be done if possible. A combination of antibiotic lock therapy and systemic therapy has been used to salvage infected ports and long-term catheters for some patients with *S. aureus* CRBSI

[40,51,52]. However, in a report of 50 patients with *S. aureus* catheter-related sepsis, delayed catheter removal was associated with increased mortality [53]. Similarly, in a meta-analysis of 11 studies, 8 of 132 patients who had a short course of treatment for *S. aureus* developed endocarditis or infection at another site [54]. Failure or delay in removing the catheter increases the risk for haematogenous complications [49,55]. In the largest published series on the use of antibiotic lock for CRBSI due to *S. aureus*, treatment failure was observed in one-half of cases [52]. This needs to be taken into account when attempting catheter salvage.

Echocardiography should be carried out in at-risk patients to diagnose possible endocarditis, which requires therapy for 4–6 weeks [56,57]. Patients who are being considered for a shorter duration of therapy should also have transoesophageal echocardiography, which is most sensitive when performed 5–7 days after the onset of bacteraemia [58].

The duration of therapy should be based on the likelihood of deep-seated complications. A longer course of therapy is prudent for immunosuppressed patients with *S. aureus* CRBSI. If there is evidence of other distant foci of infection, such as septic venous thrombosis, treatment should similarly be continued for several weeks. Patients whose catheter has been removed and have a negative echocardiogram should be treated with appropriate systemic antibiotics for 10–14 days [56,57].

The types of antibiotic 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 [39]. For MRSA, several options can be considered, including vancomycin, daptomycin or even linezolid.

7.3. Enterococcus spp.

The proportion of enterococcal bacteraemias associated with CVCs has increased dramatically since the early 1980s [4–6], reaching 35% in one UK study [59]. Management of enterococcal CRBSI is an increasing clinical challenge for which specific clinical data are lacking. Like many other organisms capable of causing CRBSI, enterococci can adhere to biomedical polymers and form a biofilm [60], thereby making antimicrobial treatment problematic.

Secondary endocarditis may complicate the management of enterococcal CRBSI [61,62]. Unlike *S. aureus* CRBSI [34] secondary enterococcal endocarditis appears to be a rare complication, but if the patient has signs and symptoms of endocarditis, persistent bacteraemia or enterococcal bacteraemia in the presence of a prosthetic valve a transoesophageal echocardiograph should be done [59,63]. The IDSA guidelines for the treatment of enterococcal CRBSI caused by susceptible isolates advise either ampicillin or vancomycin alone or in combination with an aminoglycoside [39], as data concerning the role of combination therapy for treatment

are conflicting. In cases of CRBSI due to ampicillin- and vancomycin-resistant enterococci, linezolid or daptomycin may be used based on antibiotic susceptibility results.

If a long-term catheter is retained in cases of uncomplicated infection 7–14 days of intravenous treatment is recommended in addition to antibiotic lock therapy [64].

7.4. Gram-negative bacilli

Over the past decade, although the rates of Gram-negative bacillary infection of intravascular devices in adults have decreased, there has been great concern over the increasing incidence of Gram-negative bacilli resistant to next-generation cephalosporins and the evolution of multidrug-resistant Gram-negative bacilli that produce carbapenemases [2,65].

In general, data concerning the management of CRBSI due to Gram-negative bacilli are limited. Hanna and colleagues [66] showed that documented CRBSIs caused by Gram-negative bacilli were associated with a high frequency of relapse if the CVC was retained. Similarly, with *P. aeruginosa* CVC sepsis catheter removal also improved patient outcome [67]. Failure to remove the catheter was associated with a significantly higher rate of treatment failure and bacteraemia recurrence ($P < 0001$). Several studies suggest that if the Gram-negative bacillary bacteraemia is judged to be a CRBSI, especially with bacilli that have a propensity for biofilm

production, such as *Acinetobacter baumannii*, *Pseudomonas* spp. and *Stenotrophomonas maltophilia* [68–70], then it is prudent to remove the CVC [39].

CRBSI caused by *S. maltophilia* is still rare and occurs mostly in immunocompromised hosts. Catheter removal seems to be crucial, since 92% of patients with catheter removal survived, compared with only 54% without catheter removal [69].

Results from recent studies in which Gram-negative CRBSI were treated with antibiotic lock therapy with compounds with activity against Gram-negative bacteria, such as gentamicin, amikacin or ceftazidime, and systemic antibiotics, have been encouraging [52,71]. Septic, critically ill or neutropenic patients and patients having a femoral catheter or a known focus of infection are at higher risk for infection due to multidrug-resistant Gram-negative bacilli and should receive empirical antibiotic therapy according to recent IDSA guidelines. Critically ill patients with suspected CRBSI and who have recent colonization or infection with a multidrug-resistant Gram-negative pathogen should receive initial therapy with two antimicrobial agents of different classes with Gram-negative activity while waiting for culture and susceptibility results. Finally, evaluation for endovascular infection and metastatic infection is necessary in cases of persistent bacteraemia or severe sepsis despite systemic and antibiotic lock therapy, and intravenous

antibiotic treatment is needed beyond 7–14 days after the removal of the device.

7.5. *Candida* spp.

The presence of a vascular catheter or other medical device increases a patient's risk for invasive candidiasis by a factor of seven. *Candida* spp. are the second most common cause of these device-related infections and are associated with the highest pathogen-specific mortality [72]. The burden of this infection has risen more than 200% in the past two decades and is associated with high mortality (>40%), extended hospital stays and high cost [73].

Many prospective studies show that CVC retention worsened outcome; CVC retention for >72 h was associated with a poorer outcome in a study of 404 patients with candidaemia and indwelling CVC [39,40]. The CVC should therefore be removed within 72 h in patients with suspected or documented catheter-related candidaemia, and the catheter tip should be sent for culture. In cases of limited venous access or severe thrombocytopenia in patients with candidaemia and a short-term CVC, for whom no source of candidaemia is obvious, the catheter could be exchanged over a guidewire and sent for culture, and removed if it is colonized with the same species of *Candida* as found in a percutaneous blood culture.

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 *Candida* spp. with decreased susceptibility to azoles (e.g. *C. glabrata* and *C. krusei*) an echinocandin should be used. According to IDSA guidelines antifungal therapy is recommended for all cases of CRBSI due to *Candida* spp., including cases in which clinical manifestations of infection and/or candidaemia resolve after catheter withdrawal and before initiation of antifungal therapy. The duration of therapy for uncomplicated catheter-related candidaemia should be 2 weeks after the last positive blood culture.

There are limited data on the efficacy of antifungal lock solutions. Compared with bacterial infection, *Candida* CRBSI is more difficult to eradicate with antibiotic lock therapy [74–76]. Echinocandins, lipid formulations of amphotericin B and ethanol-based lock solutions have been studied, and seem to be effective in vitro, but further clinical studies are required in the setting of catheter-related candidaemia.

7.6. Other microorganisms

Infections due to other skin microflora, such as *Corynebacterium* and *Bacillus* spp. are infrequent causes of CRBSI and the treatment approach is quite similar to that for *S. epidermidis*. Confirmation by multiple percutaneous blood culture results positive for the same

organism is required before meaningful conclusions can be drawn as to the significance of the culture results [77].

Catheter removal is usually indicated for the management of these infections unless there are no alternative intravascular access sites. CVC removal might not be necessary in patients with corynebacterial CRBSI, particularly if systemic therapy consists of non-glycopeptide antibiotics [78].

Bacillus spp. are common contaminants of blood cultures but clinically significant infection is rare [79,80]. Significant CVC infections caused by *Bacillus* spp. are mainly due to *B. cereus* and have mostly been reported in immunocompromised hosts [81]. CVC infection with *Bacillus* spp. usually requires catheter removal for complete cure [82,83]. In a patient with AIDS, *B. subtilis* bacteraemia resolved with vancomycin therapy without removing the Broviac catheter.

Micrococcus spp. are a common cause of BSI in patients with pulmonary hypertension on intravenous epoprostenol, but are rarely reported in other groups of patients and their presence on a blood culture should not be interpreted as skin contamination [84]. The clinical presentation can be acute or subacute. Treatment should be based on the organism's antibiotic susceptibilities and removal of the line should be considered if the symptoms or the bacteraemia persists.

Tsukamurella spp. (aerobic Gram-positive organisms from the order Actinomycetales) are infrequent causes of CRBSI. In a recent review, Bouza and colleagues noted that 12 of 14 patients with CRBSI caused by *Tsukamurella* spp. were being treated for an underlying malignancy, while usual underlying morbidities include primary immunodeficiencies, a variety of malignancies and chronic renal failure [85]. In the setting of CRBSI caused by a *Tsukamurella* sp., treatment in all reported cases ultimately required the removal of the infected catheter in addition to antimicrobial therapy [86,87]. The literature provides no firm conclusions regarding the ideal choice or duration of antimicrobial therapy for this infection.

Rapidly growing non-tuberculous mycobacteria are responsible for a variety of clinical syndromes in humans, including CRBSIs.

Mycobacteria should be included in the differential diagnosis of CVC-related sepsis, particularly for immunocompromised hosts [88]. *M. fortuitum* complex (*M. fortuitum* and *M. chelonae*) is a cause of catheter-related bacteraemia in patients with cancer. Appropriate treatment consists of antibiotic therapy and catheter removal [89]. Tunnel infections usually also require surgical excision.

CRBSIs due to *Achromobacter xylosoxidans*, a Gram-negative rod, have been observed in patients with cancer or AIDS [90,91].

Despite the bacterium's resistance to aminoglycosides the patients were treated successfully with a combination of ceftazidime and amikacin without removing the catheter. Infections occurring in

neutropenic patients were successfully treated with imipenem and catheter removal [92] and in the first reported outbreak of CVC-related bacteraemia due to *A. xylosoxidans*, patients were successfully treated with intravenous levofloxacin and antibiotic lock without catheter removal [93].

Agrobacterium spp. are saprophytic bacilli and opportunistic pathogens of humans, only 25 cases of infection being described by 1997. The biofilm-forming species *Rhizobium* (*Agrobacterium*) radiobacter can cause community catheter-related infections. Most cases respond to treatment only after removal of the catheter and antimicrobial susceptibility seems to be variable [94].

8. Conclusions

CRBSI is an iatrogenic problem that causes significant morbidity and mortality, excess length of stay and excess costs. The risk of infection is highest with percutaneous CVCs, somewhat lower with tunnelled or subcutaneous catheters and lowest with peripheral intravenous catheters. Management of CRBSI involves deciding on catheter removal, antimicrobial lock solution and the type and duration of systemic antimicrobial therapy. A distinction should be made between complicated and uncomplicated CRBSI. The identity of the organism is an important factor to be considered. Once infection occurs the line should generally be removed, unless there are major contraindications. Long-term catheters should be

removed in patients with infections due to *S. aureus*, *P. aeruginosa*, fungi or mycobacteria. Short-term catheters should be removed in patients with CRBSI due to Gram-negative bacilli, *S. aureus*, enterococci, fungi or mycobacteria. The antibiotic lock technique is promising and easy to perform and may help catheter retention in certain situations.

Antimicrobial therapy is initially empirical and should be directed against suspected microorganisms (usually staphylococci) and modified on receipt of the results of cultures.

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