

Central venous catheter-related infections in hematology and oncology: 2012 updated guidelines on diagnosis, management and prevention by the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology

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Background: Cancer patients are at increased risk for central venous catheter-related infections (CRIs). Thus, a comprehensive, practical and evidence-based guideline on CRI in patients with malignancies is warranted.

Patients and methods: A panel of experts by the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO) has developed a guideline on CRI in cancer patients. Literature searches of the PubMed, Medline and Cochrane databases were carried out and consensus discussions were held.

Results: Recommendations on diagnosis, management and prevention of CRI in cancer patients are made, and the strength of the recommendation and the level of evidence are presented.

Conclusion: This guideline is an evidence-based approach to the diagnosis, management and prevention of CRI in cancer patients.

Key words: guidelines, central venous catheter, catheter infection, neutropenia

introduction

Central venous catheters (CVCs) are widely used in patients with malignancies. However, cancer patients are at increased risk of catheter-related infections (CRIs) that are associated with increased morbidity and hospital costs [1–6]. These updated guidelines have been developed for healthcare personnel who insert CVC and/or are responsible for surveillance and care of CVC in patients with cancer.

methods

First, subtopics of this guideline were assigned to a panel of 14 experts in the field of infectious diseases in hematology–oncology and hospital epidemiology and infection control, respectively. Second, literature searches of the PubMed, Medline and Cochrane databases were carried out with combinations of the following search terms: central venous catheter infection, central venous catheter-related bloodstream infection, central venous catheter-associated bloodstream infection, cancer, neutropenia, definition, pathogenesis, pathogens, epidemiology, incidence, risk factors, diagnosis, treatment, management, surveillance, education and prevention. Third, the consensus process was carried out as an e-mail- and meeting-based discussion group. Criteria used to quote levels and grades of evidence are shown in Table 1 [7]. The guideline replaces our previous guideline [8],

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Table 1. Categories of evidence levels used in this guideline [7]

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ≥ 1 properly randomized, controlled trial
II	Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case–controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees

and was finally approved by the assembly of the members of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO) on 21 October 2012.

guideline

definitions

Diagnosis of infections due to CVC is based on clinical symptoms and laboratory findings not always withstanding clear definitions. However, as suggested by the Centers for Disease Control and Prevention (CDC) CRI can be subdivided in catheter colonization, different types of local CRI, infusate-related bloodstream infections (BSIs) and catheter-related BSI (CRBSI) [3, 6, 9]. Types of CRI are defined as follows:

catheter colonization. Colonization is defined by significant growth of a microorganism [>15 colony-forming units (CFU) in semiquantitative culture or >100 CFU in quantitative culture] from the catheter surface in the absence of accompanying clinical symptoms or bacteremia.

local CRI.

- Exit site infection: Clinical signs of inflammation (e.g. redness, swelling, pain, purulent exudate) located ≤ 2 cm from the catheter insertion site, in the absence of concomitant BSI.
- Tunnel infection: Clinical signs of infection >2 cm from exit site along the subcutaneous part of the CVC, in the absence of concomitant BSI.
- Pocket infection: Pocket infection is diagnosed when the subcutaneous pocket of an implanted port system shows clinical

signs of infection and inflammation, in the absence of concomitant BSI.

infusate-related BSI. Concordant growth of the same organism from the infusate and blood cultures (preferably percutaneously drawn) with no other identifiable source of infection [9].

catheter-related bloodstream infections. While the CDC distinguishes CRBSI from catheter-associated BSI (CABSBI)—the latter being considered if a patient had a CVC ≤ 48 h before the development of the BSI that is not related to an infection at another site [6]—we propose for routine clinical use a distinction between ‘definite’, ‘probable’ and ‘possible’ CRBSI as outlined in Table 2.

pathogenesis

Potential portals of entry for infecting microorganisms are the skin, catheter hubs, and infusion solutions. In catheters used for <14 days (short-term catheters), infections are mainly due to extraluminal spread of bacteria along the outer surface of the catheter. In catheters used for ≥ 14 days (long-term indwelling catheters), the intraluminal pathway predominates [12, 13].

Colonization of the insertion site by normal skin flora or pathogenic organisms is a major risk factor for CRBSI [14–16]. Endogenous lining of the interior surface of the catheter with a biofilm takes place ≤ 24 h after insertion [17]. This biofilm is composed of polysaccharides, fibrin, fibronectin or laminin, and appears to be the most important pathogenetic mechanism for the development of CRI. Microorganisms embedded into this biofilm are shielded from host defense mechanisms and from antibiotics. Crystal deposits originating from flushed fluids may further facilitate anchoring of bacteria to the luminal catheter surface [18]. Microtrauma emerging during catheter placement results in the formation of small thrombi on the intravascular catheter tip, thus creating another breeding ground for bacteria.

epidemiology

Prospective surveillance studies in adult cancer patients reported a CRBSI/CABSBI incidence of 1.1–7.5 per 1000 CVC days [19–21]. Similar incidence rates of 3.6–7.9 per 1000 CVC days CRBSI/CABSBI were found in a randomized, controlled trial that investigated two alcohol-based antiseptic solutions for preparation and care of CVC insertion sites [14, 22]. The incidence of CRBSI/CABSBI in hematology patients was found to be 20.3 and 22.0 per 1000 neutropenic days, respectively [23–25]. The German National Reference Center for Nosocomial Infections (ONKO-KISS) reported a CABSBI incidence of 12.6 and 10.3 per 1000 neutropenic days in autologous and allogeneic stem cell transplant (SCT) recipients, respectively [26].

risk factors

Neutropenia is an independent risk factor for infection related to long-dwelling tunneled CVC in patients with cancer [27]. Further, a large prospectively collected database on patients with nosocomial BSI—83.1% of those having a CVC—showed a higher mortality rate in neutropenic (36%) compared with non-neutropenic (31%) patients [28].

Table 2. Diagnostic criteria for CVC-related bloodstream infections (CRBSI)

Diagnosis	Criteria (I)	Criteria (II)
'Definite' CRBSI	Growth of same pathogen from blood culture of peripheral vein and from culture of CVC tip Growth of same pathogen from blood culture of CVC and from blood culture of peripheral vein	\pm <i>in vitro</i> susceptibility testing results in the same resistance pattern (AI) [10] and DTTP \geq 2 h (AII) or , for quantitative blood cultures, a \geq 3-fold greater colony count of microbes grown from blood culture of CVC than the colony count from a peripheral vein (AII) [5, 10, 11]
'Probable' CRBSI	Growth of the same pathogen from blood culture of CVC and from blood culture of peripheral vein	and no criteria for definitive CRBSI and detection of coagulase-negative <i>Staphylococcus</i> spp., <i>S. aureus</i> or <i>Candida</i> spp. and exclusion of other infection sites (BIII)
Exit site infection	Clinical signs of infection \leq 2 cm from the catheter exit	and BSI without criteria for definitive CRBSI (BIII)
Tunnel infection (Hickman and Broviac catheter)	Clinical signs of infection $>$ 2 cm from catheter exit site along the subcutaneous part of catheter	and BSI without criteria for definitive CRBSI (BIII)
Pocket infection (implanted port system)	Clinical signs of infection of subcutaneous pocket	and BSI without criteria for definitive CRBSI (BIII)
'Possible' CRBSI		
Catheter colonization	Growth of pathogen from CVC tip ($>$ 15 CFU in semiquantitative/ $>$ 100 CFU in quantitative culture) Pathogen detected in blood culture that is typically causing CRI (<i>S. epidermidis</i> , <i>S. aureus</i> , <i>Candida</i> spp.) Remission of fever in $<$ 48 h after CVC removal	and clinical or laboratory signs of infection (e.g. leukocytosis or elevated C-reactive protein) and no BSI (BIII) and no other focus identified (BIII) and no other focus identified (BIII)

CRBSI, catheter-related bloodstream infection; BSI, bloodstream infection; CFU, colony-forming unit; CVC, central venous catheter; DTTP, differential time to positivity of CVC blood culture and peripheral blood culture; CRI, catheter-related infection.

The ONKO-KISS multicenter surveillance project found an increased risk for CABSIs in males and in patients with acute myeloid leukemia [29]. Subclinical thrombosis of the catheterized vein, as detected by ultrasound, may be another important risk factor for subsequent CRI [15, 30], and colonization of CVC by microorganisms appears to be a major risk factor for subsequent catheter-related thrombosis [31]. Patients with hematologic malignancies are at higher risk for CRI than patients with solid tumors [32].

High level of skin colonization at the insertion site and the catheter hub/connector was shown to be a predictor for CABSIs with age and male gender being independent risk factors for skin colonization before CVC placement [13, 14, 17].

pathogens

In patients with hematologic malignancies or solid tumors Gram-positive organisms account for 60%–70% of CRBSIs with coagulase-negative staphylococci (CNS) being by far the most commonly isolated agents [33, 34]. Other Gram-positive organisms frequently detected are *Staphylococcus aureus*, enterococci and streptococci [14, 33, 34]. Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella* spp. etc.) and *Candida* spp. are found in 20%–25% and 5%–13% of patients with CRBSI, respectively [28, 33–35].

While no data are available on antimicrobial resistance rates in cancer patients with CRBSI, an increase in antibiotic

resistance in Gram-negative and Gram-positive bacteria has been reported in cancer patients with BSI [36, 37]. With respect to the general population, antimicrobial resistance rates [e.g. methicillin-resistant *S. aureus* (MRSA), methicillin-resistant CNS, vancomycin-resistant *Enterococcus faecium*, ampicillin-resistant *E. coli* and ceftazidime-resistant *P. aeruginosa*] increased in patients with BSI in the US between 1995 and 2002 [38]. However, more recent data from the USA show a decrease in the incidence of MRSA CABSIs in intensive care unit (ICU) patients [39].

diagnosis

Diagnostic procedures for detecting CRI are initiated when clinical signs of infection are present (Table 3). The clinical picture may be characterized by signs of local infection, fever and/or sepsis, or a combination of these. Diagnostic procedures should not differ between short-term and long-term catheters.

Patients with febrile neutropenia suspected of having a CRI should be examined in the same way as subjects with fever of unknown origin [40]. Basic requirements are a thorough physical examination, a chest X-ray and microbiology tests (blood cultures). Other diagnostic measures depend on clinical symptoms.

diagnostic procedures for local CRI. Local CRI is primarily diagnosed on the basis of clinical signs and symptoms [5]. In case of purulent secretion at the exit site of CVC, skin swabs do

Table 3. Standard procedures in the diagnosis of CVC-related infections (CRI)

Before removal of the CVC

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 (AII) and determine the DTTP between the peripheral and catheter blood culture sample (AII).

In case of multilumen CVC, separate blood cultures may be drawn from each lumen (AII).

After removal of the CVC

Perform a microbiological examination of the catheter tip (AII).

DTTP, differential time to positivity; CVC, central venous catheter.

not allow for a reliable differentiation between colonizing and pathogenic organisms. If tunnel infection is suspected, ultrasound imaging along the catheter with high resolution (≥ 7.5 MHz) may be helpful (BII). Compared with a clinically based strategy an ultrasound-driven strategy for early detection of septic thrombophlebitis and prompt CVC removal decreases infection-related mortality in neutropenic cancer patients [41].

microbiological diagnostics without removing the CVC

blood cultures: In patients with suspected CRI, two pairs of blood cultures with adequate volumes (≥ 20 ml) should be taken, one from a peripheral vein and one from the CVC (AII) [42, 43].

In multilumen catheters, it is advisable to take blood cultures from all lumina, as colonization can occur in one single lumen only (AII). A prospective cohort study showed that random sampling of only one lumen in triple-lumen CVC causing CRBSI has a 60% chance of detecting significant colonization [44]. However, despite superior sterile precautions, cultures taken at CVC insertion may have a higher contamination rate than peripheral blood cultures [45].

The differential time to positivity (DTTP) of results of catheter culture and peripheral blood culture is an important diagnostic indicator [46]. This applies not only to ICU patients [47] but also to hematopoietic SCT recipients [48] and neutropenic cancer patients [33].

As the information is supplied during automatic blood culture incubation, additional resources should not be required. It is important to ensure that blood cultures are sent for processing to the microbiological laboratory ≤ 12 h.

Differential quantitative blood cultures from samples taken simultaneously from the catheter and a peripheral vein have been proposed to avoid unjustified removal of the catheter and the potential risks associated with the placement of a new catheter at a new site. A central-to-peripheral blood culture colony count ratio of 3:1 to 10:1 is considered indicative of CRI [5, 49]. A meta-analysis found this method to be the most accurate test for diagnosing intravascular device-related BSI [10]. However, as the procedure is elaborate and expensive, it has not become standard clinical practice.

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 [50, 51]. However, this method may underestimate CRI in short-term

catheters where external surface colonization plays an important role. Further, this technique may carry the risk of pathogen dissemination and subsequent sepsis as well as thrombotic complications. It is thus not recommended for routine diagnostics (CIII).

microbiological diagnosis after catheter removal. If catheter removal is clinically indicated, the catheter tip should be cut to a length of ~ 5 cm and placed in a sterile dry container for transport (AII). Standard methods for microbiological diagnosis of CRI after catheter removal have previously been reviewed [10, 52].

management

A suspected CRI calls for therapeutic decisions concerning the need for catheter removal as well as choice and duration of antimicrobial therapy. Specific data from the literature on neutropenic patients with CRI are sparse. Thus, more general principles must serve as a guideline.

Removal of CVC has to be balanced with the risk of prolonging the infectious episode by keeping the CVC and the risk of reinserting another CVC (BIII). However, in case of suspected CRI, removal of CVC is strongly encouraged whenever possible.

indications for catheter removal. When CRI is clinically suspected, removal of the CVC is recommended if one or more of the following is present:

- the patient's clinical state deteriorates (BIII).
- sepsis and/or septic shock (BII) [5].
- severe complications such as endocarditis, septic thrombosis, abscess formations or osteomyelitis (BIII).
- *S. aureus* is isolated from blood cultures (AII). Prospective studies of patients with short-term and long-term catheter-associated *S. aureus* bacteremia showed that failure to remove the catheter proved to be a significant risk for hematogenous spread [53] and was the most important risk factor for subsequent relapse or death due to *S. aureus* [54]. Three retrospective studies in patients with Hickman catheters and CRI due to *S. aureus* reported a rate of successful catheter preservation ranging from 18% to 60% [55–57]. However, selection biases may have overestimated the likelihood of catheter salvage success. Notably, the failure rate was higher in tunnel or exit site infection and in methicillin resistance [57].

- Gram-negative bacilli are isolated from blood cultures. Most Gram-negative bacilli causing CRI are non-enteric organisms acquired from the hospital environment, such as *Stenotrophomonas maltophilia*, *Pseudomonas* spp. and *Acinetobacter* spp. In this situation, early removal (<72 h) of the CVC is recommended in order to prevent relapses (BII) [58–60].
- *Candida* spp. are isolated from blood cultures. In a retrospective study on neutropenic cancer patients with mucositis, the CVC was identified as a source of candidemia in only 27% [61], whereas the gastrointestinal tract had previously been reported to be an important source of candidemia [62]. Two prospective observational studies showed catheter retention to be associated with increased risk of death on univariate and multivariate analysis [63, 64]. Notably, in one of the studies, catheter removal was associated with a lower mortality rate only in patients with neutropenia [64, 65]. Other prospective observational studies that included 427 and 118 consecutive candidemic patients with several underlying diseases also found CVC retention to be a risk factor for death on multivariate analysis [66, 67]. In contrast, in a retrospective analysis of two phase III trials, designed primarily to determine the efficacy of antifungal drugs in the treatment of candidemia, CVC removal was not associated with any clinical benefit [68]. However, only 10% of the patients included in this analysis were neutropenic, and there was a lack of statistical power for evidence against CVC removal [69]. A recent retrospective study in cancer patients with candidemia reported a poorer survival if the CVC was not removed or removed >72 h [70]. Further, a prospective cohort study found the removal of a CVC at or within 5 days associated with decreased mortality [71]. In conclusion, CVC removal is recommended in cancer patients with candidemia (AII).

catheter preservation.

- In cases of uncomplicated CRI—defined as response to antimicrobial therapy (defervescence, negative blood culture) within 72 h after start of antimicrobial treatment [5]—catheter removal may not necessarily be indicated. However, the above-mentioned issues must be considered.
- Preservation of CVC may be attempted in hemodynamic stable non-neutropenic ICU patients without proven bacteremia, no local infection and no intravascular foreign body (e.g. pacemaker, prosthetic heart valve), given the CVC is carefully watched (AI) [72].
- In cases of a BSI with CNS long-term catheters (port system, Hickman catheter) may be left in place with a combination of systemic antibacterial therapy applied (BII). No randomized trials have evaluated the treatment of CNS CRBSI. However, in two retrospective cohort studies, CVC retention did not have an impact on mortality [73] or on the resolution of CNS bacteremia [74] but was a significant risk factor of recurrence, in particular in patients with a port system [74].
- If *Corynebacterium jeikeium* has been detected as a cause for CRI in neutropenic cancer patients. However, there are no prospective data on whether or not to remove the CVC [75]. A retain of CVC along with vancomycin treatment may be

acceptable in hemodynamic stable patients with tunneled CVC (BII) [76].

Of note, CVC removal is not always practical in patients with hematological malignancies. An exchange over a guidewire with uncoated CVC may contribute to the development of CRBSI and can thus not be routinely recommended [77]. However, a matched retrospective cohort study in cancer patients with CRI found a catheter exchange over a guidewire for a minocyclin/ri-fampin-coated catheter safe [78]. A CVC exchange over a guidewire may only be used in those patients where the risk of reinsertion outweighs the persistence of CRI complication (BIII).

local infections. Exit site infections usually respond to management by local measures and antibiotics. However, in patients with tunnel or pocket infection, catheter explantation is usually required (BIII) [5, 79].

initial antimicrobial treatment. The choice of the first-line empirical drugs should take into account the underlying malignancy, clinical presentation and severity of acute illness.

Current evidence shows that the addition of anti-Gram-positive treatment, namely glycopeptides, before documentation of a Gram-positive infection, does not improve outcomes in febrile neutropenia (EI) [80, 81]. The widespread emergence of multi-resistant bacterial strains should discourage strategies, such as adding vancomycin without proof of antibiotic-resistant Gram-positive bacteria as causative pathogen and/or in patients with signs of severe sepsis and shock (DIII).

After receipt of culture results, antimicrobial treatment in CRI should be modified according to *in vitro* susceptibility testing results (AII). However, in case of CVC removal and defervescence, the initial antimicrobial regimen may be continued (BIII). Depending on the causative pathogen antibiotic treatment should be continued for at least 7 days after the first sterile blood culture has been taken (AII) [82, 83]. However, specific data from neutropenic patients for the management and duration of antimicrobial treatment are sparse.

Table 4 comprises recommendations for targeted antimicrobial treatment of the most commonly involved pathogens in patients with CRI.

antibiotic-lock technique. The use of the antibiotic-lock technique (ALT) for the treatment of CRI was investigated in small randomized trials, prospective case series or retrospective cohort studies [84–87]. The ALT mostly consisted of vancomycin, teicoplanin, daptomycin, amikacin or gentamicin usually in combination with heparin. The solution is instilled into the CVC and allowed to dwell for several hours or days. The procedure can be repeated several times. ALT resulted in overall cure rates of up to 100% [86, 87]. The optimal duration of ALT is unknown. ALT was reported to be less effective in port-associated CRI compared with infection of short-term CVC [88]. ALT for 10–14 days might be a treatment option for ‘highly needed’ infected catheters (BIII).

Table 4. Antimicrobial therapy of CVC-related bloodstream infections (CRBSI) depending on causative pathogen

Pathogen	Therapy	Duration ^a
<i>Staphylococcus aureus</i> (methicillin-sensitive) ^b	Isoxazolylpenicillin (penicillinase-resistant penicillin)	≥2 weeks ^c
<i>S. aureus</i> (methicillin-resistant) ^b	Glycopeptide, linezolid, quinupristin/dalfopristin	≥2 weeks ^c
Coagulase-negative staphylococci	According to susceptibility pattern; glycopeptides only in case of methicillin-resistance	5–7 days after defervescence (in patients with persistent neutropenia)
Enterococci	Aminopenicillin; glycopeptide and aminoglycoside in case of ampicillin resistance; Linezolid or quinupristin/dalfopristin in case of vancomycin resistance	5–7 days after defervescence (in patients with persistent neutropenia)
<i>Stenotrophomonas maltophilia</i>	Co-trimoxazole	≥2 weeks
<i>Candida albicans</i> ^b	Fluconazole or echinocandine or amphotericin B lipid-based formulations	≥2 weeks
Non-albicans <i>Candida</i> spp. ^b	Amphotericin B lipid-based formulations or echinocandins or voriconazole	≥2 weeks
All other pathogens	According to susceptibility pattern	Not defined

^aFollow-up blood cultures necessary after cessation of antibiotic/antifungal therapy in order to rule out persistence of infection (AII).

^bCatheter removal required (AII).

^cHigher incidence of organ infection if treatment is continued for <2 weeks (AII) [82].

CVC, central venous catheter.

prevention

surveillance—education. Prospective surveillance programs along with intensive training strategies to improve the handling of CVC are able to reduce CRI rates by up to 68% not only in ICU patients [89–94] but also in neutropenic patients with hematologic malignancies [23]. Simulation-based training in CVC insertion reduced CRBSI in a prospective cohort study in ICU patients [95]. Education and process control has been shown to decrease both CRI (in particular CABS) [96–99] and mortality (AII) [100]. Thus, treating institutions should be encouraged to establish surveillance and education programs for nurses and physicians [4, 94, 101].

There is no role for taking prophylactic blood cultures from implanted CVC in the absence of any signs of infections (CIII).

hand hygiene—skin preparation. Hand hygiene procedures (alcohol-based hand rub), aseptic technique and maximal sterile barrier precautions are important factors in preventing CRI (AII) [4, 6, 90, 97, 100, 102]. Maximum sterile barrier precautions include wearing a sterile gown, gloves and cap and using a large sterile drape. Ultrasound-guided placement may be helpful to reduce the number of mechanical complications and cannulation attempts (BI) [103, 104].

For cutaneous antisepsis, an alcohol containing >0.5% chlorhexidine-based solution (CBA) should be used as it proved to be more efficacious in decreasing CRBSI compared with 10% polyvidone-iodine or 70% alcohol-only solutions for catheter insertion (AI) [94, 105–107]. Although a meta-analysis of >4000 catheters—of which 1493 were CVC—suggested that CBA reduced the risk of CRI relative to polyvidone iodine [108], alcoholic polyvidone-iodine solutions (A-PVP) or 70% propanolol are safe alternatives if there is a contraindication to chlorhexidine (AI) [6, 94, 105, 106, 109, 110]. This recommendation is

supported by a recent cohort study that revealed no major clinical advantage of CBA use over A-PVP for preventing CRI [111].

One randomized, controlled study showed that the serial combination of alcoholic chlorhexidine solution with aqueous polyvidone-iodine was superior to either of the regimens alone [112]. In another randomized, controlled trial skin disinfection with 0.1% octenidine plus 30% 1-propanol and 45% 2-propanol proved superior to 74% ethanol with 10% 2-propanol in terms of skin colonization at the CVC insertion site, positive culture at the catheter tip and CABS [22]. This study supported results of two prior observational studies demonstrating octenidine in alcoholic solution to be a better option than alcohol alone for the prevention of CRI [113, 114].

Thus, both serial combination of alcoholic chlorhexidine solution with aqueous polyvidone-iodine or octenidine/propanolol solutions are also useful for cutaneous antisepsis (AI).

selection of catheters and sites. As randomized studies showed similar infection rates between single-, double- and triple-lumen CVC [115, 116], a preferred use of single-lumen catheters is not supported [117]. The use of femoral lines is associated with a greater risk of infectious and thrombotic complications than the use of subclavian lines [118–121]. Thus, femoral catheterization should be avoided (DIII). While no randomized studies have directly compared infection rates as primary outcome measure between internal jugular vein and subclavian vein catheterization, the site of catheter insertion (internal jugular vein versus subclavian vein) was not noted to be a risk factor for CRI in a recent prospective randomized study on the use of antimicrobial impregnated CVC [122]. A Cochrane analysis found subclavian and internal jugular central venous access routes to have similar risks for catheter-related complications

[121]. Another prospective observational study also found no differences in CRI rates between different insertion sites [123]. However, the risk for uncontrolled hemorrhage or pneumothorax may be higher by using subclavian lines. In a recent prospective observational study, the subclavian vein access resulted in more overall complications than the internal jugular vein access [124]. As demonstrated by one randomized study, sutureless securement devices are able to reduce the risk for infection for CVC (BI) [125].

systemic antimicrobial prophylaxis. Systemic antimicrobial prophylaxis before insertion of the catheter does not result in a significant reduction of CRI (EI) [126].

antimicrobial catheters. CVC impregnated with antiseptics (chlorhexidine and sulfadiazine silver) on the external or on both the external and internal surfaces have been evaluated in numerous randomized, controlled trials [6, 107, 110, 127–131]. While most of the studies showed a significant reduction in catheter colonization, a significant reduction in CRBSI was not consistently demonstrated. Thus, routine use of antiseptic catheters cannot generally be recommended in cancer patients (CI).

Antimicrobial-impregnated catheters (minocycline/rifampicin or miconazole/rifampicin) reduced the incidence of CRI in four of five randomized studies (AI) [132–137]. Of note, the duration of catheterization was unusually long (63 and 66 days, respectively) in the study carried out in cancer patients [134] and there is concern that resistance may develop. However, minocycline or rifampicin resistance has not been observed in a retrospective clinical cohort study over a period of 7 years [138]. Although not generally recommended, the use of antimicrobial-impregnated catheters may be useful in patients with long-term CVC if the CRI rate remains high despite implementation of educational programs and appropriate process control (BII).

antibiotic-lock technique. ALT proved to be effective for prevention of catheter hub colonization with Gram-positive bacteria and subsequent bacteremia during chemotherapy-induced neutropenia [139]. Two meta-analyses showed a reduction of CRI or BSI by using ALT solutions [126, 140]. However, the test for heterogeneity—seeking to determine whether there are genuine differences underlying the results of the studies—was statistically significant in one of the meta-analysis [140]. In a prospective, randomized, double-blind trial in patients with hematological malignancies daily administrations of ethanol locks effectively reduced the incidence of CABSIs [141]. In contrast, another randomized study on the efficacy and safety of daily ethanol lock for the prevention of CRBSI showed a 3.6-fold, nonsignificant, reduction for patients receiving ethanol [142].

Depending on the baseline CRI rate, it is justified to flush a long-term CVC with a combination of an antibiotic and heparin, if the CRI rate at the institution is high [126]. However, the beneficial effects of ALT must be balanced by the potential for allergic reactions, toxicity and emergence of antimicrobial resistance (BI).

topical antimicrobials. No data are available demonstrating beneficial effects of topical application of antibiotic/antiseptic ointments at the catheter insertion site in patients with cancer. Given the risk of selecting resistant bacteria and fungi, topical antimicrobial ointments cannot be recommended (EII) [143].

catheter site dressing. Sterile gauze or transparent film should be used to cover the CVC insertion site [6]. A Cochrane review on the use of gauze, tape and transparent polyurethane dressings for CVC found that CRBSI were higher in the transparent polyurethane group when compared with gauze and tape (odds ratio = 4.19). However, this finding was based on small trials, and the confidence intervals were wide indicating high uncertainty around this estimate [144]. Two systematic reviews on the risk for

Table 5. Management of CVC-related infections (CRI)

Compliance with hygiene principles during insertion and standardized aseptic placement help to avoid infections (AII).
Education programs for nurses and physicians help to reduce the incidence of CRI (AII).
Alcoholic chlorhexidine solution with alcoholic polyvidone-iodine solutions or octenidine/propranolol solutions should be used for disinfection of the catheter insertion site (AI).
Ultrasound-guided placement may be helpful to reduce the number of mechanical complications and cannulation attempts (BI).
Routine catheter replacement to provide shorter residence times does not reduce infection rates (DI).
Systemic prophylactic antibiotic treatment before catheter insertion is not recommended (EI).
Topical application of antibiotic ointments for reducing staphylococcal colonization at the catheter insertion site is not recommended (EII).
More frequent replacement does not reduce the incidence of infection (DI).
Primary catheter removal is necessary in patients with CRBSI due to <i>Staphylococcus aureus</i> (AII).
Primary catheter removal is necessary in patients with CRBSI due to <i>Candida</i> spp. (AII).
Primary catheter removal is necessary in patients with tunnel and pocket infection (BIII).
Preservation of CVC may be initially attempted in clinically stable patients in the presence of coagulase-negative staphylococci or <i>Corynebacterium jeikeium</i> (BII).
Prompt empirical vancomycin therapy is not required (EI).
At least 2 weeks of systemic antimicrobial treatment is recommended in immunocompromised patients (BIII).
An antimicrobial-lock technique may be an option for 'highly needed' infected catheters (BIII).

CRI, catheter-related infection; CRBSI, catheter-related bloodstream infection; CVC, central venous catheter.

Table 6. Unresolved issues**Diagnosis**

Is it useful to document bloodstream clearance after completion of antimicrobial treatment in all patients with CRBSI, irrespective of catheter removal?

Can a single blood culture positive for CNS be disregarded in all cases?

Management

If catheter-drawn blood cultures are positive, but those from peripheral veins are negative, what is the optimal therapeutic approach?

How to proceed with unconfirmed CRI, pending blood culture results?

Is there a documented benefit from routine transesophageal echocardiography in patients with *Staphylococcus aureus* CRBSI? And if so, is there a difference between patients in whom the CVC is retained and those who underwent prompt CVC removal?

Is systemic antimicrobial therapy indicated in all patients with catheter-related bacteremia caused by CNS after catheter removal?

How should *Stenotrophomonas maltophilia* bacteremia be treated when co-trimoxazole fails?

If in an individual patient with catheter-related candidemia the CVC cannot be removed, should antifungal treatment with an agent that penetrates a biofilm preferred?

If a CVC of a patient with candidemia is removed, should there be a time interval before a new catheter is inserted, in order to avoid prompt colonization of the new CVC?

If ALTs are used in addition to systemic antimicrobial therapy, what is the optimal duration of this treatment?

How long should antimicrobial treatment be continued in a patient in whom the CVC could not be removed?

If in a febrile patient, one lumen of a multilumen CVC is clotted should the CVC be removed?

CRBSI, catheter-related blood stream infection; CNS, coagulase-negative staphylococci; CVC, central venous catheter; ALTs, antibiotic lock techniques.

CRBSI using transparent dressings versus gauze dressings found no difference between different dressing types in CRBSI, catheter tip colonization or skin colonization [145, 146]. Thus, gauze, tape or transparent polyurethane dressings can all be recommended for catheter site insertion dressing (AI). Chlorhexidine-impregnated sponge dressings showed a reduction in CRI rates compared with standard dressings in two randomized trials [147, 148]. However, giving the disadvantages of the sponge such as concealing the insertion site, soiling or detachment, transparent chlorhexidine-impregnated gel dressing should be preferred as it proved superior to standard dressings in a randomized, controlled trial (AI) [149].

Daily bathing with chlorhexidine reduces both CRBSI in the medical ICU [150], and CABSIs in SCT recipients [151]. However, a reduction in CRI has not yet been shown in hematology patients (CIII).

Gauze dressings should be replaced every 2 days, transparent dressings every 7 days, unless local contamination, signs of inflammation or detachment are present (BI) [4, 6, 152].

replacement of CVC and administration sets. Routine catheter replacement to prevent CRI has not been shown to lower infection rates (DI) [4, 153, 154]. Infusion and tubing systems should be replaced as previously recommended [4, 6, 155].

Recommendations on management and prevention of CRI are summarized in Table 5.

unresolved clinical issues requiring further studies

As outlined in Table 6, there are a number of unresolved issues underlining the need for further studies in patients with cancer.

disclosure

MH served on the speakers' bureau for Gilead and MSD; SM served on the speakers' bureau for MSD and Pfizer; OP served

on the speakers' bureau for Astellas, Gilead and MSD, and received research support from BioRaf, Fresenius and Pierre Fabre; GM served on the speakers' bureau for Gilead, MSD and Pfizer and received honoraria from Gilead, MSD and Pfizer. All remaining authors have declared no conflicts of interest.

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