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REVIEW ARTICLE

Central venous catheter-related infections in hematology and oncology

Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO)

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Abstract Catheter-related infections (CRI) cause considerable morbidity in hospitalized patients. The incidence does not seem to be higher in neutropenic patients than in nonneutropenic patients. Gram-positive bacteria (coagulase-negative staphylococci, *Staphylococcus aureus*) are the pathogens most frequently cultured, followed by *Candida* species. Positive blood cultures are the cornerstone in the diagnosis of CRIs, while local signs of infection are not necessarily present. Blood cultures should be taken from peripheral blood and from the venous catheter. A shorter time to positivity of catheter blood cultures as compared with peripheral blood cultures supports the diagnosis of a CRI. In many cases, a definite diagnosis requires catheter removal and microbiological analysis. The role plate method with semiquantitative cultures has been established as standard in most laboratories. Antimicrobial treatment of CRI should be directed by the in vitro susceptibility of the isolated pathogen. Primary removal

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of the catheter is mandatory in *S. aureus* and *Candida* infections, as well as in case of tunnel or pocket infections. Future studies will elucidate whether the rate of CRI in neutropenic patients may be reduced by catheters impregnated with antimicrobial agents.

Keywords Catheter-related infections · Guidelines · Neutropenia · Antimicrobial treatment · Infection prophylaxis · Biofilm

Definitions

In clinical practice, diagnosis of central venous catheter-related infections (CRI) is based on symptoms and test results not always withstanding strict definitions. In many cases, CRI can only be presumed backed-up by clinical symptoms and test results listed in Table 1. A gold standard for diagnosing CRI is not established. This guideline refers to definition criteria specified below.

Catheter colonization

Catheter colonization is defined by the detection of microorganisms on the catheter surface by a suitable method (see below). In the absence of bacteremia, the term "Catheter infection" may be used when counts of colonizing microorganisms exceed certain limits (see below). The focus of this paper deals with various forms of CRI. Catheter colonization will not be addressed in detail.

Local infection at the catheter insertion site

Clinical signs of inflammation (redness, swelling, pain, purulent exsudate) directly related to the catheter insertion site represent a local infection, while symptoms of systemic infection may not necessarily be present.

Catheter-related bacteremia or fungemia

The diagnosis is established when the same organism has been detected both in blood cultures and in catheter cultures (for methods see "Diagnosis" section).

In practice, the identity of isolated organisms is assumed when in vitro susceptibility testing results are identical. However, as shown by more sensitive methods, this may not hold true in all cases, so this approach may result in an overestimation of CRI. Recent studies on infections due to coagulase-negative staphylococci demonstrated genetically different organisms by DNA fingerprinting in a quarter of cases despite identical in vitro susceptibility test results [1]. However, a more specific definition is not applicable to daily clinical practice.

This clinical definition of catheter-related bloodstream infection (BSI) is distinct from the definition by the Centers for Disease Control and Prevention of nosocomial BSI [2], which has been developed for surveillance purposes. According to this CDC definition, a common skin contaminant isolated from at least one blood culture in a patient with an indwelling intravascular device and the institution of appropriate antimicrobial therapy is sufficient to establish the diagnosis of a nosocomial BSI (laboratory-confirmed BSI).

Tunnel and pocket infections

Clinical signs of infection at the subcutaneous part of a tunneled central venous catheter (CVC) characterize a tunnel infection. Spread of the infection for at least 2 cm into the tunnel is required as an essential criterion [3]. A pocket infection is diagnosed when the subcutaneous

Table 1 Diagnostic criteria for central venous catheter-related infections (CRI)

Diagnosis	Criteria		
Definite CRI	Pathogen detected at the catheter tip by a standard method[a] plus same pathogen with the same susceptibility pattern detected in blood culture	DTTP >2 h	Pathogen detected in quantitative catheter and peripheral blood cultures with a catheter CFU to peripheral CFU ratio ≥10
Probable CRI	Local infection at the insertion site coupled with positive blood culture	Remission of previously refractory fever within 48 h after catheter removal plus positive blood culture	Catheter tip colonization levels above the limit specified for the method
Possible CRI	Pathogen detected in blood culture that is typically implicated in causing catheter infections (*S. epidermidis*, *S. aureus*, *Candida* spp.)	Positive blood culture and no other focus identified in a patient with an indwelling CVC	

[a] For standard methods, see "Diagnosis" section

pocket of an implanted port system shows clinical signs of infection and inflammation.

Pathogenesis

Potential portals of entry for organisms are the skin, catheter hubs, and infusion solutions. Colonization of the insertion site by normal skin flora or pathogenic organisms is a major risk factor. Skin lesions secondary to chemotherapy or graft-vs-host disease may compromise the natural protective integrity of the skin. Nasal and oral mucosa, as well as the gastrointestinal tract, have been identified by molecular typing as a potential source of microorganisms such as staphylococci [4, 5].

When screened by electron microscopy, almost all intravascular catheters are found to be colonized by microorganisms even if there is no clinical sign of infection and catheter cultures are negative. Endogenous lining of the interior surface of the catheter with a biofilm takes place within 24 h after insertion [6]. This biofilm is composed of polysaccharides, fibrin, fibronectin, or laminin and is formed by both microorganisms and the host. Microorganisms are embedded into this biofilm, which shields them from host defense mechanisms such as phagocytosis or antibodies, as well as from antibiotics. This biofilm appears to be the most important pathogenetic mechanism for the development of CRI.

The adherence of organisms to specific materials depends on physical properties of the catheter, such as surface quality and electric charge, and on surface properties of the bacteria, such as hydrophobia. Hydrophobic staphylococci and *Candida* spp. colonize polyvinyl chloride and silicon catheters more frequently than catheters made of Teflon® or polyurethane [7]. Microtrauma emerging during catheter placement results in the formation of small thrombi on the intravascular catheter tip, thus creating another breeding ground for bacteria.

After colonizing the catheter, the microorganisms proliferate within the biofilm and start migrating. They can spread from here to the bloodstream through infusions, manipulations, or physiological catheter motion and, hence, cause systemic infection [6]. In catheters used for less than 14 days, infection is mainly due to extraluminal spread of the bacteria along the outer surface of the catheter. In long-term indwelling catheters, the intraluminal pathway predominates.

Epidemiology of central venous CRIs

Literature data on the incidence of CRI are difficult to compare due to inconsistent definitions, heterogeneity of patient populations (e.g., surgical patients, patients with burn injuries, cancer patients, bone marrow transplant recipients, subjects with HIV injection, neonates, etc.), use of different types of catheters, and different local strategies of infection prevention. Generally, 5–35% of patients who are admitted to intensive care units (ICU) present with nosocomial infections (NI), of which 95% occur in catheterized patients (corresponding to an incidence density of 19.8 episodes per 1,000 patient days). NI include colonization of the host by potentially dangerous pathogens, such as microorganisms from exogenous and endogenous sources, including resistant strains such as:

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Vancomycin-resistant enterococci
- Azole-resistant *Candida* spp.
- Extended-spectrum β-lactamase Gram-negative pathogens

Primary blood stream infections (bacteremia or fungemia, including those infections resulting from an IV line or arterial line) represent 19% of all NIs, of which 87% were found to be catheter-related [110, 111].

CVC-related BSIs are estimated to be as high as:

- 4.0 episodes per 1,000 device days for coronary ICUs
- 5.1 episodes per 1,000 device days for surgical ICUs
- 5.3 episodes per 1,000 device days for medical ICUs
- 6.9 episodes per 1,000 device days for pediatric ICUs [112, 113]

Precise epidemiologic data in neutropenic patients are sparse. Therefore, surveillance management should be established for patients at risk including the following distinct components:

- Epidemiologic surveillance and intervention
- Administrative controls for medical equipment, for health-care personnel and for patients
- Engineering controls [114]

To specify CRI rates, most authors refer to the number of CRIs per 1,000 days of catheter emplacement (CRI/1,000 days CVC). The lowest infection rates – 0.1 infections per 1,000 catheter days – were reported in oncology patients with port systems [8]. Nontunneled CVCs are associated with a substantially higher rate of infection [115].

The rate of catheter-related BSIs in hospitalized patients with peripherally inserted CVCs was comparable to that observed in patients with percutaneously inserted CVCs in one prospective study [9]. Tunneled catheters primarily used in high-risk patients (allogeneic bone marrow transplant recipients) are associated with an infection rate of 5 to 6 per 1,000 catheter days [10, 11]. The risk of CRIs in tunneled catheters is elevated during neutropenic periods as compared to nonneutropenic periods [10–12]. However, there is no definite evidence that neutropenic patients carry a fundamentally higher risk of CRIs than nonneutropenic subjects.

Most reviews on CRIs are based on the assumption that CRIs are associated with a significant risk of disease-related mortality. However, more recent studies do not support this hypothesis, since no increase in mortality could be demonstrated in association with catheter-related bacteremia [9, 13–15].

Risk factors

Type and extent of immunosuppression correlate with the incidence of CRI [12]. Risk of septic complications increases with the duration of neutropenia. In patients with nosocomial BSI, Wisplinghoff et al. reported significantly different mortality rates in neutropenic (36%) compared to nonneutropenic (31%) patients (p value=0.053) [16].

Tunneled catheters used in allogeneic bone marrow transplant recipients are associated with an infection rate of five to six per 1,000 catheter days. In some studies, the risk of CRIs in tunneled catheters was elevated during neutropenic periods as compared to nonneutropenic periods [10–12]. Henrickson et al. found a significantly reduced rate of total line infections (Gram-positive and Gram-negative line infections) using antibiotic flush of tunneled central venous catheters (TCVC), e.g., Broviac, Hickman: Gram-positive infections occurred with greater frequency in neutropenic patients (ANC<500/ml), whereas 11 Gram-negative TCVC infections demonstrated no variation in relationship to the patients' ANC. The time to develop a line infection was significantly increased by using antibiotic catheter flush [115].

Duration of catheterization [17, 18], frequency of manipulations (blood samplings, injections, etc.) [17, 19], site of catheter insertion [20–22], and administration of (high-caloric) parenteral nutrition [23] have been identified as risk factors with a significant impact on CRI rates. After adjustments for confounding parameters (i.e., type of nutrition, mechanical ventilation, and duration of hospitalization), the patient-to-nurse ratio was found to be a major independent risk factor, at least in critically ill surgical patients [68].

Two studies in hemato-oncological patients suggest that even subclinical thrombosis of the catheterized vein, as detected by ultrasound, may be an important risk factor for subsequent CRI [24, 25]. At the same time, colonization of CVC by microorganisms appears to be a major risk factor for subsequent catheter-related thrombosis [26].

Surveillance

Generally, there is a strong impact on surveillance studies, but parameters have to be defined according to the hospitals' own guidelines of good clinical practice. In most countries of the European Community, there are official recommendations concerning the installation of surveillance systems in order to minimize the incidence of hospital-related infections (e.g., extended spectrum of beta lactamase bacteria, vancomycin-resistant enterococci, MRSA). In Germany, several local or multicenter models of infection surveillance are established in order to reduce the incidence of treatment-related infections and spread of microorganisms. The predictive value of prophylactic blood culture in implanted CVCs of neutropenic patients (e.g., Port-a-Cath, Hickman, Broviac) without any clinical symptoms of infections is not proven.

Pathogens

A broad spectrum of pathogens may cause CRIs; however, Gram-positive bacteria are predominant. A US surveillance study in cancer patients with or without CVCs analyzed all pathogens isolated from blood cultures and found gram-positive organisms accounting for more than 70% of all nosocomial BSIs in the year 2000 [16].

Coagulase-negative staphylococci are by far the most commonly isolated agents of catheter-related bacteremia. *Staphylococcus aureus*, corynebacteria, enterococci, Gram-negative bacteria (*Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Acinetobacter baumannii*), and *Candida* spp. are frequently detected as well [27–29]. A prospective double-blind study in 126 pediatric oncology patients with 153 TCVCs, e.g., Broviac, Hickman, and 36,944 line days studied revealed 58 blood stream infections (43 Gram-positive, 14 Gram-negative, 1 fungal). As there were 14 mixed infections, 80 organisms were recovered from these positive cultures: 58 Gram-positive (72%), 20 Gram-negative (25%), and 2 fungal (3%).

The TCVC infection rate was 1.72 per 1,000 line days in the control group and could be reduced dramatically by catheter flush using either vancomycin/heparin/ciprofloxacin or vancomycin/heparin vs heparin alone. Exite site infections (n=49) were equally distributed among the three groups [6].

Carratala et al. investigated the use of heparin vs heparin and vancomycin for catheter flush. Colonization of the catheter hub occurred in 15.5% of 57 neutropenic patients treated with heparin (10 IU/ml) but in none of 60 patients treated with heparin and vancomycin (10 IU/ml and 25 mg/ml, respectively).

Catheter-related bacteremia occurred in 7% of 57 patients receiving heparin but in none of the 60 patients receiving heparin and vancomycin. The organisms that caused catheter hub colonization were *Staphylococcus epidermidis* in seven patients, *Staphylococcus capitis* in one patient, and Corynebacterium species in one patient.

The organisms that caused catheter-related bacteremia were *S. epidermidis* (n=3 patients) and *S. capitis* (n=1 patient), respectively [116].

Diagnosis

Diagnostic procedures for detecting CRI are initiated when clinical signs of infection are present (see Table 1). The clinical picture may be characterized by signs of local infection, fever, and/or sepsis, or a combination of these. General and specific diagnostic procedures are required for the appropriate clinical work-up.

General aspects

Patients with febrile neutropenia suspected of having a CRI should be examined in the same way as subjects with fever of unknown origin (see [30, 31]). Basic requirements are a thorough physical examination (skin, oral mucosa, paranasal sinuses, chest organs, abdomen, perianal region), a chest x-ray, and microbiology tests (blood cultures). Other diagnostic measures depend on clinical symptoms.

Diagnostic procedures for local infection of the insertion site

Local infection of catheter insertion sites is primarily diagnosed on the basis of clinical signs and symptoms. The presence of at least two of the three following symptoms is a criterion for diagnosis: redness, induration, or tenderness within 2 cm of venipuncture site. Concomitant systemic infection may or may not be present [3].

Concomitant local infection was found in approximately 3% of bacteremia cases particularly in CRI caused by coagulase-negative staphylococci [32]. In case of purulent secretion at the exit site of CVC, skin swabs do not allow for a reliable differentiation between colonizing and pathogenic organisms. Therefore, "targeted" antimicrobial therapy based upon results of swab cultures may not be adequate for catheter-related systemic infection (DIII). If tunnel infection is suspected, ultrasound imaging along the catheter with high resolution (≥7.5 MHz) may be helpful [33] (C III).

Microbiological diagnostics without removing the venous catheter

Blood cultures

In patients with suspected CRI or local infection without signs of systemic infection, two pairs of blood cultures should be taken (one from a peripheral vein and one from the CVC). Adequate volumes (≥20 mL) are important. In multilumen catheters, it might be advisable to take blood cultures from all lumina, as colonization can occur in one single lumen only [34] (C III).

Study results suggest that difference in time between positivity of results of catheter culture and peripheral blood culture might be an important diagnostic indicator [differential time to positivity (DTTP)]. This method requires no additional resources since the information is supplied anyway during automatic blood culture incubation. It is important to ensure that blood cultures are sent for processing to the microbiological laboratory within 12 h. DTTP of 2 h (cut-off limit) is a highly sensitive and highly specific predictor of catheter-related bacteremia [35]. This has been confirmed by recent studies in hematopoeitic stem cell transplant patients [36], in neutropenic patients [29], and in cancer patients with both short-term and long-term catheter implants [37]. Only one study in critically ill patients could not reproduce the favorable results of this method [38].

Quantitative blood cultures can also improve specificity. In most cases of CRI, much higher bacterial counts are found in the catheter blood culture than in the peripheral blood culture. A hub colony-forming unit (CFU) to peripheral CFU ratio of ten or greater may be interpreted as indicating CRI [39]. For the use of this method, special transport bottles (Isolator®), immediate sample work-up, and culturing procedures requiring significant resources in terms of staff and materials are required. A recent meta-analysis found this method to be the most accurate test [9]; however, it has not become standard clinical practice. In cases when no peripheral blood culture can be obtained, qualitative blood cultures drawn through the catheter-hub can help to identify CRI [40]. Another interesting approach is the quantitative detection of bacterial 16S ribosomal DNA in blood samples drawn through the catheter [41]. In summary, DTTP is recommended for routine diagnostic purposes (AI), while quantitative blood culturing is not a standard method – despite its validation in scientific studies – due to the complexity and amount of resources involved (D II) (Table 2).

Endoluminal brushing

Endoluminal brushing, a method of sampling the internal CVC surface in situ, may be useful in cases where no blood can be drawn through the CVC [42, 43]. However, this method may underestimate CRI in short-term catheters where external surface colonization plays an important role. This technique is not available in Germany.

Cytospin of catheter hub blood sample

Combination of gram staining and acridine orange staining in a cytospin slide preparation of a blood sample taken from

a CVC was shown to have a 96% sensitivity and 92% specificity [44].

Cultures from the catheter hub

Some authors took swabs from catheter hubs to diagnose CRI. The method has yielded controversial results in terms of sensitivity and specificity and is not recommended [45] (DII).

Microbiological diagnosis after catheter removal

If catheter removal is clinically indicated (see below), the catheter tip should be cut to a length of approximately 5 cm and placed in a sterile dry container for transport. The catheter tip should be worked-up within 12 h. If transport to the laboratory cannot be arranged immediately, the catheter tip should be refrigerated at 4–8°C.

The role plate method with semiquantitative cultures has become standard for microbiological diagnosis of CRI after catheter removal [46] (AII). Only bacteria adhering to the outer surface of the catheter are captured by this method. Growth of at least 15 CFUs on the plate is interpreted as evidence of a CRI.

A number of methods have been tested in search of improved sensitivity and specificity, including quantitative cultures from the interior surface of the catheter vortexing and ultrasound treatment of removed catheter material to disengage adhesive bacteria [28] (A II). The Brun-Buisson method is based on quantitative analysis after vortexing of the catheter. A cut-off limit of 10^3 CFUs is interpreted as positive [47, 48] (A II).

In a prospective trial in ICU patients, the quantitative methods have not been shown to be superior to the role plate technique [49]. In a recent meta-analysis, the estimates of accuracy were very close for quantitative and semiquantitative segment culture methods [9]. Placing the catheter tip in broth and subsequent culturing is not recommended since this method is associated with a high rate of false-positive results (EII). A meta-analysis by Rijnders et al. of 29 published clinical trials showed that catheter colonization above the limit specified for the applied method is highly predictive of catheter-related bacteremia [50] (B II). All mentioned methods of catheter tip culture have not been validated in catheters coated with antibiotics or antiseptics.

Management

A diagnosis of CRI calls for therapeutic decisions concerning the need for catheter removal, as well as choice and duration of antimicrobial therapy (Table 3). Specific data from the literature on neutropenic patients with CRI are sparse so that more general principles must serve as a guideline. For the clinical management of CRIs, it is helpful to identify the organism(s) involved and to differentiate between complicated and uncomplicated bacteremia:

– Uncomplicated catheter-related bacteremia: response to antibiotic therapy (defervescence, negative blood

Table 2 Standard microbiological methods after catheter removal

Characterization of Tests	Method	Description	Advantages	Disadvantages
Qualitative segment culture	conventional microbiologic culture assay	The segment is immersed in broth media and incubated, any growth after 24-72h	Easy to use	High false positivity rate (E II)
catheter in situ:	Blot's differential time to positivity (A II)	Blood cultures sampled of catheter and peripheral veins, time interval between positive results will be defined	highly sensitive and specific predictor of CR bacteremia, diagnosis while catheter still in place	High false positivity rate (E II)
Semi-quantitative segment culture (e.g., Maki)	Maki's roll plate method with semi-quantitative cultures (A II)	A 5-cm segment is rolled 4 times across a blood agar plate and incubated, > 15 CFU	Easy to use considered a standard procedure (A II)	captures only organisms adhering to the outer surface of the catheter
Quantitative segment culture (e.g., Sherertz or Brun-Buisson)	Sherertz's sonication method (A II)	A segment is flushed with broth or sonicated in broth, followed by serial dilutions, surface plating on blood agar, and incubation, > 1000 CFU	Higher sensitivity than the Maki method	Complex handling, not in widespread use (A II)
	Brun-Buisson's vortexing method with quantitative cultures (A II)		Higher sensitivity than the Maki method	

Adapted in part from Safdar et al. Ann Intern Med 2005 [9]

Table 3 Standard procedures in the diagnosis of central venous CRIs

Procedure
Before removal of the venous catheter
Rule out other possible sources of infection by clinical examination and imaging procedures, if necessary
Inspect the catheter insertion site or pocket or tunnel for signs of local infection. Palpate the pocket or tunnel
Take one pair of blood cultures (aerobic and anaerobic) from the catheter and one from a peripheral vein for microbiological evaluation and to determine the DTTP between the peripheral and catheter blood culture sample (A II)
In case of multilumen CVC, separate blood cultures may be drawn from each lumen
After removal of the venous catheter
Perform a microbiological examination of the catheter tip using a standard technique (see Table 2) (AII)

culture) within 48 h after start of antimicrobial treatment.

– Complicated catheter-related bacteremia: blood cultures remaining positive after more than 48 h of antibiotic therapy; development of endocarditis, osteomyelitis, septic thrombosis or embolism, or abscess formation. These are conditions which always require a longer duration of antimicrobial therapy and may necessitate surgical intervention.

Indications for catheter removal

Catheter removal is necessary if *S. aureus* is isolated from blood cultures of a patient with an indwelling CVC (A II). Attempts to preserve the catheter in subjects with CRI due to *S. aureus* have no more than a 20% chance of success [51, 52] and are associated with a high risk of secondary complications such as endocarditis or osteomyelitis. Catheter removal is recommended in patients with CRI due to *Candida* spp. (B II). However, a study on 404 cancer patients with CVC and candidemia identified the catheter as source of infection in only 27% [37]. Therefore, candidemia in the presence of a CVC should give reason for a thorough search for other potential portals of entry, primarily the gastrointestinal tract. In all cases of complicated CRI, catheter removal is also required (B II). Catheter removal is recommended in clinically unstable patients (severe sepsis, septic shock), patients with persistent fever, and patients with breakthrough fever after discontinuation of antimicrobial therapy.

Preservation of CVC may be attempted in clinically stable patients, in whom coagulase-negative staphylococci, *Corynebacterium jeikeium*, *A. baumannii*, *S. maltophilia*, *P. aeruginosa*, and *Bacillus* spp. have been detected as infections with these organisms, when treated appropriately, are associated with a low risk of secondary complications (B III).

In clinically stable patients with fever of unknown origin, the catheter should not routinely be removed without microbiological evidence of CRI (see "Diagnosis" section). A randomized trial in nonneutropenic ICU patients demonstrated equal outcomes (duration of ICU stay, ICU mortality) when CVC in patients with fever of unknown origin without microbiological signs of CRI were left in place compared to early removal of the device [53].

Exit site, tunnel, and pocket infections

Catheter exit-site infections usually respond to management by local measures (procedures) and antibiotics. However, in patients with tunnel or pocket infection, catheter explantation is usually required [54, 55] (B III).

Initial antimicrobial treatment

Treatment of CRI in hematologic and oncologic patients is based on the same principles as treatment of fever of unknown origin in neutropenic patients. However, preemptive antimicrobial treatment taking into account the most predominantly involved microorganisms may lead to more rapid clinical success.

The Guidelines of the Infectious Diseases Working Party (AGIHO) recommendations for broad empirical antimicrobial therapy in neutropenic patients are published elsewhere (http://www.dgho-infektionen.de/agiho). In summary, antibiotic treatment has to be started after the first febrile episode without delay, covering a broad spectrum of Gram-positive and Gram-negative bacteriae, including staphylococci and *Pseudomonas* species. In neutropenic patients, antimycotic treatment should be started if defervescence has not been achieved within 4 days. Therapy modifications should be adjusted according to resistograms. Narrowing the therapeutic spectrum, one should be aware of diagnostic failure due to colonization by different organisms or secondary infections like systemic mycoses. Antibiotic treatment should be continued for at least 2 weeks after the first sterile blood culture has been taken [30]. With respect to the overall response and survival rates, an initial treatment with a glycopeptide antibiotic is not required. After the receipt of culture results, antimicrobial treatment may be modified according to in vitro susceptibility testing results [56–58] (A II).

Targeted antimicrobial therapy

Before initiating pathogen-specific antimicrobial therapy, the significance of the detected pathogen needs to be critically reviewed. Coagulase-negative staphylococci and *Corynebac-*

terium spp. must have been detected in at least two separate blood cultures displaying the same resistance pattern before etiological significance can be assumed. Swab test results may be misleading (see "Diagnosis" section) and should be interpreted with the utmost caution. Apart from that, it is important to emphasize that the assumption of an isolated venous CRI may be incorrect and other important infectious complications may be present as well.

In Table 4, recommendations for targeted antimicrobial treatment of the most commonly involved pathogens in patients with CRIs are comprised. The impact of *S. aureus* bacteremia on clinical management has to be stressed specifically because of the high risk of hematogenous spread. Independent risk factors for hematogenous complications of catheter-related *S. aureus* bacteremia are duration of clinical signs and symptoms, hemodialysis, presence of a long-term intravascular catheter or noncatheter device, and infection with MRSA. Therefore, sufficiently long treatment periods are necessary to avoid complications (e.g., endocarditis, osteomyelitis) [59, 60]. At least 2 weeks of full-dose treatment with appropriate systemic antibiotics is recommended in immunosuppressed patients [61] (BIII).

Therapy with a penicillinase-resistant penicillin is more effective and, therefore, preferable to treatment with glycopeptide antibiotics in patients not affected by an MRSA infection. Glycopeptides are indicated in patients with intolerance to penicillin or methicillin-resistant staphylococci. Newer drugs active against multiresistant Gram-positive bacteria (linezolid, quinupristin/dalfopristin) should be reserved for patients who are intolerant to or infected by organisms resistant to glycopeptide antibiotics.

For treatment of fungemia or proven fungal infections of CVL intravenous administration of lipid-based amphotericin B formulations, voriconazole and caspofungin are recommended according to the AGIHO guidelines for treatment of systemic fungal infections in neutropenic patients [30].

Antibiotic lock technique

This refers to the instillation of highly concentrated antibiotics (e.g., vancomycin, gentamicin) into the catheter lumen (or into all lumina in the case of multilumen catheters). This approach can be used in long-term catheters and has been successful in treating CRI in nonneutropenic patients [62]. The use of antibiotic lock in addition to parenteral antibiotic therapy has been shown to reduce the relapse rate of CRI in a small randomized study [63]. Larger prospective, randomized trials in neutropenic patients have not been conducted (C III).

Prophylaxis

Application of stringent criteria for the use of CVC systems are necessary. A strict compliance with hygiene principles during insertion (especially hand hygiene) including stan-

Table 4 Antimicrobial therapy of venous catheter-related bacteremia depending on causative pathogen

Pathogen	Therapy	Duration[a]
S. aureus (methicillin-sensitive)[b]	Isoxazolylpenicillin (penicillinase-resistant penicillin)[c]	At least 2 weeks i.v.![d]
S. aureus (methicillin-resistant)[b]	Glycopeptide, linezolid, quinupristin + dalfopristin	At least 2 weeks i.v.![d]
Coagulase-negative staphylococci	According to susceptibility pattern; glycopeptide only in case of methicillin-resistance	For 5–7 days after defervescence (in patients with persistent neutropenia)
Enterococci	Aminopenicillin plus aminoglycoside glycopeptide plus aminoglycoside in case of ampicillin resistance Linezolid or quinupristin/dalfopristin in case of vancomycin-resistance	For 5–7 days after defervescence (in patients with persistent neutropenia)
Candida albicans[b]	Azole antifungal Alternative: amphotericin B lipid-based formulations or caspofungin	≥2 weeks
Nonalbicans *Candida* species[b]	Amphotericin B lipid-based formulations or caspofungin or voriconazole	≥2 weeks
All other pathogens	According to susceptibility pattern	Not defined

[a] Follow-up blood cultures are always necessary after cessation of antibiotic therapy in order to rule out persistence of infection
[b] Catheter removal is required whenever these pathogens are involved
[c] For methicillin-sensitive strains (vast majority), treatment with penicillinase-resistant penicillin is superior to treatment with a glycopeptide [59]
[d] Higher incidence of organ infection if treatment is continued for less than 2 weeks [61]

dardized aseptic placement [64, 65] (extensive use of sterile covers, sterile gloves, and sterile clothing including mask and cap) help to avoid infections [5] (AI). Ultrasound-guided placement may be helpful to further reduce CRI rates [66, 67] (BI). Well-staffed, qualified, and experienced teams for CVC insertion and management have been demonstrated to be major factors in preventing CRI [24, 68] (BI). Educational programs for nurses and physicians can help to reduce CRI rates [69–75] (A II).

Based on nonrandomized studies, the preference of single-lumen over multilumen catheters has been recommended [76–78]. However, more recent randomized studies have shown no correlation between infection rates and the number of lumina [79, 80]. Therefore, a preference of single-lumen catheters for reason of infection control is not supported (DII).

Access via the subclavian vein is preferable to an approach via the internal jugular vein in terms of preventing

Table 5 Diagnosis, therapy and management of central venous CRIs

Recommendations/evidence
Diagnosis
Skin swab for diagnosis of CRI (DIII)
Ultrasound imaging along the catheter tunnel for diagnosis of CRI (CIII)
Blood cultures should be drawn from all lumina of the catheter (C III)
One pair of blood cultures (aerobic and anaerobic) to be taken from the catheter and one from a peripheral vein for microbiological evaluation (A II)
DTTP is recommended for routine diagnostic purposes (AI)
Quantitative blood culturing is not a standard method (D II)
Endoluminal brushing may be useful if blood cultures cannot be drawn via CVC line (C II)
Cultures from the catheter hub are not recommended for routine diagnostics (DII)
Semiquantitative culturing for microbiological diagnosis of CRI after catheter removal is standard (AII)
The procedure of quantitative culturing from the interior surface of the catheter and vortex and ultrasound treatment of the catheter to disengage adhesive bacteria are standard (AII)
Placing the catheter tip in broth and subsequently culturing the pathogen is not recommended (EII)
Catheter colonization above the limit specified for the applied method is highly predictive of catheter-related bacteremia (B II)
Primary catheter removal is necessary in patients with CRI due to *S. aureus* (A II)
Primary catheter removal is necessary in patients with CRI due to *Candida* spp. (B II)
Primary catheter removal is necessary in patients with tunnel and pocket infection (B III)
In all cases of complicated CRI (i.e., metastatic organ or severe soft tissue infections), primary catheter removal is also indicated (B II)
Preservation of CVC may be initially attempted in clinically stable patients in the presence of the following pathogens: Coagulase-negative staphylococci, *C. jeikeium*, *A. baumannii*, *S. maltophilia*, *P. aeruginosa*, and *Bacillus* spp. (B III)
Therapy
Antimicrobial treatment of suspected CRI is based on the same principles as treatment of fever of unknown origin
Prompt empirical vancomycin therapy is not required (A II)
At least 2 weeks of systemic antimicrobial treatment is recommended in immunosuppressed patients (BIII)
For in vitro susceptible pathogens, therapy with a penicillinase-resistant penicillin is more effective and, therefore, preferable to treatment with glycopeptide antibiotics (B II)
Management
Antibiotic lock in addition to systemic antibiotic therapy has shown to reduce the relapse rate of CRI (C III)
Compliance with hygiene principles during insertion and standardized aseptic placement help to avoid infections (AI)
Ultrasound-guided placement helps to reduce CRI rates (BI)
Education programs for nurses and physicians help to reduce the incidence of CRI (A II)
Access via the subclavian vein is associated with a lower CRI rate as compared to internal jugular vein (AI)
Alcoholic chlorhexidine solution, alcoholic polyvidone–iodine solutions or 70% propanolol should be used for disinfection of the catheter insertion site (A I)
Routine catheter replacement to provide shorter residence times does not reduce infection rates (DI)
Systemic prophylactic antibiotic treatment prior to catheter insertion is not recommended (EI)
Topical application of antibiotic ointments for reducing staphylococcal colonization at the catheter insertion site and as a nasal ointment is not recommended (EI)
More frequent replacement does not reduce the incidence of infection (EI)
Impregnation of CVCs with antiseptics (chlorhexidine/silver sulfadiazine) or antibiotics (minocycline/rifampicin) reduces incidence of catheter colonization (AI)

infection [20, 21], but the risk of other complications such as severe hemorrhage (particularly in thrombocytopenic patients) or pneumothorax should also be taken into account (AI). Use of the femoral vein should be avoided due to the high microbial colonization rate in adults [20] and the higher risk of deep venous thrombosis [81] (DIII).

Chlorhexidine solutions should be used in preference to aqueous polyvidone–iodine solutions for catheter insertion and changing dressings [82–84] (AI). Alcoholic chlorhexidine solution, alcoholic polyvidone–iodine solutions, or 70% propanolol are safe alternatives [85, 86] (A I). One recent randomized controlled study showed that the serial combination of alcoholic chlorhexidine solution with aqueous polyvidone–iodine was superior to each regimen alone [87]. The use of octenidine hydrochloride (0.1%) for disinfection at the catheter insertion site during dressing changes has been shown to be well tolerated and associated with very low bacterial counts at the insertion site and low CRI rates and, therefore, provides a further option to minimize CRIs [88].

Routine catheter replacement with the aim of lowering the incidence of infection has not been shown to reduce infection rates [89] (DI). Systemic prophylactic antibiotic treatment prior to insertion of the catheter does not result in a significant reduction of CRI [90, 91] (EI). Although one meta-analysis suggests a benefit in terms of CRI reduction by flushing long-term catheters with vancomycin [91], this method cannot be recommended as the studies which the meta-analysis is based on did not use consistent clinical definitions of CRI (DIII). Topical application of antibiotic ointments (e.g., mupicorin) for reducing staphylococcal colonization at the catheter insertion site and as a nasal ointment is not recommended due to the risk of selection of resistant bacteria and fungi [92, 93] (EI).

Sterile gauze or transparent film may be used for sterile cover of the CVC insertion site [94]. Sterile gauze should be changed every 2 days and transparent film only once a week [95], unless local contamination, signs of inflammation, or detachment are present [96, 97] (BI). Routine more frequent replacement does not reduce the incidence of infection (EI).

Infusion systems should be replaced at least every 72 h [98, 99], except for infusion systems of lipid emulsions which should be changed every 24 h [100, 101] or immediately in case of blood contamination (BII). Transfusion systems for red blood cells or platelets have to be equipped with a standard filter. German regulations require filter change after 6 h [102]. Earlier replacement without any sign of contamination does not lower infection rate (EI).

Impregnation of CVCs with antiseptics (chlorhexidine/silver sulfadiazine) or antibiotics (minocycline/rifampicin) lowers the incidence of catheter colonization (AI), but the clinical implication of this fact is still undetermined [48, 103–108]. So far, only one randomized trial in cancer patients with nontunneled minocycline/rifampicine coated CVCs showed reduction in catheter-related BSIs after an unusually long period (median duration of catherization 66 days) [109]. Therefore, the use of impregnated catheters cannot be generally recommended at present (CIII) (Table 5).

Unresolved clinical issues requiring further studies

Standards for indication of TCVC, type of CVC, use of antibiotic flush and duration of central venous implants differ between oncologic centers. There are several parameters influencing the infection rate, such as the site of insertion of the catheter, the duration of implants, parenteral nutrition, blood drawn from the catheter, and the patient-to-nurse ratio. Type and tunneling of catheters, catheter coating, or catheter flush may contribute to low reported rates of infections.

At least in pediatric patients, the grade of neutropenia is a risk factor for central line infection. Therefore, patients' stratification should be performed according to the underlying disease (e.g., leukemia, stem cell transplantation, solid tumors), type (coated vs noncoated catheters), and duration of CVL implants (catheter days), as well as intravenous supportive care (intravenous nutrition, antimicrobial therapy).

It has been shown in some studies that antibiotic flush can reduce the incidence of probable, possible, and definite infections. However, it is not clear whether antibiotic flush will induce resistance of bacterial pathogens to antibiotics. There is a need for prospective randomized double-blind studies in patients – either adult or pediatric – with hematologic and oncologic malignancies, respectively. Clinical trials could be useful in order to establish operating procedures in neutropenic patients with different malignancies and to reduce costs.

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