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REVIEW

Central venous catheter associated infections in the ICU: A Dutch approach

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Abstract

Central venous catheters (CVCs) are an indispensable means of intravascular access in the treatment of critically ill patients. Infections associated with these catheters occur most frequently in intensive care unit settings. Despite the successful implementation of infection prevention programs, CVC-associated infections remain relatively common. Thorough knowledge of local epidemiology, diagnosis and treatment of CVC-associated infections is therefore essential for the intensivist. In this paper we present new Dutch data on the epidemiology of causative micro-organisms and we summarise the evidence on diagnostic strategy and optimal empirical treatment of CVC-associated infections.

Introduction

Effective treatment of critically ill patients requires reliable vascular access. In Dutch intensive care units (ICUs) at least 29,000 central venous catheters (CVCs) are used annually for this purpose. CVCs pose a risk for central line associated infections, resulting in increased morbidity, prolonged hospitalisation, and increased healthcare expenditure. In the Netherlands the incidence of CVC-associated infections has been 0.8-1.3 infections per (1,000) catheter days on the ICU in the past years.[1]

Currently, there is no Dutch guideline for the clinical diagnosis and empirical treatment of a suspected CVC-associated infection. The clinician must rely on a ten-year-old international guideline, while Dutch practice in both diagnostic strategy and empirical treatment may vary considerably from this guideline.[2] In general, empirical antibiotic therapy is based on the local epidemiology and resistance patterns of the most common causative pathogens of the infection. To date, limited data have been published on the most common pathogens of CVC-associated infections in the Netherlands, while these data constitute the cornerstone of determining empirical treatment.

In this paper, we want to respond to the question related to CVC-associated infections that every practising ICU clinician is faced with: What is the optimal diagnostic and therapeutic strategy for a suspected CVC-associated infection?

To be able to do so we need to know first about the aetiology of micro-organisms causing CVC-associated infections in the Netherlands. Further we need to address some other burning management issues related to CVC-associated infections: Should the central venous catheter be removed or retained? In which circumstances is removal mandatory? And when is removal enough as a therapeutic strategy?

Methods/ search strategy

Recent Dutch data on pathogens causing CVC-associated infections were obtained by consulting the national Infectious Disease Surveillance Information System for Antibiotic Resistance (ISIS-AR). The data in this system include all isolates and antibiotic resistance patterns provided by 34 medical microbiological laboratories in the Netherlands and cover 81 hospitals throughout the country. All isolates from 2017 categorised as cultures of the tip of a central venous catheter and blood cultures were selected. A definite CVC-associated infection was defined as a peripheral blood culture and a culture of the tip of the catheter both turning positive within a maximum of 24 hours difference, growing the same microorganism (including skin contaminants).

We also used data of the PREventie van ZIEkenhuisinfecties door Surveillance (PREZIES) system for specific Dutch data on pathogens causing CVC-associated infection. PREZIES is a collaboration of hospitals and the Dutch National Institute for Public Health and the Environment (the RIVM). In this database definite and probable hospital-acquired infections are registered. There are 53 participating hospitals, of which 15 hospitals provided data annually over the period 2014-2018. PREZIES (criteria of version 2017-2019) defines CVC-associated infections as definite

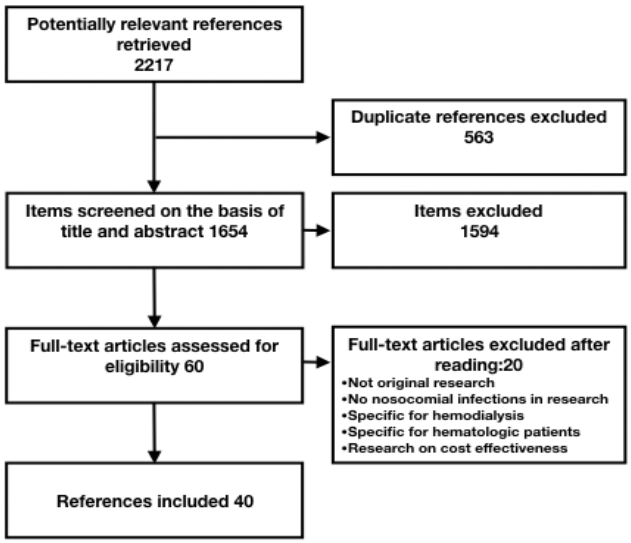

Figure 1. Data collection

when clinical signs (fever, chills, hypotension) are documented in combination with positive peripheral blood cultures and cultures of the tip of the CVC. In patients in whom a 'definite' CVC-associated infection cannot be diagnosed, due to the lack of appropriate peripheral blood cultures or cultures of the tip of the CVC, a diagnosis of probable CVC-associated infection is made. In the PREZIES data presented here, definite and probable CVC-associated infections are combined.[1]
Furthermore, we searched the literature using PubMed and the Cochrane database, for the search strategy used, see *Supplement 1*. The titles and abstracts of all the articles identified in the electronic search were reviewed. For pragmatic reasons, only articles in English and Dutch were reviewed. Additionally, the reference lists of relevant studies were checked to see if references included reports of other studies that might be eligible for this review. Whenever possible, the studies that seemed to fulfil the criteria of inclusion were obtained in full (*figure 1*).

Results

Micro-organisms causing CVC-associated infections

In the ISIS-AR database, 506 CVC-associated infections were identified in 2017. Coagulase- negative staphylococci (CoNS) (56%) was the most common causative pathogen, followed by *Staphylococcus aureus* (18%), *Enterobacterales* (10.6%) and *Enterococcus* spp (6.6%).[3] The 2014-2018 PREZIES database reported on 416 cases of CVC-associated infections in 33,761 CVCs among 25,410 patients from 53 hospitals. A diagnosis of definitive CVC-associated infection was made in 268 cases. A probable CVC-associated infection was established in 148 cases (36%). For definitions used by PREZIES see: www.rivm.nl/documenten/bijlage-2-definities-lijnsepsis-2017.
In the combined group of definitive and probable CVC-associated infections, CoNS (69%) was the most commonly isolated causative pathogen, followed by *Enterococcus* spp (7.5%), *S. aureus* (7.3%), *Enterobacterales* (5.8%) and *Candida albicans* (5.5%).[1] Our literature search resulted in four major retrospective cohort studies about the distribution of pathogens.[4-7] The combined results are presented in *table 1*.

Interestingly, the distribution of causative pathogens for CVC-related infections in the Netherlands is somewhat skewed towards Gram-positive microorganisms, especially CoNS, compared with international data (mainly US data). This could be attributable to the use of selective digestive decontamination (SDD) in Dutch hospitals. Unfortunately, no specific Dutch data are available on this potential influence. A recent randomised trial on the effects of long-term use of SDD in a Spanish hospital did describe the influence of SDD on the incidence of CVC-associated infections.[8] More CVC-associated infections were described in the group treated with SDD but no data were shared on the type of microorganisms that were cultured. We presume that these were equally dominated by the Gram-positive spectrum. A shift from Gram negatives to CoNS should be considered 'desirable' as the latter rarely cause severe infection and thus only need to be treated in selected cases (see under Empirical treatment).

Diagnostic strategy

The diagnosis of a CVC-associated infection is based on 1) establishing the presence of bloodstream infection and 2) demonstrating that the catheter is the source of the infection.
Although these directives seem simple, they often pose diagnostic problems in critically ill patients. There are no specific clinical signs that should prompt a high index of suspicion for a CVC-associated infection, with the exception of purulence at the insertion site and catheter dysfunction.[2,9-12] In most cases fever is the only presenting symptom and the CVC is one of the possible foci of infection. In these cases, there should be an emphasis on finding the cause of fever with a low threshold for blood cultures. In fact, peripheral blood cultures drawn with a single puncture are imperative to diagnose a microbiologically definite CVC-associated infection. After completing these diagnostics, watchful waiting is a reasonable initial approach.[13,14]
To establish if the CVC is in fact the source of infection, the catheter should be cultured as well. There are two ways to culture the CVC: by culturing the tip of the catheter or by drawing cultures from all lumina of the CVC (*table 2*).[15,16] Although drawing cultures from the CVC might seem to be an attractive option, to diagnose a definite CVC-associated infection in this way, strict criteria should be met: 1. Presence of clinical signs and symptoms; 2. Cultures drawn from all lumina of the CVC at exactly the same time as peripheral blood cultures are drawn; 3. Strict laboratory criteria (i.e. simultaneous (semi) quantitative cultures drawn from the CVC with a colony count that is at least threefold greater than colony count of peripheral blood

Table 1. Pathogens causing CVC-associated infections [1,3-7]

	ISIS-AR	PREZIES 2014-2018*	Combined literature
N	**506**	**416**	**30,041**
Gram-positive micro-organisms	%	%	%
CoNS	56	69	17-43
S. aureus (incl MRSA)	18	7.3	10-20
Enterococcus spp.	6.6	7.5	6.4- 17
E. faecium	4.0	3.7	
E. faecalis	2.4	1.2	
Other	0-0.2	2.6	
Corynebacterium spp.	0.2	0.4	
Enterobacterales			
E. coli	2.4	1.4	1.9-27.8
Enterobacter spp.	2.6	1	1.9-5.0
Klebsiella spp.	3.4	0.8	2.8-9.0
Serratia spp.	1.8		0.8-2.8
Proteus mirabilis	0.4		0-1
Other		2.6	
Non-fermenting bacteria			
Pseudomonas aeruginosa	2.4	1	2.8-5.4
Other	0.6	1.2	1-1.3
Yeast/fungi			
Candida spp	4	7,5	6.5-16

culture or positive cultures drawn from the CVC that become positive at least 2 h before peripheral blood cultures become positive).[2,15] Unfortunately these criteria are rarely feasible in clinical practice. Furthermore, this approach risks cultures from the CVC becoming positive as a result of colonisation, while peripheral blood cultures remain negative. Rather than performing this elaborate and error-prone procedure to establish a diagnosis of CVC-related infection, pulling the CVC is easy and often therapeutic by reducing the microbial load in a true CVC-associated infection. In which circumstances a CVC should be retained or pulled directly will be discussed in the section on removal of the CVC (see under Empirical treatment). Finally, it is important to emphasise that the underlying goal, when drawing cultures from a CVC, is that the line is to be retained. This is often desirable in clinical settings outside of the ICU where the threshold for removing and replacing a CVC is much higher. The literature that supports this practice is indeed predominantly non-ICU based.[17,18] In an ICU setting, there should generally be a much lower threshold to remove the CVC.

In the rare instances in which no peripheral blood cultures can be taken, cultures can only be drawn from the CVC. Results of cultures drawn from a catheter without concomitantly drawn peripheral cultures have a low positive predictive value for CVC-associated infections. In a systematic review of 2677 paired blood cultures obtained from a CVC and a peripheral venepuncture, diagnostic accuracy was compared with true bacteraemia. True bacteraemia was defined on the basis of the number of positive cultures, the type of micro-organism isolated and the clinical evaluation of the patient. Based on this review, cultures drawn from the CVC have an excellent negative predictive value 97-99% for a CVC-associated infection. However, the positive predictive value is low (17-58%).[16,19,20]

Culturing the CVC tip without a concomitant peripheral blood culture is discouraged, given the very poor positive predictive value of tip cultures (55%, range 24-70%).[21-24] Positive tip cultures without concomitant positive peripheral blood cultures will rarely have clinical consequences, except for when *S. aureus* and *Candida* are cultured (see below).

Table 2. Definitions of catheter-related infections

Possible CVC-associated infection
• CVC has been in place for more >48 hours before bloodstream infection • CVC is in place or was in place one day before • Clinical manifestations of infection (i.e. fever, chills, and/or hypotension) • No apparent other source of bloodstream infection
Definite (laboratory-confirmed) CVC-associated infection
• Meeting criteria possible CVC-associated infection PLUS • ≥1 (preferentially 2) set(s) of positive blood culture(s) from peripheral vein • Positive (semi)quantitative culture(s) of the tip of the CVC with same microorganism as in blood culture

Empirical treatment

Removal of the CVC

Removing a CVC is a crucial step in treating a CVC-associated infection. In fact, the delayed removal of a source of bacteraemia is associated with an elevated mortality rate and complications of infection.[25-27] How fast a CVC needs to be removed depends on the clinical circumstances. Immediate removal of a CVC is warranted in the setting of a tunnel abscess, suppurative thrombophlebitis, endocarditis or evidence of metastatic infection. Persistent bacteraemia after 72 hours of antimicrobial therapy, infections due to *Pseudomonas aeruginosa, S. aureus* or fungi, sepsis with haemodynamic instability or severe clinical deterioration are other reasons to remove the CVC immediately.[2,28] If fever is the only clinical sign pointing towards a CVC-associated infection and the CVC is clinically indicated, watchful waiting after taking peripheral blood cultures is a reasonable initial approach. In a small randomised study of 80 suspected CVC-associated infections in 64 patients in which fever was the only presenting symptom, this strategy resulted in

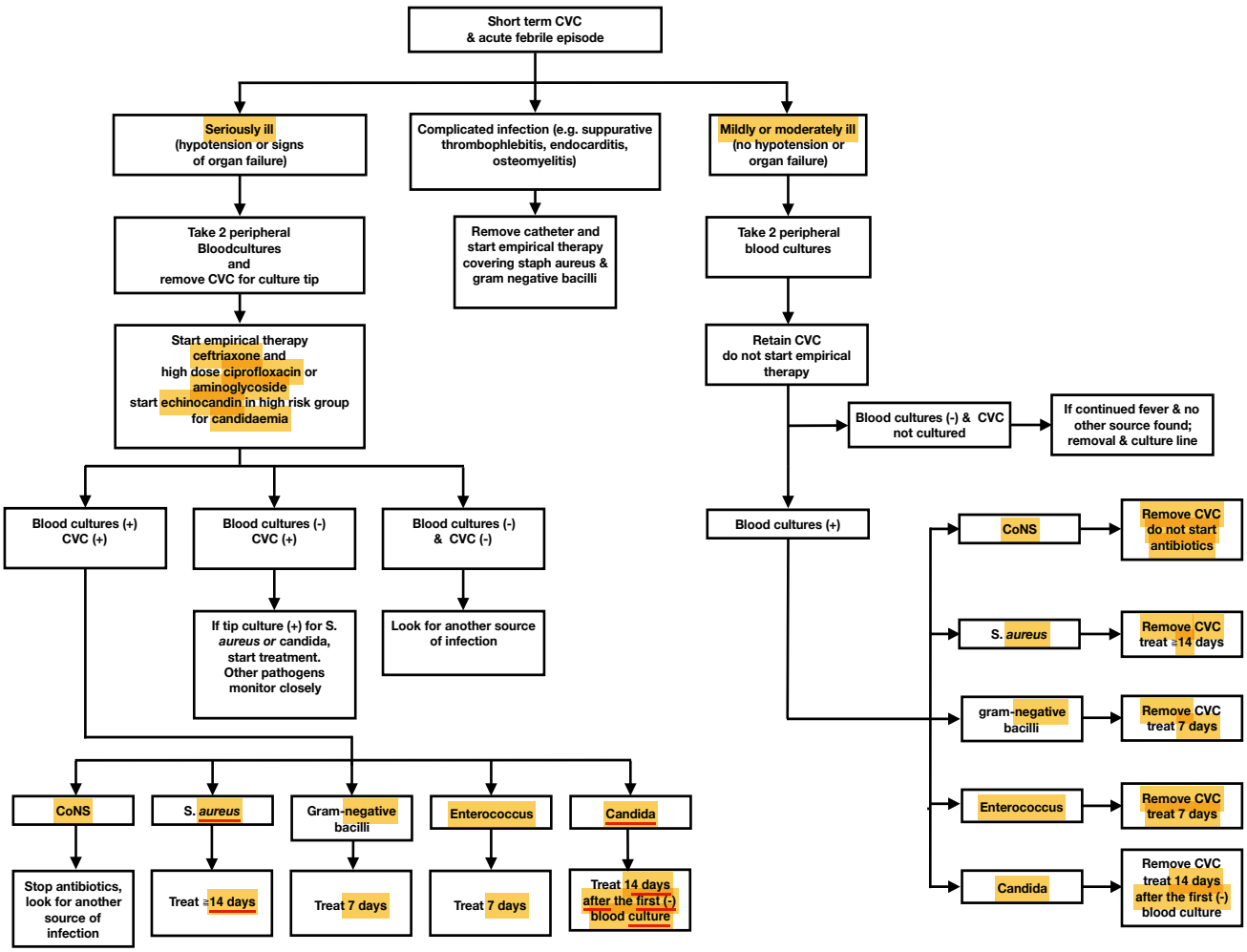

Figure 2. Diagnosis and empirical treatment of suspected line infections

a 62% reduction of unnecessary CVC removals compared with immediate CVC exchange with no change in defervescence or complications.[14]

In the case of an infection with CoNS, which rarely causes complicated infection in patients without prosthetic valves or other prostheses, many clinicians will withhold antibiotic treatment after removal of the catheter. There is, to our knowledge, only one small trial to endorse this common practice.[29] Despite the lack of evidence, the revised Dutch Working Party on Antibiotic Policy (SWAB) sepsis guideline advises that in uncomplicated CVC-associated infection with CoNS, removal alone is acceptable practice.[2,29,30] In patients with prosthetic valves or other prostheses, the CVC should be removed and antibiotic therapy is mandated (see under Empirical antibiotic treatment).

Empirical antibiotic treatment

Antibiotic therapy for a CVC-associated infection is most often initiated empirically and should only be started with a high index of clinical suspicion. Immediate empirical treatment of a CVC-associated infection is warranted in the settings of sepsis, haemodynamic instability or severe clinical deterioration.

To our knowledge, there are no randomised controlled trials available on empirical therapy for CVC-associated infections. Empirical therapy should therefore be based on epidemiological data of causative pathogens and their resistance patterns. In the ICU, regular colonisation cultures may also guide the choice of empirical therapy for CVC-related infections. In the available studies, CoNS, *S. aureus, Enterobacterales* and *Enterococcus* spp. were the most common causative micro-organisms in the Netherlands. CVC-associated infections with *Candida* are relatively uncommon.[1,3]

Although it seems appropriate to empirically cover all these pathogens, this is not necessary in most cases. In patients with a low risk of complicated enterococcal or CoNS infection, (e.g. without prosthetic valves and prosthetic joints), empirical therapy covering these pathogens can be withheld.

In three recent studies, empirical coverage of CoNS and *Enterococcus* spp. was not associated with an improved outcome.[29, 31,32] Given the lack of benefit, even the single dose of vancomycin which is common practice at the time of line removal is discouraged in patients with a low risk of complicated enterococcal or CoNS infections.[30] There is no evidence that any 'single dose' at the time of line removal is rational. However, in patients with an elevated risk of complicated enterococcal or CoNS infections (e.g. prosthetic valves and prosthetic joints), empirical treatment should be initiated and should include a glycopeptide.[34]

Based on the pathogens found in the Netherlands, empirical antimicrobial treatment should at least cover *S. aureus* and *Enterobacterales*. Current international guidelines advise empirical therapy with glycopeptides to cover *S. aureus* in the setting of high prevalence of methicillin-resistant staphylococcus aureus (MRSA). This advice would lead to gross overtreatment in the Netherlands, given the low prevalence of MRSA (1.4%).[33] For adequate coverage of *S. aureus*, flucloxacillin (or cefazolin in case of penicillin allergy) is an appropriate initial choice. Empirical coverage of *S. aureus* can be attained with a third-generation cephalosporin as well.

The initial choice for coverage of *Enterobacterales* should be based on local resistance patterns but would conventionally mean a third-generation cephalosporin or an aminoglycoside. De-escalation should be performed as soon as culture and susceptibility data become available.[2]

Concerning *Candida* spp., it is important to note that early and adequate antifungal therapy is an important determinant of survival in patients with candidaemia.[28,35] Bearing in mind the survival benefit of early treatment, it is advised that in high-risk groups (i.e. patients with total parenteral nutrition, haematological malignancy, receipt of bone marrow or solid-organ transplant) who present with sepsis, empirical therapy for possible candidaemia is started.[2] The presence of a femoral line as the suspected site of infection is not sufficient to defend initiation of empirical treatment for *Candida* spp.[36] In the general ICU population with ICU-acquired sepsis and who are colonised with *Candida* spp., it is unclear whether to initiate antifungal therapy. In two randomised trials, empirical treatment (in suspected fungal infection in ICU patients with sepsis) with micafungin or fluconazole showed no clinical benefit compared with placebo.[37,38] Therefore antifungal therapy should not automatically be initiated in colonised ICU patients while awaiting blood culture results. A practical guide of the recommendations on diagnosis and treatment is given in *figure 2*.

Special considerations

As a consequence of the culture strategy, in which CVCs are often promptly removed, it is possible that culture(s) of the tip of the CVC become positive while blood cultures remain negative. Whether treatment is warranted in these circumstances depends on the pathogens found. If *S. aureus* is found, treatment for a minimum of five days is advised pending peripheral blood cultures, given the elevated risk (4.8-24%) of *S. aureus* bacteraemia, even after catheter removal.[39-42] For the treatment of isolated line tips with Gram-negative pathogens (including *Pseudomonas* spp.) there is insufficient evidence of clinical benefit to start treatment.[43] All studies on subsequent bacteraemia after a positive tip culture have to be interpreted with caution: for instance, it is not always clear whether a blood culture was taken in all patients and not all antibiotic use is always registered. If a tip culture grows *Candida* spp., the risk of definite candidaemia is about 4-8.8%.[42,44] Given the increased mortality of untreated candidaemia it may be considered to start treatment with a positive line tip for seven days while awaiting definitive blood cultures. If blood cultures remain negative, empirical therapy for candidaemia should be stopped.

Conclusions

Establishing whether fever in ICU patients is due to a CVC-associated infection is a common diagnostic challenge in an ICU population. The focus in these cases should be on performing adequate diagnostics and making it plausible that the line is the source of infection. If fever is the only clinical sign indicating a CVC-associated infection, watchful waiting after taking peripheral blood cultures is a reasonable initial approach. Removal of the CVC is advocated in sepsis with haemodynamic instability or severe clinical deterioration if the CVC is the suspected source of infection. In this setting, the clinician should also initiate empirical antibiotic therapy, based on epidemiological data. In the Netherlands, the most common pathogens are CoNS *S. aureus, Enterobacterales* and enterococci. Empirical therapy should cover *S. aureus* and *Enterobacterales* with a third-generation cephalosporin or flucloxacillin/cefazolin combined with an aminoglycoside. Empirical treatment should not cover enterococci or CoNS, even in complicated line infections such as those associated with sepsis, unless the patient has mechanical heart valves or joint prostheses.

Disclosures

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Supplement 1. Search strategy in PubMed (performed on 9 May 2019)

http://www.njcc.nl/files/pdf/19-68.pdf

Supplement 2. For definitions used by PREZIES

www.rivm.nl/documenten/bijlage-2-definities-lijnsepsis-2017.