REVIEW

Clinical management of catheter-related infections

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Central venous catheters represent a major source of nosocomial bloodstream infections, which cause considerable excess morbidity. It is currently unknown to what extent these infections contribute to mortality. Most catheter-related infections (CRIs) are caused by Gram-positive organisms (mainly coagulase-negative staphylococci). Definite diagnosis of CRI necessitates removal of the catheter in most cases. However, the recently described technique of differential time to positivity may allow diagnosis of CRI with the catheter left in place. Removal of the catheter has been standard clinical practice for the management of CRI in the past and is still recommended in many cases. In specific situations, such as infections of implanted catheters with coagulase-negative staphylococci, a trial of catheter salvage may be justified. In catheter-related bloodstream infection *Staphylococcus aureus* and *Candida* spp., the catheter should be removed immediately, due to the high risk of metastatic infection and increased mortality. A clinical work-up for the detection of additional foci (including transesophageal echocardiography in *S. aureus* infections) is advisable in these cases. All CRIs should be treated with antibiotics to which the causative agent has been shown to be susceptible. In addition to systemic antimicrobial therapy, antibiotic lock therapy may be applied, especially in patients with implanted long-term catheters if catheter salvage is attempted.

Keywords Central venous catheters, bloodstream infection, *Staphylococcus aureus*, Candida coagulase-negative staphylococci, antibiotic lock, bacteremia

Accepted 27 December 2001

Clin Microbiol Infect 2002; 8: 545–550

BACKGROUND

Central venous catheters represent a leading source of nosocomial infection. In clinical studies, 11–37% [1–3] of nosocomial bacteremias have been related to central lines. The incidence rate of catheter-related infections (CRIs) is about 5 million per 1000 catheter days in the USA. An estimated 75 000 infections per year will result in additional expenditure of $300 million to $2.3 billion [4].

Many new papers on the pathogenesis, prevention and diagnosis of CRIs have been published during recent years. In this review, we will mainly focus on the clinical management of these infections.

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DEFINITIONS

Clear definition should be used, when describing the clinical diagnosis of CRI. The term 'catheter infection' should be avoided, since it does not clearly distinguish between colonization (of the catheter) and infection (of the host). Catheter-related bloodstream infection (CRBSI) is the most important clinical manifestation. Diagnosis of CRBSI requires the demonstration of the same pathogen on the catheter surface and in blood cultures [5]. Another clinical form of CRI is exit-site infection, which is defined as skin inflammation at the site of the catheter insertion and which may or may not be accompanied by CRBSI. Tunnel infection is characterized as a soft tissue infection along the tunnel of an implanted catheter at least 2 cm from the exit site [6]. Accordingly, pocket infections are defined as subcutaneous infections around a port reservoir. Septic thrombophlebitis is characterized by bacteremia and purulent

phlebitis, and is one of the most serious complications of CRI [7].

ATTRIBUTABLE MORBIDITY AND MORTALITY

While there is broad consensus that CRIs cause excess morbidity, data on attributable mortality are not consistent. In their sentinel study, Pittet et al. found an attributable mortality of 35% in critically ill surgical patients with bloodstream infections [8]. The attributable mortality of CRI has been estimated at 25% [9,10]. In contrast, a recently published case–control study did not find any excess mortality for CRI, although these infections caused prolonged hospitalization for an average of 20 days. Hospital costs were estimated to be increased by 3000 Euro per case in this study [11]. The favorable outcome of patients with CRI in this study may be explained by the predominance of infections caused by coagulase-negative staphylococci (63%). It has been shown in many other studies that mortality from infections with these organisms is considerably lower than from infections caused by *Staphylococcus aureus* or Gram-negative rods. These observations have been confirmed by another study which showed that outcome in nosocomial bacteremia is better when it is caused by intravenous catheters as compared to other sources, such as pneumonia or abdominal infections [2].

RISK FACTORS

Several host factors that predispose for CRI have been identified. Malignant hematologic disorders and AIDS increase the risk of CRI about four times, but the most important risk factor is neutropenia, with an 11-fold increased risk [12]. Other risk factors include the type of catheter and the site of insertion. In general, infection rates are substantially lower in patients with tunneled catheters than in patients with non-tunneled catheters [5,13].

It has been shown by several studies that a reduction of infection rates can be achieved with impregnated catheters [14–16]. The best results have been observed with the use of a catheter impregnated with minocycline and rifampicin on both the luminal and external surfaces. Compared to a catheter impregnated with silver sulfadiazine and chlorhexidine on the external surface, this type of catheter reduced the risk of CRBSI significantly [16].

In the past, multilumen catheters have been associated with an increased risk of infection [17–19]. However, a recently published randomized study did not find a difference between single- and multi-lumen catheters [20].

Among the possible insertion sites for central venous catheters, the subclavian vein is associated with the lowest risk of infection [5].

ETIOLOGY

Most CRIs are caused by Gram-positive organisms. Coagulase-negative staphylococci are most frequently cultured, followed by *S. aureus*, Gram-negative bacilli and *Candida* species [13,21]. Isolation of the causative agent is crucial, as clinical management of infections varies according to the organism. Another argument for a rigorous search for the pathogen is resistance. Many of the organisms causing CRIs are resistant to commonly used antimicrobials. Frequent patterns in CRIs include methicillin resistance of coagulase-negative staphylococci and *S. aureus*, vancomycin resistance of enterococci, β-lactam resistance of Gram-negative bacilli, and fluconazole resistance of *Candida* species.

DIAGNOSIS

The role plate technique of Maki et al. [22] is the most frequently used method to diagnose CRI. A diagnosis of CRBSI is established when the catheter yields more than 15 colony-forming units per segment and the blood culture is positive for the same organism. With another technique, using sonication and flushing of the lumen, diagnostic sensitivity may be increased [23]. Both techniques require the removal of the catheter. With quantitative blood cultures drawn from the catheter and from peripheral venipuncture, it is possible to diagnose CRI with the catheter left in place [24]. However, the technique requires specific blood culture systems and sophisticated logistics and has therefore not been widely used in clinical practice.

Recently, a very elegant method has been described using the differential time to positivity (DTP) of blood cultures drawn simultaneously from peripheral veins and central lines [25]. Using a cut-off of 2 h for DTP, Blot et al. showed that this

method has excellent sensitivity and specificity, as well as positive and negative predictive values [26]. Further studies are needed to evaluate the utility of this method under different clinical conditions.

CATHETER REMOVAL

The question of whether the catheter has to be removed is dependent on different factors concerning the patient, the pathogen, and the catheter itself. It is advisable to remove the catheter in any patient with severe sepsis or septic shock. When the patient is in a stable condition, the catheter may be left in place under certain circumstances. Raad et al. have shown in a retrospective review that infections caused by coagulase-negative staphylococci may be successfully managed with the catheter in situ in 50% of patients. However, recurrent bacteremia occurred in 20%, as compared to 3% of patients with immediate catheter removal [27]. Other studies have shown more favorable results. In pediatric patients, catheter salvage was successful in five of six (83%) infections with coagulase-negative staphylococci [28]. Very similar results have been reported by other investigators, showing a cure rate of 88% without catheter removal in children with malignant diseases and port infections caused by coagulase-negative staphylococci [29]. Given the relatively low pathogenicity of coagulase-negative staphylococci [2], an attempt at catheter salvage is justified in these infections, especially in the case of implanted long-term catheters. This approach is supported by a guideline that has been established recently by the Infectious Diseases Society of America (IDSA) [4]. Any attempt at catheter salvage has to be accompanied by appropriate antibiotic therapy.

In the case of *S. aureus* infection, rapid catheter removal is recommended by most experts. Many studies with different catheter types have shown that catheter salvage is successful in only a minority of patients. In patients with hemodialysis catheters and *S. aureus* infections, 12 of 62 episodes (19%) could be managed without catheter removal [30]. Similar results have been reported in patients with Hickman catheters [31]. In contrast to these figures, a much higher success rate (68%) has been described in a pediatric population with implanted port catheters [29].

The risk of deep-seated metastatic infections, such as endocarditis, osteomyelitis and septic thrombosis is a major argument for rapid catheter removal in cases of CRBSI due to *S. aureus*. Complicated *S. aureus* infections resulting from bacteremia have been described with rates of 16% and more [32,33]. It has also been reported that increased mortality in *S. aureus* bacteremia may be related to non-removal of the catheter [34]. Taking these results together, rapid catheter removal is advisable as standard procedure in *S. aureus* CRBSI, and catheter salvage may be limited to special situations [4].

Little evidence is available in the current literature to serve as a guideline for catheter management in Gram-negative infections [35]. In a retrospective review which investigated infections due to *Stenotrophomonas maltophilia* and *Pseudomonas* species, catheter removal was found to be associated with lower mortality [36]. Likewise, in bacteremia due to *Acinetobacter baumannii*, catheter removal has been shown to reduce mortality [37]. Therefore, most experts currently recommend rapid catheter removal in cases of Gram-negative infections.

When the infection is caused by *Candida* species, attempts at catheter salvage are not indicated. In a retrospective review of candidemia at the National Cancer Institute, nine of 11 patients with the catheter left in place had an unfavorable outcome [38]. These results are supported by a large prospective study performed by Nguyen et al., demonstrating that a significant increase in mortality is associated with non-removal [39]. Thus, in the presence of candidemia, intravenous catheters should be removed immediately.

Rarely, CRIs are caused by mycobacteria. These infections can only be managed successfully with catheter removal [40].

Irrespective of the pathogen, tunnelled catheters or ports should be removed in the presence of tunnel or pocket infection [41]. Likewise, in the case of septic thrombosis, attempts at catheter salvage are not recommended as they will eventually result in metastatic infection.

ANTIMICROBIAL THERAPY

Although removal of the catheter alone may result in clinical cure in selected cases, it is generally recommended to treat CRBSI systemically with appropriate antibiotics. Choice and duration of antimicrobial therapy depend on the isolated pathogen, the resistance pattern, and the presence

of complications, such as deep-seated infections. Vancomycin is often given in cases of suspected or established CRI. However, its use should be reserved for infections with pathogens that are not susceptible to β-lactams. Since no randomized trials have been performed to examine optimal treatment modalities for CRIs, recommendations are based mainly on observational studies and expert opinion.

Most coagulase-negative staphylococci are resistant to β-lactam antibiotics and require treatment with glycopeptides. The optimal duration of treatment is not established, but most experts recommend antibiotic treatment for 7–10 days.

Staphylococcus aureus infections should be treated with appropriate antibiotics (preferably β-lactams) given intravenously for at least 2 weeks. However, in cases of complicated infections, such as endocarditis, osteomyelitis or septic thrombosis, or in patients with prolonged fever under appropriate antimicrobial therapy, much longer periods are needed (4–6 weeks for endocarditis, and 6–8 weeks for osteomyelitis) [4].

Recently, new antimicrobial agents targeting Gram-positive infections (quinoprustin/dalfopristin and linezolid) have been introduced into clinical practice. Their specific value in CRI has not yet been established and they should be retained for infections with organisms resistant to vancomycin or for patients with intolerance to other susceptible antibiotics.

Gram-negative infections may include a wide range of pathogens and have to be treated according to culture results and antimicrobial susceptibility testing. There are no data available on the optimal duration of therapy, but treatment periods of 7–10 days might be sufficient in most cases.

Intravenous fluconazole is the drug of choice for CRBSI due to *Candida* spp. [42]. In the rare cases caused by organisms not susceptible to fluconazole (such as *C. krusei*), treatment has to be changed to amphotericin B as soon as species differentiation is available.

In the near future, new azole antifungals with extended spectra will probably be available. However, their application in CRI has not yet been studied. Caspofungin, another newly developed antifungal agent of the echinocandin class, has shown substantial efficacy against a wide range of *Candida* species and will also extend our therapeutic armamentarium for fungal infections.

ANTIBIOTIC LOCK THERAPY

The instillation of antibiotics in high concentrations into the catheter over a period of 12–24 h has been demonstrated to be effective in eliminating catheter-related bacteremia in several studies [43–45]. Different substances have been used according to the susceptibility of the underlying organism (e.g. vancomycin, ciprofloxacin, gentamicin). Although controlled trials comparing different approaches have not been performed, the method has been recommended by an expert committee of the Infectious Diseases Society of America for the treatment of uncomplicated infections in patients with implanted long-term catheters [4].

ADDITIONAL PROCEDURES

In all cases of CRBSI, control blood cultures should be obtained until eradication of the pathogen from the bloodstream has been demonstrated. If a CRI is suspected, any removed catheter should be examined microbiologically to establish the diagnosis.

Especially in cases of central catheter-related bloodstream infections due to *S. aureus* and *Candida* spp., it is clinically important to rule out metastatic infections. Endocarditis is the most devastating consequence of staphylococcal infection. Therefore, the role of echocardiography is an important consideration in the clinical management of these infections. In recently published studies, it was shown that transesophageal echocardiography (TEE) is a very sensitive and cost-effective method with which to diagnose endocarditis associated with *S. aureus* infection [46,47]. These results have led to the recommendation that TEE should be performed in each patient with *S. aureus* bloodstream infection unless contraindications are present [4].

The value of other diagnostic procedures aimed at detecting metastatic infections has been investigated less systematically. From a clinical point of view, it seems advisable to perform scintigraphy and X-ray examinations in the case of patients all with clinical symptoms of bone infection.

In patients with prolonged fever or persisting bacteremia despite adequate antibiotic therapy, the aforementioned examinations are mandatory. In addition, abdominal sonography and computer tomography of the chest and abdomen should be performed to search for infectious foci. Patients with Candida bloodstream infections should undergo

ophthalmoscopic examination to rule out endophthalmitis.

CONCLUSION

An accurate diagnosis, adequate antimicrobial therapy and a rational decision concerning catheter removal are the main steps in the clinical management of CRI. In the past, a definite diagnosis of CRBSI could be established only after catheter removal in virtually all cases. The newly developed technique of DTP will eventually allow an exact diagnosis with the catheter left in place and may help the clinician in guiding therapy. Intravenous therapy should be applied for a sufficient period of time, especially for infections due to *S. aureus* and *Candida* spp. Removal of the catheter will be necessary in the majority of cases. However, in selected cases, such as uncomplicated infections due to coagulase-negative staphylococci, catheter salvage may be attempted.

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