


REVIEW



A state of the art review on optimal practices to prevent, recognize, and manage complications associated with intravascular devices in the critically ill

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Abstract

Intravascular catheters are inserted into almost all critically ill patients. This review provides up-to-date insight into available knowledge on epidemiology and diagnosis of complications of central vein and arterial catheters in ICU. It discusses the optimal therapy of catheter-related infections and thrombosis. Prevention of complications is a multi-disciplinary task that combines both improvement of the process of care and introduction of new technologies. We emphasize the main component of the prevention strategies that should be used in critical care and propose areas of future investigation in this field.

Keywords: Intravascular catheter, Thrombosis, Pulmonary emboli, Sepsis, Critically ill

Introduction

Effective treatment of critically ill patients requires reliable vascular access in order to monitor patient status and deliver critically needed fluids, blood products, and medications. Unfortunately, mechanical, thrombotic, and infectious complications are not infrequent and result in substantial morbidity, mortality, and excess cost. This monograph offers expert advice on best practices regarding the insertion and care of intravascular catheters. The panel was invited by the first author on the basis of their expertise in epidemiology diagnosis, prevention, and treatment of catheter-related bloodstream infection from all over the world. None of the experts declined the invitation. The first version of each section was written

by three of the experts, and the text was reread and commented on by all the experts for improvement and modification during two other rounds. No methodology was used to capture evidence in particular, except for relying on systematic reviews whenever possible.

Epidemiology of infectious and non-infectious complications

Central venous catheters (CVC)

CVCs are frequently used in critical care with up to two-thirds of patients admitted to French ICUs being exposed to at least one such device [1].

Jugular, subclavian, and femoral veins are the major insertion sites. Pneumothorax, hemothorax, arterial puncture, cardiac dysrhythmia, and hematoma as well as infection and thrombosis are complications directly related to catheter insertion. The incidence of mechanical complications is primarily related to the choice of insertion site and number of punctures performed, which can

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be reduced by ultrasound (US) guidance. Mechanical complications are associated with significant morbidity and mortality with one study finding a nearly threefold increase in risk of death due to iatrogenic pneumothorax [2]. The occurrence of catheter-related bloodstream infection (CRBSI) can also be devastating, with a significant impact on mortality [3, 4] and costs [5].

Among patient factors, immunosuppression consistently increases risk [1, 6]. The daily risk of catheter infections does not increase over time [7]. Consequently, the benefit of routinely replacing CVCs after a stipulated period of time to prevent catheter infection has not been observed. As the cumulative risk of infection increases with the number of days the CVC is in place, prompt removal of unnecessary CVCs is mandatory [7]. In fact, in the before–after quasi-experimental Michigan Keystone Project, prompt CVC removal, together with hand hygiene, use of full-barrier CVC insertion precautions, skin disinfection with chlorhexidine, and avoidance of the femoral site decreased the incidence of central line-associated bloodstream infection (CLABSI) from 7.7 at baseline to 1.4 per 1000 catheter-days [8].

The least studied CVC complication is thrombosis. Most of them are asymptomatic and occur despite the use of venous thromboprophylaxis [9]. A prospective observational study [10] found that the presence of pulmonary embolism in mechanically ventilated patients was associated with lower limb deep venous thrombosis in one-third of the cases. More than half of them were related to a femoral catheter. In this study, upper limb thrombosis associated with catheter insertion was not a risk factor for pulmonary emboli.

Peripherally inserted central catheters (PICCs)

The use of PICCs has grown dramatically in critically ill patients [11, 12]. Compared to traditional CVCs, PICCs offer a number of advantages including (a) safer insertion via the upper extremity, thus avoiding pneumothorax; (b) convenient placement by nurse-led vascular access teams; and (c) clinical advantages in specific patients (e.g., those with coagulopathies, morbid obesity, head and neck injuries) where CVC placement is more challenging. However, like CVCs, PICCs are associated with risks [12]. As a result of their length and small diameter, PICCs are more prone to dislodgement, thrombophlebitis, and catheter malfunction compared to traditional CVCs [12, 13]. A systematic review of 62 studies found that the risk of deep venous thrombosis (DVT) among patients with PICCs was greatest for patients receiving PICCs in the ICU, averaging 13% in this subset [14]. When compared to CVCs, the risk of DVT was 2.5-fold higher (95% CI 1.54–4.32), likely due to insertion in smaller veins that are prone to venous stasis in hypercoagulable patients [14]. For

these reasons, PICCs should not be used for short-term (<15–20 days) catheterization in the ICU [15]. Initial findings of lower CRBSIs in PICCs were likely due to confounding by original studies examining outcomes in outpatient care, where indication and use are not comparable to inpatient care. A systematic review found no significant difference in rates of CRBSI between CVCs and PICCs in hospitalized (including critically ill) patients [16].

Hemodialysis catheters

About one-tenth of critically ill patients require a hemodialysis catheter (HDC) for renal replacement therapy (RRT) [17]. Although HDCs are inserted in central veins, the epidemiology of their complications cannot be directly extrapolated from other CVCs because HDCs differ in design (dual-lumen catheter with larger diameter), purpose (dedicated to extracorporeal blood venous circulation for RRT), handling (frequent hub disconnection and manipulation and locking between sessions), and insertion site (subclavian site discouraged to preserve the vascular network). A higher rate of placement failures and hematoma has been reported in jugular compared to femoral veins when using the landmark technique for HDC placement [18]. Rates of HDC-related colonization and CRBSI range from 9 to 28/1000 catheter-days [18–20] and 1–3/1000 catheter-days, respectively. While there is no difference of CRBSI between the femoral and the jugular insertion site, HDC colonization is reported to be higher at the femoral site in obese patients [18, 19]. The risk of DC colonization was demonstrated to be steady over time for intermittent hemodialysis [21, 22] but to increase sharply after 10 days for continuous RRT [21]. In two observational studies, the risk of HDC colonization for HDCs replaced for dysfunction did not differ between HDCs inserted by new puncture or exchanged over a guidewire [20, 23]. In a randomized study including a mixed ICU and non-ICU population, minocycline–rifampicin-coated HDCs failed to decrease the rate of colonization, but did reduce infection (0/66 versus 7/64 CRBSI in the treatment versus control arm, respectively) [24]. Studies on the efficacy of non-antibiotic antimicrobial locks for preventing HDC infections have yielded conflicting results but differ by the types of lock solutions and duration of dwell time exposure [25–27].

The rates of asymptomatic and symptomatic HDC-associated DVT are approximately 16.5% and 0.5%, respectively, with no differences between femoral and jugular placement [18]. HDC dysfunction resulting in HDC replacement ranges from 10% [28] to 26% [27]. No difference between the right jugular and femoral sites (both of which outperformed the left jugular site) was observed. Performance was lower at the femoral site compared to the jugular when for HDC <24 cm or blood flow >200 ml/min [28].

Arterial catheters

The complications of arterial cannulation (AC) include transient vascular occlusion, hematoma, hemorrhage, infection, pseudoaneurysm, air embolism, and neurologic injury [29]. Transient vascular occlusion may result from mechanical obstruction and subsequent thrombosis and occurred more frequently for radial access. Hematoma formation occurs in approximately 6% of all femoral access attempts with 0.15% being life-threatening retroperitoneal hemorrhage. The risk of CRBSI associated with AC is comparable to the risk observed for CVCs [9, 30]. However, compared to CVCs, the daily risk increases with time for ACs after day 7. Risk is higher for femoral as compared to radial access [7]. Arterial line CRBSIs are associated with pseudoaneurysm, thromboarteritis, and arterial rupture. Iatrogenic pseudoaneurysms predominately occur after cannulation, especially in the case of multiple access attempts and coagulopathy and may lead to severe complications such as pseudoaneurysm rupture, distal embolization, and compression neuropathy [29]. Mechanical complication risk is decreased by US-guided access. Limiting the duration of AC insertion also reduces the risk of arterial thrombi and infection occurrence.

Recent advances and ongoing controversies in diagnosis and treatment of vascular catheter-related infection (Box 1)

Mechanisms of infection

Colonization of the catheter occurs via two main pathways: the extraluminal route and the intraluminal route. Colonization of short-term CVCs (<15–20 days) occurs predominantly from the skin puncture site, whereas colonization of long-term CVCs is usually related to intraluminal bacterial spread from a contaminated hub [31]. In both cases, the source of microorganisms is usually commensal skin flora or flora of another person who manipulates the catheter without aseptic technique. Accordingly, coagulase-negative staphylococci are responsible for 40–50% of bloodstream infections, followed by *S. aureus* (10–20%), gram-negative bacilli, especially *Pseudomonas aeruginosa*, *Stenotrophomonas* sp., and *Acinetobacter baumannii*, are recovered in one-third of cases. *Candida* sp. are recovered in 3–10% of cases.

Biofilm formation on the inner and outer surfaces of the catheter contributes to the development of CRBSI [32]. A biofilm is a complex structure formed by bacteria that have attached to an artificial surface or tissue [33]. Bacterial attachment to the catheter surface begins within 24 h after catheter insertion. The bacteria proliferate and secrete a polysaccharide matrix, which provides a medium for the attachment of additional organisms. Formation of a biofilm is virtually inevitable but does not

always lead to clinical manifestations of infection, probably because the bacteria contained in the biofilm are characterized by slow growth and limited virulence. Biofilm-associated intravascular catheter infections are typically resistant to antimicrobials, not only because some antimicrobials cannot penetrate into the biofilm but also because the organisms are metabolically quiescent or slow growing. In addition, biofilms thwart host immune defense mechanisms.

The pathogenesis of catheter-associated fibrin sheath formation and thrombosis is poorly understood but biofilm formation is the first event. Subsequently, fibrin and other constituents, such as laminin, collagen, and even muscle cells, convert the film to a mature sheath [34]. Metallic cations, such as magnesium, calcium, and iron, stabilize the biofilm and contribute both to its development and bacterial growth [35]. Catheter thrombosis on the fibrin sheath may be facilitated by platelet activation, decreased levels of protein C and antithrombin III, hyperfibrinogenemia, and homocysteine elevation [32].

Diagnosis of catheter-related infections

The diagnostic methods that are currently accepted are summarized in Table 1. There are important differences between CRBSI and CLABSI that need to be understood in order to properly interpret available studies. To meet the definition of CRBSI, a positive peripheral blood culture must match a blood culture drawn through the catheter hub or a microorganism grown from a catheter culture (e.g., catheter tip). However, to meet the CLABSI definition a positive peripheral blood culture is not required, nor is a positive catheter culture required. The definition can be met with only a positive blood culture drawn through a catheter hub. As such, this definition requires a single blood culture positive for a pathogen (or two cultures positive for a common commensal) not recovered from another site during the 3 days preceding and 7 days following the detection of the index bacteremia. The CLABSI definition is adapted for surveillance and is not meant to be used as a clinical definition because of its lower specificity [36, 37]. Considerable variability therefore occurs among experts [38, 39] and hospitals [36] in the classification of CLABSI. In addition, this definition is influenced by the number of blood cultures performed before introducing new antimicrobials and the number of non-blood cultures and other diagnostic tests performed to characterize infectious foci responsible for secondary BSI.

Fever is non-specific and erythema at the catheter entry site is present in less than half of the cases of CRBSI [40]. Usually, when CRBSI is suspected, the common practice in the ICU is to remove the CVC and to replace it at a new site. However, only about 15–25% of CVCs so

Table 1 Definitions of infection-related catheter complications

	Definition	Comments
Catheter tip colonization	Catheter tip culture that yields ≥ 15 cfu/plate (semiquantitative), 10^2 cfu/ml (quantitative sonication), or 10^3 cfu/ml (quantitative vortexing)	Qualitative culture should no longer be used
Exit site infection	Tenderness, erythema, or induration > 2 cm at catheter exit site; may be associated with other signs and symptoms of infection, such as fever or purulent drainage at exit site, with or without concomitant bloodstream infection	Positive culture of exudate confirms the exit site infection microbiologically NB: colonization without clinical signs does not define exit site infection
Catheter-related bloodstream infection (CRBSI)	One positive blood culture obtained from peripheral vein and clinical manifestation of infection and (1) catheter tip colonization or (2) a differential time to positivity of more than 120 min and no obvious source of bloodstream infection except the catheter or (3) simultaneous quantitative cultures of blood with a ratio of > 3:1 cfu/mL of blood (catheter vs. peripheral blood); NB: Quantitative culture of the catheter exit site reflects the extraluminal contamination. Its negative predictive value is higher than 99%	Simultaneous quantitative culture from a peripheral vein and the catheter of > 3:1 ratio is rarely used NB: Note that this definition differs from the definition of CLABSI used for infection-control surveillance activities NB: the exclusion of other sources of infection results in important variability in the final classification. Purulence at the catheter exit site is clear evidence indicating the catheter is the source of infection
Central line-associated bloodstream infection (CLABSI)	One positive blood culture and clinical manifestation of infection in a patient with a catheter in place with no other source of bacteremia except the catheter	Easy to use for surveillance purposes. However, risk of overestimation of BSI incidence due to catheter infection especially in ICU and in oncological patients (see [127])
Catheter-related clinical sepsis	Clinical manifestation of infection that disappears within 48 h of catheter removal and a positive catheter tip culture and no other obvious treated source of infection	Represents 30–50% of catheter-related infections with general manifestations. Not easy to collect routinely but may need antimicrobial treatment (see text)
Catheter-related thrombophlebitis	Clinical definition: induration or erythema, warmth, and pain or tenderness along the tract of a catheterized or recently catheterized vein Alternatively, imaging evidence of vascular thrombosis and clinical manifestations concordant with location of a catheterized or recently catheterized vein	
Tunnel infection	Tenderness, erythema, and/or induration further than 2 cm from the catheter exit site, along the subcutaneous tract of a tunneled catheter (e.g., Hickman or Broviac catheter), with or without concomitant bloodstream infection	
Port infection	Infected fluid in the subcutaneous pocket, the external surface, and/or the catheter tip of a totally implanted intravascular device; often associated with tenderness, erythema, and/or induration over the pocket; spontaneous rupture and drainage, or necrosis of the overlying skin, with or without concomitant bloodstream infection	

removed indeed proved infected upon quantitative catheter tip culture [1, 27, 41–43].

Diagnostic tests performed after catheter removal

Qualitative broth culture has a high sensitivity but a very low specificity, and is unable to distinguish contamination from infection. Quantitative culture techniques have been developed and used to explore either the extraluminal surface of the catheter (semiquantitative Maki roll-plate technique) or the extra- and intraluminal surfaces via sonication or vortex wash [44–47]. Quantitative culture techniques have not been proven to be more accurate than the semiquantitative roll-plate method for short-term CVCs [48–50]. The sensitivity of catheter culture [51, 52] may be decreased by prior antimicrobials and this point should be kept in mind when interpreting negative or borderline culture results and emphasizes the need for diagnostic testing (blood and catheter cultures) before starting antimicrobials.

Diagnosis of CRBSI with catheter in place

Diagnostic techniques allowing an accurate diagnosis while keeping the catheter in place [53] are an attractive option for diagnosis unless CRBSI is suspected to be the cause of severe sepsis, in which case the catheter should be promptly removed [48].

Quantitative culture of catheter exit site A negative quantitative culture of the catheter exit site in case of suspicion of infection almost always rules out the diagnosis of CRBSI (NPV = 99.2%) and unnecessary catheter replacement, but routine surveillance cultures are not helpful [54, 55].

Simultaneous blood cultures from catheter and peripheral vein Simultaneous blood cultures, drawn through the catheter and a peripheral vein, without removal or exchange of the catheter, are an accurate means to diagnose CRBSI. Differential quantitative blood culture using the lysis centrifugation technique is cumbersome, rarely available, and is further limited by the lack of standardized cutoff points (published cutoffs vary from $\geq 3:1$ to $\geq 8:1$) [46]. The time to positivity of a blood culture is closely related to the bacterial concentration in the blood. Therefore, the differential time to positivity (DTTP) of hub-drawn blood culture as compared to peripherally drawn blood culture has been proposed as a means to diagnose CRBSI [56]. If a cutoff of 120 min is used, sensitivity, specificity, PPV, and NPV are greater than 90% [56]. This technique theoretically only explores the intraluminal route of infection, but recent papers suggest that it can be used for both short-term and long-term CRBSI diagnosis [56–58]. Unfortunately, aspiration of blood for culture, drawn

through the catheter lumen, is not possible in one-fourth of the cases primarily because of luminal occlusion [59]. Furthermore, each lumen may represent a source of infection and it has been shown that the sampling of one out of three lumens of triple-lumen catheters misses 37% of CRBSI cases [60]. The 120-min cutoff may depend on the time of growth for specific etiologic agents. For example, the 120-min cutoff is less accurate for *Candida* sp. and *S. aureus* [61]. The accuracy of the technique is based on sampling the same amount of blood from both the catheter and peripherally.

Is systemic treatment necessary in patients with positive catheter tip culture but negative blood cultures?

A review of available trials showed that only 17% of patients with positive catheter cultures had CRBSI [62]. A positive catheter tip culture in the absence of a positive blood culture was associated with only a 1.3% incidence of subsequent BSI in one ICU [63]. Therefore, the consequence of a positive catheter culture without positive blood cultures in a non-symptomatic patient is a challenge at the bedside.

The Infectious Diseases Society of America (IDSA) guidelines [48] recommend that catheter tips should not be cultured routinely, but only upon removal for suspected CRBSI. However, in the ICU, where abnormal temperature is present in more than half of the patients at the time of catheter removal and two of the four SIRS criteria are present in about 90% of patients, most catheter tips end up being cultured [43, 64]. Finally, the presence of SIRS criteria or local signs was not predictive of subsequent infections in ICU cohorts studied [63, 65–67]. Studies that have explored this topic are summarized in Table E1.

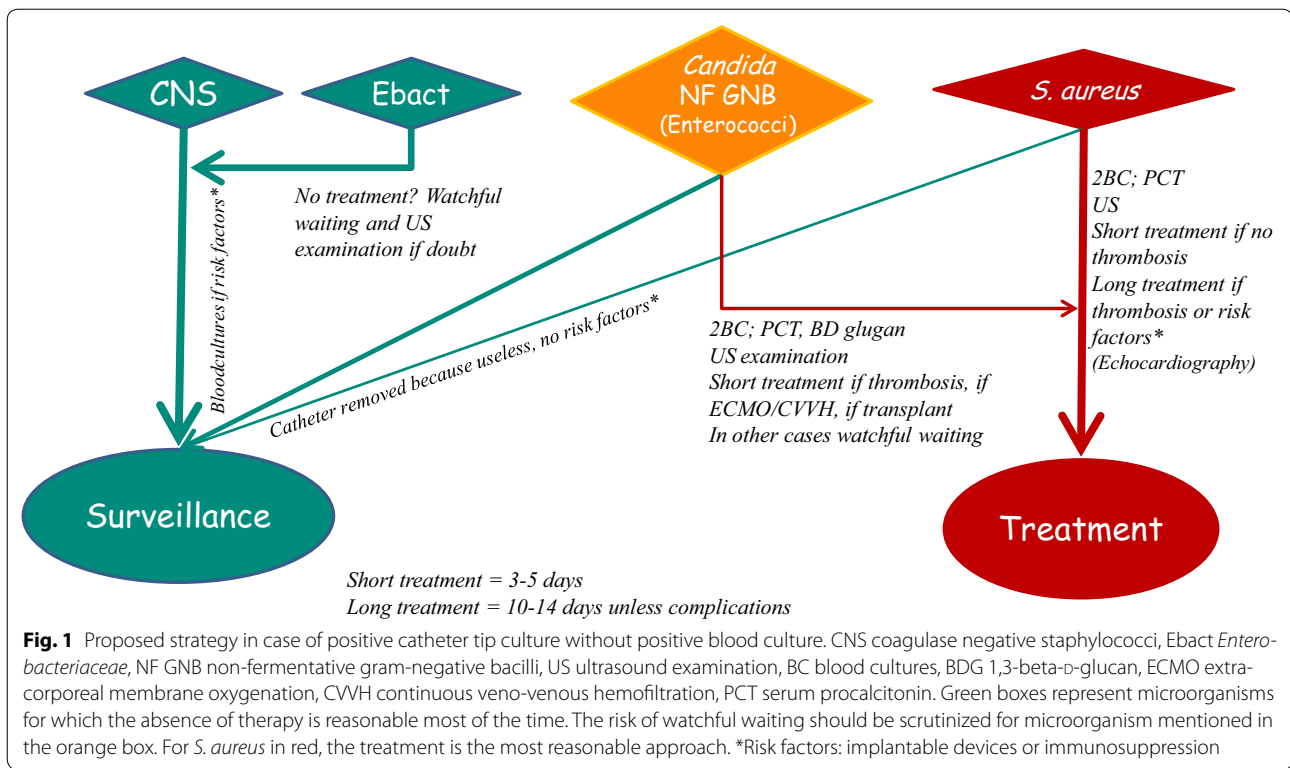
Other factors that may be considered for therapeutic decision

The decision of whether antibiotic treatment is initiated in the case of a positive catheter tip culture depends on the identified microorganism. The risk of BSI may be higher if *S. aureus* or non-fermentative gram-negative bacilli are recovered from a catheter tip (see Table E1). Other favorable factors are an immunocompromised status and thrombosis of the catheterized vein [68].

Duration of therapy is not known. A maximum of 7 days is accepted by the expert panel. A reasonable diagnostic and therapeutic strategy is proposed in Fig. 1.

Treatment of catheter-related bloodstream infections

Treatment of CRBSI usually involves initiation of empiric therapy prior to the availability of culture results with



subsequent targeted treatment based on organism identification and antimicrobial susceptibility testing results. General principles include source control (removal of an infected catheter which in turn depends on pathogen and type of catheter) and administration of high dose (intravenous) bactericidal agents with the narrowest spectrum possible. Duration of therapy is based on clinical features as well as the identified microorganism. Lock therapy and catheter salvage should not be proposed for ICU patients.

Empiric treatment

Empiric therapy (i.e., that initiated prior to availability of culture data) should be individualized to the patient's characteristics, risk factors, and local epidemiology. CRBSIs are frequently due to gram-positive organisms and, accordingly, vancomycin is the cornerstone of the empiric regimen in settings with high prevalence of MRSA [1]. Empiric coverage for gram-negative organisms, particularly for *P. aeruginosa*, should be based on clinical and epidemiological factors, such as severity of disease, known colonization or exposure to healthcare settings with increased probability of colonization, and neutropenia or hematologic malignancy [48]. In addition, previous multidrug-resistant (MDR) gram-negative infection, critical illness, neutropenia, prior antibiotic therapy, or presence of a femoral catheter are recognized risk factors for MDR gram-negative infections [69].

Where patients are colonized with an MDR, the choice of the empiric treatment regimen should be based on previous susceptibility profiles. A carbapenem or a beta-lactam with beta-lactamase inhibitor with or without an aminoglycoside is generally recommended [70, 71].

Empiric coverage for candidemia should be considered if multiple sites are colonized with *Candida* spp. or for patients with bone marrow or organ transplants, hematologic malignancy, femoral catheterization, or when patients are receiving total parenteral nutrition or prolonged administration of broad-spectrum antibiotics. Empiric treatment consists mainly of an echinocandin, whereas fluconazole may represent an option in settings without recovery of *C. glabrata* or *C. krusei* and in patients without exposure to fluconazole in the previous 3 months [48, 72]. The targeted treatment depends on the microorganisms recovered and is discussed in the electronic supplement and summarized in Table 2.

Duration of treatment

The duration of treatment depends on several factors such as the pathogen, the type of the catheter, the host, and the presence of complications (Table 3). It is mostly based on experts' opinions and old cohort studies. No strong evidence exists to support the actual recommendations.

Table 2 Proposed targeted therapy of CRBSI

Pathogen/clinical scenario	Conditions and comments	Duration of treatment ^a
Uncomplicated CRBSI		
General concept for gram-negative bacilli	Negative blood cultures following catheter removal or guidewire exchange Antibiotic therapy choice based on in vitro susceptibility, bactericidal mechanism, narrowest spectrum possible	7–14 days
General concept for gram-positive cocci excluding <i>Staphylococcus aureus</i>	Negative follow-up blood cultures following catheter removal or guidewire exchange Antibiotic therapy choice based on in vitro susceptibility, bactericidal mechanism, narrowest spectrum possible No clinical evidence of complicated infection, risk factors for endocarditis, or hardware infection	≤ 7 days for low virulence organisms and 10–14 days otherwise
<i>Staphylococcus aureus</i>	Requires ALL of the following: Negative follow-up blood cultures following catheter removal or guidewire exchange Anti-staphylococcal penicillin or first-generation cephalosporin for MSSA; vancomycin or daptomycin for MRSA If MRSA, MIC must be ≤ 1.0 g/L Prompt response to institution of therapy No indwelling devices (such as prosthetic heart valves or vascular grafts) are present There is no clinical evidence of metastatic staphylococcal infection Infective endocarditis has been excluded with echocardiography	14 days
<i>Candida</i> sp.	Negative follow-up blood cultures following catheter removal or guidewire exchange Antifungal therapy with echinocandin or fluconazole, choice based on in vitro susceptibility Ophthalmologic exam negative for fungus if echinocandin to be used	14 days
All organisms if catheter removal is not possible	Salvage treatment with antibiotic lock and systemic treatment Low success rates; exceptionally used when catheter exchange/removal is not possible in patients without sepsis or shock	4 weeks
(<i>Enterococcus</i> spp.)	Shorter treatment may be applied for enterococcal CRBSIs in both the setting of catheter removal and salvage, if complicated infection is excluded <i>E. faecalis</i> requires thorough investigation for complicated infection, similarly to <i>S. aureus</i>	7–14 days
Coagulase-negative staphylococci	After catheter removal, in the absence of risk cardiac factors, short treatment is feasible	5–7 days
10–14 days		
Complicated CRBSI		
General concept all organisms	Persistent bacteremia following catheter removal and receipt of effective antimicrobial therapy Initiate search for complications (i.e., echocardiogram) and metastatic foci	4–6 weeks
General concept all organisms	Complications related to bacteremia (i.e., suppurative thrombophlebitis, endocarditis, osteomyelitis, metastatic infection)	4–6 weeks plus treatment adjusted to manage the complication

Table 2 continued

Pathogen/clinical scenario	Conditions and comments	Duration of treatment ^a
<i>Staphylococcus aureus</i>	Source control of metastatic complications (i.e., abscess drainage, tube thoracostomy, arthroscopy, surgical debridement) MSSA anti-staphylococcal penicillin or first-generation cephalosporin (contraindicated if CNS involvement) MRSA vancomycin (caution MIC \geq 1.5 g/L) or daptomycin (caution lung involvement) MRSA poor response to first-line therapy switch to ceftaroline or use combination therapies	4–6 weeks plus treatment adjusted to manage the complication
<i>Candida</i> sp.	Endocarditis requires surgical evaluation CNS/eye involvement contraindicates echinocandin; use amphotericin/5-FU followed by fluconazole if susceptible	4–6 weeks plus treatment adjusted to manage the complication

MRSA methicillin-resistant *Staphylococcus aureus*, MSSA methicillin-susceptible *Staphylococcus aureus*, MIC minimum inhibitory concentration, CNS central nervous system

^a Proposed duration of therapy referred to old cohort studies or experts' recommendations. Shorter duration of therapy in case of uncomplicated bloodstream infections should be tested

Essential preventive measures critical care specialists should offer (Box 2)

Although attention to catheter insertion and maintenance is of utmost importance in the prevention of CRBSI, it must be kept in mind that the only sure way to prevent CRBSI, as well as other catheter-related complications, is to avoid a catheter. An increasing body of literature indicates the safety of peripheral intravenous lines for low-dose, short-term vasopressor infusions. To this end, minimization of catheter use or alternatives are an important aspect of CRBSI prevention.

Optimal route for arterial and venous access

The femoral route for central venous access is considered contaminated and prone to thrombosis [73]. Although the subclavian site for vein access in ICU patients has proven superior with regard to infectious and thrombotic complications compared to femoral access in a randomized study [73], the subclavian site was associated with mechanical complications in 17% of patients [42, 73]. In a pragmatic multicenter, randomized trial of 2532 central venous catheterizations, subclavian, internal jugular, and femoral access routes have been compared for the risk of mechanical, thrombosis, and infectious complications. This study showed that both internal jugular and femoral access increased the risk of CRBSI as compared with the subclavian site [42]. This study also showed that the time to intravascular complications differed between sites ($p=0.02$), and the subclavian site proved safer than the jugular site [hazard ratio (HR) 2.5, 95% confidence interval (CI) 1.1–5.6] or the femoral site (HR 3.1, 95% CI 1.4–7.1), particularly for dwell time > 5 days. The rate of complications was similar between internal jugular and femoral routes. Therefore, the optimal route for venous

access depends of the expected duration of catheterization and the type of complication most concerning for an individual patient: immediate mechanical versus cumulative intravascular risks (Fig. 2).

Regarding arterial access, a meta-analysis of 59 observational studies [74] found that the risk of AC infection was higher for femoral site compared with radial site access (relative risk 1.93, 95% CI 1.32–2.84; $p=0.001$).

Ultrasound for insertion

Systematic reviews have shown that the use of ultrasound, compared to anatomic landmarks, is associated with a 10–80% greater procedural success, lower number of attempts, shorter time to catheterize the vessel, and a 50% reduction of mechanical complications especially for internal jugular and subclavian access [75, 76]. Ultrasound also allows for prompt recognition of complications [77], such as pneumothorax. Similarly, the use of ultrasound improves insertion success, reduces access time, and improves safety when placing PICCs [78], or arterial and peripheral venous catheters, particularly when difficult vascular access is anticipated.

Indeed, access to appropriate equipment is necessary [79]. A recent review of the literature and summary recommendations suggests combining anatomic landmarks and ultrasound to improve safety. Online training for use of ultrasound, while growing, must be paired with real-time coaching in order to increase success and ensure adoption.

Cutaneous antisepsis

Skin antisepsis is one of the most important preventive measures. Numerous studies have been conducted to identify the best antiseptic solution for skin

Table 3 Elements of bundle of catheter care and maintenance (adapted from https://www.jointcommission.org/assets/1/6/CLABSI_Toolkit_Tool_3-18_CVC_Insertion_Bundles.pdf)

Organization	Insertion bundle elements	Maintenance bundle elements
Michigan Keystone Intensive Care Unit Project	<p>Hand hygiene before catheter insertion</p> <p>Use of full barrier precautions</p> <p>Chlorhexidine skin preparation</p> <p>Avoidance of the femoral vein for inserting CVCs (except in children)</p> <p>Prompt removal of CVCs</p>	
Institute for Healthcare Improvement 5 Million Lives Campaign	<p>Hand hygiene</p> <p>Maximal barrier precautions upon insertion</p> <p>Chlorhexidine skin antiseptics</p> <p>Optimal catheter site selection, avoid femoral vein for CVC insertion in adults</p> <p>Daily review of line necessity; prompt removal of unnecessary lines</p>	<p>Daily review of line necessity, with prompt removal of unnecessary lines</p> <p>Aseptic lumen access</p> <p>Catheter site and tubing care</p>
Canadian Patient Safety Institute Safer Healthcare Now!	<p>Hand hygiene</p> <p>Maximal barrier precautions</p> <p>Chlorhexidine skin antiseptics</p> <p>Optimal catheter type and site selection</p> <p>In adults, subclavian vein insertion preferred; avoid femoral vein insertion</p> <p>In children, insertion site choice individualized</p>	
United Kingdom Department of Health High Impact Intervention Central venous catheter care bundle	<p>Catheter type</p> <p>Use single-lumen catheter unless otherwise indicated</p> <p>Use antimicrobial-impregnated catheter if estimated duration of 1–3 weeks and high risk of catheter-related bloodstream infection</p> <p>Insertion site</p> <p>Subclavian or internal jugular vein</p> <p>Personal protective equipment</p> <p>Maximal sterile barriers during insertion (sterile gown, sterile gloves, large sterile drape)</p> <p>Eye and full body protection</p> <p>Skin preparation</p> <p>2% chlorhexidine gluconate in 70% isopropyl alcohol is used; allow to dry for at least 30 s</p> <p>Hand hygiene</p> <p>Hand hygiene before and after each episode of patient contact</p> <p>Dressing</p> <p>Sterile, transparent, semipermeable dressing</p> <p>Safe disposal of sharps</p> <p>Sharps are disposed of safely at the point of care</p> <p>Documentation</p> <p>Document details of insertion in the medical record</p>	<p>Hand hygiene</p> <p>Hand hygiene immediately before and after each episode of patient contact</p> <p>Site inspection</p> <p>Insertion site inspected daily for signs of infection; record finding in medical record</p> <p>Dressing</p> <p>Intact, dry, adherent transparent dressing is present</p> <p>Clean insertion site with 2% chlorhexidine gluconate in 70% isopropyl alcohol prior to dressing changes</p> <p>Catheter injection ports</p> <p>Cover injection ports with caps or valved connectors</p> <p>Catheter access</p> <p>Use aseptic technique to access the line</p> <p>Clean ports and hubs with 2% chlorhexidine gluconate in 70% isopropyl alcohol prior to accessing catheters</p> <p>Administration set replacement</p> <p>Replace immediately after administration of blood or blood products</p> <p>Replace after 24 h after administration of lipid-containing total parenteral nutrition</p> <p>Replace within 72 h of all other fluid sets</p> <p>Catheter replacement</p> <p>Catheter is removed if no longer required or decision not to remove is recorded</p> <p>Details of removal are documented in the medical record</p>
Health Protection Scotland: Preventing infections when inserting and maintaining a CVC	<p>Perform surgical scrub</p> <p>Use maximal sterile barrier precautions (headwear, mask, sterile gown, and sterile gloves)</p> <p>Apply a sterile body drape to the patient</p> <p>Aseptic technique is maintained throughout catheter insertion</p> <p>2% chlorhexidine in 70% isopropyl alcohol is used for insertion site skin preparation and allowed to dry before catheter insertion</p> <p>Use the subclavian site is used if possible, or internal jugular vein; femoral vein insertion should be avoided whenever possible</p> <p>Use a sterile transparent, semipermeable dressing</p>	<p>Need for the CVC is reviewed and recorded on a daily basis</p> <p>CVC dressing is intact</p> <p>CVC dressing has been changed in the last 7 days</p> <p>2% chlorhexidine gluconate in 70% isopropyl alcohol is used for cleaning insertion sites during dressing changes</p> <p>Hand hygiene is performed immediately before accessing the line or site</p> <p>Use an antiseptic containing 70% isopropyl alcohol for at least 15 s to clean the access hub prior to accessing</p>

	Insertion Success	Mechanical*	Thrombosis	Infection
Femoral	Good	Good	Poor	Average
Jugular	Good	Average	Poor	Average
Subclavian	Poor	Poor	Good	Good

*Risk of major mechanical complications. This risk is significantly lower for ultrasound-guided jugular insertion ([75])




Good	
Average	
Poor	

Fig. 2 Specific advantages and attendant risks of each central venous site in the ICU. *Risk of major mechanical complications. This risk is significantly lower for ultrasound-guided jugular insertion [75]

decontamination and their main findings can be summarized as follows [6, 41, 80]: (1) application of sterile 2% (w/v) alcoholic chlorhexidine gluconate (CHG) to decontaminate the skin prior to insertion of a vascular catheter represents standard of care; (2) no cleansing of the skin with soap or detergent is necessary unless the skin is obviously contaminated; (3) neither aqueous nor alcoholic povidone–iodine should be used as a first-line agent for skin decontamination.

Adequate skin decontamination also requires correct application technique, including the dose for the skin surface area and allowing adequate drying time. The optimal modality of antiseptic application remains controversial [81]. Application of the antiseptic either using applicators or sterile gauze handled with a pincer may increase antiseptic diffusion into the deeper layers of skin while keeping the hands of the operator away to reduce the risk of contamination. Single-use vials containing sterilized antiseptic further reduce the risk of contaminated solutions from multi-use bottles but may increase costs. Although CHG is the most effective disinfectant, it is associated with more cutaneous skin reactions [41, 82]. Although rare, severe allergy and anaphylaxis to CHG has also been reported. Given the widespread use of CHG in medicine, the development of CHG resistance and cross-resistance to clinically relevant antibiotics has become a concern. To date, decreased microbial susceptibility to CHG (tolerance), measured with increased minimum bactericidal concentration (MBC), has been observed [83] and is primarily due to the presence of multidrug efflux pumps. However, the clinical impact of this is uncertain as the concentration of CHG in clinical use still far exceeds the MBC. However, CHG tolerance has been associated with MRSA decolonization protocol failure [84]. Ubiquitous use of CHG, including in body washes, oral care, and decontamination of medical devices, however, warrants closer monitoring for emergence of resistant strains to

CHG and cross-resistance to antibiotics [85]. Developing the armamentarium of new effective antiseptics should therefore be a priority moving forwards.

Chlorhexidine bathing

A growing body of literature indicates that routine patient washing with chlorhexidine or universal decolonization protocols result in CLABSI reduction [86–88]. A recent meta-analysis of available randomized controlled trials (RCTs) suggests that the intervention is mainly active on gram-positive commensals [89].

Impregnated materials

A wide variety of antimicrobial-impregnated devices, designed to prevent CRBSI, have been introduced into clinical use, including impregnated CVCs, antimicrobial dressings, coated needleless connectors, and passive port protectors. The use of these devices should be proposed when a continuous quality improvement program failed to reach its objective [85].

CHG dressings

Both CHG-impregnated sponges and CHG-gel dressings are associated with a 60% decrease in the risk of arterial and central venous catheter infections including CRBSIs [43, 64]. CHG-containing dressings have demonstrated efficacy in reducing the risk of CRBSI in ICU patients [90], although these are associated with a 1% risk of contact dermatitis in adults.

Implementation of CHG dressings into clinical areas therefore needs to be considered, especially in adult patients when the risk of infection is high despite the use of appropriate bundles of catheter care.

Antimicrobial coated or impregnated CVCs

A meta-analysis of five RCTs evaluating CHG–silver sulfadiazine-impregnated catheters incorporated into

both the internal and the external surfaces has shown to halve the risk of CRBSI [OR 0.51 (0.26–1.00)] [91]. However, this analysis found significant heterogeneity between studies. Catheters impregnated intraluminally and extraluminally with minocycline–rifampin reduce the risk of CRBSI as compared to polyurethane catheters and to externally coated chlorhexidine–silver sulfadiazine-impregnated catheters (OR 0.23, 95% CI 0.14–0.40) [92]. Their use decreases the risk of CRBSI as compared to non-impregnated controls [5 studies in ICU, OR 0.26 (0.15–0.47)] [91]. However, many of the studies were performed in the era before infection preventive bundles were routine and whether impregnated catheters are cost-effective in such settings is not known. Although the emergence of antimicrobial resistance is of concern, particularly with the minocycline–rifampin-coated catheter, this was not observed in controlled trials and in a large monocenter cohort (9200 CVCs/500,000 CVC days) [93]. Nevertheless, rifampin and minocycline are sometimes used as therapy in severe infections due to *Acinetobacter baumannii* and MRSA and this should be considered when making institutional decisions regarding the introduction of a coated or impregnated CVC.

Other catheters impregnated with Oligon, silver zeolite, carbon, and platinum have been tested but have not proven their efficacy [91].

Catheter lock for preventing thrombotic and infectious complications

The antimicrobial lock therapy (ALT) consists in instilling an antimicrobial solution into a catheter lumen for a certain period of time to achieve a high local antimicrobial concentration, thus overcoming sessile bacteria and fungi resistance and preventing or treating CRBSI. ALT is intended for catheters not used continuously and targets endoluminal catheter infections. Therefore, most available data evaluating this strategy comes from long-term devices. In these patients, lock solutions with antibiotics (such as vancomycin or gentamicin) mixed in heparin to obtain antimicrobial–anticoagulant lock solutions can reduce long-term CRBSI [94] but may lead to the emergence of antibiotic-resistant organisms [95] and could lead to systemic toxicity due to lock solution spillage from catheters.

The use of fibrinolytics in lock solutions reduced tunneled dialysis catheter infection and dysfunction [96]. Cationic chelator-based solutions combined with anti-infectious agents not used for parenteral administration have been successfully used for preventing long-term catheter infections. In contrast, lock solutions with citrate alone, taurolidine citrate, or concentrated ethanol have yielded conflicting results on their efficacy

for CRBSI prevention or maintaining catheter patency [97–100].

The extrapolation of these studies to short-term catheters inserted in critically ill patients is questionable because of differences in catheter type, use, and accessibility for ALT. Studies on ALT in ICU patients are scarce and addressed mainly hemodialysis catheters, since their lumens are idle and available for ALT only between renal replacement therapy sessions [25–27]. The results of a large study comparing interdialytic lock with unfractionated heparin and 4% citrate are not yet available [101]. Today, the routine use of prophylactic ALT for short-term catheter cannot be recommended.

Relationship between thrombosis and infection

Some clinical data [68, 102] suggest a close relationship between catheter thrombosis and infection, especially in the superior vena caval territory [73, 103]. The diagnosis of catheter thrombosis should therefore increase suspicion for catheter-related infection.

Thrombosis risk is particularly pronounced for PICCs as they often migrate from the cavoatrial junction [104] and are inserted into smaller veins.

Anticoagulant and antithrombotic agents have been used to prevent and manage thrombotic complications of central venous catheters. Several RCTs conducted in ICU patients have yielded conflicting results on the impact of heparin flushing to maintain line patency and there is insufficient evidence to recommend this practice [105]. There is a lack of clinical trial data to support the specific use of systemic anticoagulant therapy to prevent catheter-related thrombosis in critically ill adults. Although an individualized risk–benefit evaluation is required, patients with cancer, inherited or acquired thrombophilia, or recurrent thrombosis of unknown etiology may benefit from systemic anticoagulation to prevent catheter-related complications [106]. It is not uncommon for catheter lumens to become occluded. Where not contraindicated (e.g., infection), the use of fibrinolytic therapies can safely restore patency with associated reduction in cost [107, 108].

Essential components of bundles of care

Insertion and maintenance bundles have been developed to prevent microbial colonization of central venous catheters, thereby mitigating risk of CRBSI. Implementation of such bundles has been demonstrated to reduce the incidence of CLABSI by 52% (95% CI 32–66%) on the basis of high-quality studies [109]. Examples of some bundles are noted in Table 3. Although nearly half of US ICUs reported having a CLABSI prevention bundle policy in a 2011 paper, only 38% of institutions that monitored bundle implementation reported full bundle

compliance [110]. Monitoring adherence to the process of care is key in obtaining positive results from bundle implementation. Importantly, the full impact and sustainability of bundles at the institutional level can only be achieved once a safety culture is adopted by the organization [111, 112].

Role of nursing care

The IV catheter care bundle includes a best practice checklist for catheter insertion, appropriate post-insertion catheter care, and prompt removal of the catheter when no longer required for patient care [113–115]. Nursing staff have an important role during these processes, but any personnel involved with the care of intravascular catheters should be trained and competent. The checklist is a tool to ensure the catheter insertion procedure is followed correctly, and it empowers healthcare workers to challenge and halt the procedure if this is not followed correctly. Appropriate post-insertion catheter care includes the following [116]: maintain a clean and dry catheter site and ensure that the dressing is intact; cleanse the skin with an antiseptic agent and allow it to dry when the dressing is replaced; unless clinically indicated, replace sterile, transparent, semipermeable polyurethane dressings every 7 days [43] or daily if a gauze and tape dressing is used because of bleeding or excessive perspiration. Frequent dressing disruption may increase the risk of catheter-related infections over 12-fold in comparison to CVC without disruptions, especially with CVC inserted into jugular femoral veins [117]. Aseptic technique should be utilized when accessing or manipulating the catheter. Access devices or ports and infusion sets should be replaced as per local guidelines and manufacturers' instructions. Although needle-free access devices may reduce the risk of infection, compliance with appropriate cleaning of these access devices is of paramount importance in reducing the risk of infection.

Knowledge, education, behavioral interventions: what is useful?

The most important intervention that reduced the incidence of CLABSI in the past decade was practice change [118]. The adoption of best practice strategies reduced CLABSI rates by more than 50%. Education and training are at the heart of any behavior change strategy. However, rather than the evidence base, individual experience and personal perceptions are the main drivers for practice [119]. Thus, isolated knowledge delivery by ex cathedra teaching or handing out written protocols is not sufficient to change behavior. A systematic review on organization and structure of infection control identified three key components addressing knowledge, education, and behavioral interventions directly or indirectly:

(1) education and training involves frontline staff and is team- and task-oriented; (2) guidelines should be used in combination with practical education and training; and (3) implementation follows a multimodal strategy, including tools such as bundles and checklists, developed by multidisciplinary teams, taking into account local conditions [109, 120]. Behavioral change interventions pass within an organizational culture [121]. Multimodal strategies improve the likelihood of implementation success because they take into account the local context. A multimodal strategy is the combination of best practice procedures and technology, promoted by different "modes" such as lectures, visual cues, simulations, bedside training, knowledge tests, or other imaginative ideas to raise interest and awareness of healthcare professionals aimed at changing behavior. Education and training should be both hands-on at the bedside and by use of skills laboratories. Training should be a peer-to-peer action; involving frontline staff in the process of planning improves acceptance and allows healthcare professionals to identify with a behavioral change program.

Bundles per se are not multimodal strategies but mnemonic milestones in complex procedures, originally established as an implementation tool. Bundled and non-bundled strategies were both effective in CLABSI reduction in a recent systematic review [122]. However, defining memorable and measurable milestones help in the planning, execution, and evaluation of behavioral change interventions [118, 123, 124].

Unanswered questions and roadmap for future investigations

Pathophysiology–epidemiology

- Not only infectious but also non-infectious complications may lead to severe adverse events. Large multicenter epidemiological studies exploring the risks of infectious and non-infectious complications and their severity in ICU patients are lacking.
- It is also important to develop outcome indicators combining infectious and non-infectious complications of catheters in ICU.
- More research is needed to understand thrombosis formation, the dynamics of catheter tip colonization and the interplay between them, during the course of central venous catheterization. Specific predictive markers of catheter thrombosis should also be developed and tested.

Diagnostic strategies

- The value of early diagnostic techniques aimed to avoid unnecessary catheter removal should be investigated.

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- The utility of molecular techniques in the diagnosis of CRBSI is not known and requires careful investigations.

Therapeutic strategies

- The benefit of an antibiotic therapy in patients with positive catheter culture without blood culture should be investigated (especially for non-staphylococcal isolates).
- The optimized duration of therapy for low virulence organisms following catheter removal is not known either in CRBSI or clinical sepsis. Comparison between very short antimicrobial therapy (1 dose in 48–72 h) versus 7–10 days is needed. Short- and long-term strategies should integrate both the nature of the microorganism and the underlying conditions.
- The balance between benefits and risks of anticoagulant therapy in case of asymptomatic catheter thrombosis should be studied in further interventional trials.

Prevention and nursing care

- Is routine insertion of CVC indicated in patients with low dose of vasopressor and adequate peripheral IV access?
- The role of PICCs compared to CVC in ICU patients requires further study and should combine infectious and non-infectious complications including thrombosis and infections. The respective advantages of femoral versus radial arterial catheters in terms of both infectious and non-infectious complications remain limited and require further interventional trials.
- Adequate securement of the catheter is important in preventing mechanical and infectious complications. Although sutures are widely used for intravascular catheter securement, suture colonization may increase the risk of infection. The appropriate securement of intravascular catheters in critically ill patients requires further evidence.
- Alcoholic 2% (w/v) CHG is currently recommended for skin antisepsis; the ideal concentration as well as the concentration of alcohol in the antiseptic solution requires further evidence. For example, although high concentration of alcohol has a rapid antimicrobial action and drying time may be clinically appropriate, lower concentration of alcohol may improve the skin permeation of the antiseptic agent. The value of successive application of povidone–iodine and chlorhexidine has been suggested [125, 126] in clinical studies and requires further investigation.
- New antiseptic solutions should be tested.
- The benefit of CHG dressings to prevent infection for hemodialysis and ECMO catheters needs to be tested in clinical trials.

- The added value of antimicrobial-coated catheters in the context of low CRBSI rates should be evaluated.
- The use of needle-free access devices or use of open ports/hubs to access intravascular catheters requires further evidence, taking into account the compliance with the appropriate decontamination of these access points. Furthermore, the method of cleaning is open for debate, whether alcohol alone or with another antiseptic agent is required and the delivery method of the antiseptic agent to achieve the best efficacy.
- There is a lack of clinical trial data to support the specific use of systemic anticoagulant therapies or thrombolytics to prevent catheter-related thrombosis in critically ill adults.

Box 1: Key messages for diagnosis and treatment of catheter-related complications in critically ill patients

Mechanical complications including malfunction, occlusion, and thrombosis are more frequent than infectious complications.

Ultrasound guidance should always be used for inserting internal jugular catheters.

Catheter-related bloodstream infection (CRBSI) is a clinical definition that should be clearly differentiated from central line-associated bloodstream infection (CLABSI) which is mainly used for epidemiological purposes.

Empiric antimicrobial treatment of CRBSI should target *S. aureus*. Empiric therapy while awaiting culture confirmation for other etiologies should be based on clinical variables, patients risk factors, and previous colonization status.

Catheter removal is the main therapeutic intervention and always recommended, especially in the case of sepsis or shock.

Treatment of patients with clinical sepsis and with a positive catheter tip culture but without positive blood culture may be beneficial when *S. aureus* is recovered, and to a lesser extent for gram-negative non-fermentative bacteria. Data are insufficient to recommend treatment of other etiologies in this case.

The duration of antimicrobial therapy of uncomplicated CRBSI is controversial and, depending on the causative pathogen, may not need to exceed 7–10 days following catheter removal.

Positive blood culture after 72 h of therapy indicates complicated CRBSI. Endocarditis and thrombophlebitis are the most common causes of failure. *S. aureus* CRBSI requires a high index of suspicion for endocarditis and metastatic infections.

Symptomatic catheter thrombosis requires catheter removal and anticoagulant therapy. Appropriate therapy

of asymptomatic catheter thrombosis in critically ill patients is undefined.

Box 2: Key elements of prevention of catheter-related infection

Hand hygiene.

Strict aseptic surgical condition at catheter insertion.

Preferential use of subclavian venous and radial arterial insertion sites.

Avoidance of insertion and immediate removal of unnecessary catheters.

Immediate replacement of soiled, moistened, or detached catheter dressings.

Use of alcoholic 2% chlorhexidine gluconate for skin antisepsis and catheter care.

Institution of a continuous quality improvement program.

Audit and feedback of the process of care, infection rates, and periodic re-education of providers.

The use of CHG-impregnated dressings or antimicrobial-impregnated catheters should be limited to situations where a continuous quality improvement program failed.

Electronic supplementary material

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Compliance with ethical standards

Conflicts of interest

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