Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica

LOS PROFESIONALES DEL ENFERMO CRÍTICO

Diagnosis and treatment of catheter related bloodstream infection. Clinical Guidelines of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC) and Spanish Society of Intensive Care Medicine and Coronary Units (SEMICYUC)

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1. Introduction. Justification and aims.

The use of intravascular devices to administer intravenous fluids, medications, blood products, and parenteral nutrition, to monitor hemodynamic status, and to provide hemodialysis, has become an essential component of modern medicine. According to national data of the study of nosocomial infections prevalence in Spain (i.e., EPINE), it is considered that about 70% of patients admitted to our hospitals are carriers of one of these devices at some point during their stay [1]. Local or systemic infection is one of the main associated complication [2]. Catheter-*r*elated infections incidence varies considerably depending on type and intended use, the insertion site, the experience and education of the individual who places the catheter, the frequency with which the catheter is accessed, the duration of catheter placement, the characteristics of the patient, and the use of proven preventative strategies. Catheter-related bloodstream infections (CRBSI) are among the most frequent infections acquired in the hospital. Currently it is estimated that between 15 and 30% of all nosocomial bacteremias are catheter-related [3]. CRBSI have significant associated morbidity, increasing hospital cost [4] estimated approximately in 18,000 euros per episode, and the length of stay [5]. Attributable mortality ranges between 12 and 25% [6]. Over recent years, there has been a remarkable growth of knowledge about epidemiology, the most appropriate methodology for diagnosis, management and, in the preventive strategies. The vast amount of information accumulated and the inherent complexity of this type of infection make it necessary to sort and analyze the available information. On the other hand, there are few current guidelines available on this topic. The last Spanish catheter- related infections guidelines were published in 2004 [7]. The aim of this new guide is to update recommendations for diagnosis and management of catheter related bloodstream infections. This document only targets microbiological diagnosis and antimicrobial therapy; therefore, other aspects of infection management or prevention are excluded. Only adult patients with these infections are covered.

2. Methods

The two participant Societies (Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica and Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias) nominated three coordinators of this project (FC, JGM and JLdP: a microbiologist, an intensivist, and an infectious disease physician). This coordinator group chose the rest of the members of the panel incorporating microbiologists, intensivists, and infectious disease physicians. The Scientific Committee of both Societies approved their proposal. The present Statement has been written following the SEIMC guidelines for consensus statements (www.seimc.org), as well as the recommendations of the Agree Collaboration (www.agreecollaboration.org) on evaluation of the methodological quality of clinical practice guidelines. Strength and quality of recommendations were graded in accordance with the ESCMID guidelines (Table 1).

The coordinator group identified 39 key topics that were formulated following the PICO format, which defines the population, intervention, comparator, and outcome of interest. The scientific Committees of both societies approved these key questions that were distributed for its development to the different members of the panel (2 or 3 each one). With the parts sent by each participant, the coordinator group wrote the first draft, which was sent to the panel for their critical review. Before its final approval, the document was published in the intranet of both Societies and open to suggestions and comments by any of their members. All the authors and coordinators of the Statement have agreed the contents of the document and the final recommendations.

3. Catheter-related bloodstream infection diagnosis (Table 2)

3.1. General aspects

When should catheter-related bloodstream infection be suspected?

CRBSI should be clinically suspected if fever, chills or hypotension and signs of infection at the insertion site proximally in the canalized peripheral vein or in the skin overlying the subcutaneous tunnel in tunneled catheters [8]. Several circumstances should arise the suspicion that a given episode of bacteremia is catheter-related. The most evident situation is a patient with local signs of infection at the catheter. Also, bloodstream infections are often caused by microorganisms that usually colonize or infect the skin such as *Staphylococcus aureus*, coagulase-negative staphylococci, *Corynebacterium spp*, *Bacillus spp*, *Candida spp*, among others. In addition, CRBSI should be considered in the setting of persistent or recurrent blood cultures for a given microorganism [8]. Clinical suspicion of CRBSI should also arise in patients with intravenous catheters who have focal infections known to result from the hematogenous spread of microorganisms (i.e., septic emboli). This is the case in endocarditis or suppurative thrombophlebitis, particularly if caused by *Staphylococcus* spp. or *Candida* spp. in patients with a venous catheter. Septic emboli secondary to a CRBSI are more frequently found in lungs [9], but virtually any organ can be affected by a septic metastasis arising from an infected catheter [10,11].

Recommendations:

- CRBSI should be suspected in patients with intravenous catheters and fever, chills and other signs of sepsis, even in the absence of local signs of infection, especially if no alternative source is identified (A-III).
- Clinical suspicion of CRBSI should also arise in patients with intravenous catheters who have metastatic infections resulting from hematogenous spread of microorganisms (i.e., septic emboli) (A-III).
- Persistent or recurrent bacteremia caused by microorganisms that usually colonize or infect the skin in patients with intravenous catheters should lead to the suspicion of CRBSI (A-III).

How is a complicated catheter-related bloodstream infection defined?

There are several factors associated with worse outcomes in patients with CRBSI. Identifying these risk factors can help in the management of those patients. There is no a universally accepted definition of complicated CRBSI. Endocarditis is one of the main complications associated with CRBSI that requires prolonged therapy and that mandates catheter removal. The presence of suppurative thrombophlebitis makes a CRBSI complicated. Metastatic foci of infection, usually with the need of prolonged therapy and catheter removal. Local complications, such as tunnel infection or port abscess, even in the absence of septic thrombophlebitis, need catheter removal and, thus make a CRBSI to be complicated [10,11] Systemic severity (septic shock) in patients with suspected CRBSI is another circumstance that should lead to prompt catheter removal. Non-resolving fever or bacteremia (≥72 hours) should lead to a detailed reassessment of the patient ruling out local or distant infectious complications and so, should be considered as a complicated CRBSI. Significantly immunocompromised hosts with CRBSI should be closely monitored for treatment failure.

Recommendations:

- Patients with CRBSI with endocarditis, suppurated thrombophlebitis, septic metastasis, extraluminal infections, septic shock, non-resolving CRBSI, or immunocompromised should be categorized as complicated CRBSI (A-III).

3.2. Diagnosis without catheter withdrawal (conservative diagnosis)

How should blood cultures be taken?

Because the aim of blood cultures is to detect a true bacteremia and avoid contamination leading to unnecessary treatment, a proper diagnostic methodology is needed. This is particularly important when catheter-related bacteremia is suspected, because the common etiologic agents are also the most frequent contaminants.

Currently, conventional blood cultures are performed using commercial systems with automated detection of growth. These systems consist of an

aerobic and an anaerobic bottle, considered one blood culture set. Some studies showed a sensitivity of <80% for one blood culture set, and >99% for 3 or more culture sets [12–14]. In order to achieve optimal detection of bacteremia, the volume of blood is the essential factor. Therefore, Clinical and Laboratory Standards Institute (CLSI) recommends that at least 20 ml be inoculated in 2 blood culture sets, taken from different venipunctures sites [15] .

Blood must be obtained using an aseptic methodology to reduce the risk of contamination [16–18] to <3 % of all blood cultures[19], considered to be the acceptable range. Venipunctures must be performed after disinfection of the skin. The three key factors when choosing antiseptics are antimicrobial spectrum, method of application, and duration of antimicrobial effect. The most commonly used antiseptics are alcohol-, chlorhexidine-, and iodine-based products [20–24]. A recent meta-analysis of 6 randomized control trials concluded that: 1) overall, alcoholic products appear to be superior to non-alcoholic solutions, 2) alcoholic chlorhexidine solutions showed significant reduction in contaminations compared with aqueous povidone-iodine [23]. The most widely studied alcoholic chlorhexidine gluconate concentration is 2%. On the other hand, a recent study showed that the choice of antiseptic agent did not impact contamination rates when blood cultures were obtained by a phlebotomy team. The use of proper technique is perhaps the single most important aspect, including time to performance and allowing adequate time for the disinfecting solution to exert its antimicrobial effect. Alcoholic chlorhexidine products have a 30-second drying requeriments, whereas povidone iodine preparations require 1.5-2 minutes. No studies have evaluated the effect of disinfection of catheter access hubs before blood samples are drawn[16], but it appears to be a rational intervention aimed at minimizing risk of contamination.

The timing of obtaining the blood cultures may vary. Although most blood culture systems contain different methods to minimize the effect of antibiotics [25,26], if possible, samples must be obtained before antibiotic therapy is started [16,25–27]. Blood cultures obtained from intravascular catheters are associated with higher sensitivity and negative predictive values [17]. In patients with suspected CRBSI two sets of blood cultures should be taken, one from a peripheral vein and the other from the catheter hub. For multiple lumen venous catheters, several studies suggest that blood cultures be drawn from all lumens (i.e., same

volume from each lumen) to establish a diagnosis of CRBSI. Eliminating ≥1 lumen blood cultures is associated with a considerable number of missed CRBSI episodes [28–30].

Once obtained, blood must be inoculated immediately in the blood culture bottles, these bottles should be appropriately marked (peripheral vein, catheter, etc.), and incubated immediately and simultaneously in the automated machine in order to perform an interpretation based on the time to positivity of each blood culture set. Because the rubber caps are not sterile, these are usually disinfected with an alcoholic solution, which must be dried before inoculation. Because the incidence of true anaerobic bacteremia is low [31], it may be preferable to inoculate first the aerobic bottle with the optimal volume of blood, and secondly the anaerobic bottle with the remaining volume.

Recommendation:

- Obtain blood cultures using aseptic methodology prior to the initiation of antimicrobial therapy (A-I)
- Skin preparation for obtaining percutaneously drawn blood samples should be performed with proper techniques, including time to perform the procedure and leaving adequate time for efficacy of disinfecting solution (A-I). Alcohol-containing products are associated with low rates of contamination. Alcoholic chlorhexidine solutions reduce blood cultures contamination more efficiently than aqueous povidone-iodine (A-I).
- In patients with suspected CRBSI, two pairs of blood cultures should be drawn, one from a peripheral vein and the other from the catheter (A-I).
- For multiple lumen venous catheters samples for blood culture should be obtained from all lumina (A-II).

How should conventional blood cultures be interpreted?

Identification of the isolated microorganism is considered crucial for the interpretation of the significance of the result. *Propionibacterium* spp., *Bacillus* spp*,* and most *Corynebacterium* spp. almost always represent contamination [16,26,32]. Contamination is defined as the isolation of an organism in a blood culture that is not present in the patient's bloodstream [19]. Unfortunately, some of the microorganisms frequently considered contaminants are also a common cause of CRBSI, as is the case for coagulase-negative staphylococci, the leading cause of CRBSI. Other organisms causing bacteremia, like *S. aureus* and *Enterococcus* spp*.*, can also be detected as contaminants, albeit in a low percentage of cases [33]. For skin commensals, a minimum of 2 positive blood cultures with an identical strain are needed to be considered as a cause of bacteremia [25].

Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS), has been the most widely evaluated new technology, as approach to rapid microbial identification of blood cultures isolates [34–40]. Though the performances of MALDI-TOF MS identification vary according to the enrichment and purification method, this technology has shown a high sensitivity and specificity for rapid microbial identification from positive blood cultures [34–40]. Some limitations related to the identification of some Gram-positive microorganisms (*Streptococcus* spp.), non-fermenter Gram-negative, and non-albicans *Candida* [39]. Using MALDI-TOF MS in the clinical setting could improve time to identifications of microorganism, and time to effective and optimal antimicrobial therapy [41] .

Detecting the actual time of positivity of each blood cultures has been considered critical in the diagnosis of CRBSI. Several studies have confirmed that the measurement of differential time to positivity (DTP) between blood cultures drawn through a central venous catheter and those from a peripheral vein was highly diagnostic for suspected CRBSI[42,43]. Blot and colleagues [44,45] reported that a cut-off DTP value of 120 minutes has a sensitivity between 94%-100% and a specificity of 91% to 96.4%. Other studies showed similar results for the same cut-off value: sensitivity ranged from 72% to 96.4% and specificity from 90.3% to 95% [42,43] Raad and colleagues [46] showed that a DTP ≥120

minutes is associated with 81% sensitivity and 92% specificity for short-term catheters (<30 days) and 93% sensitivity and 75% specificity for long-term catheters (>30 days). Although this diagnostic test has been implemented in routine clinical practice, some authors have reported that DTP was not useful for the diagnosis of CRBSI in a medical-surgical intensive care unit [47]. These differences may be attributed to the definition used for CRBSI[48] and the type of microorganism causing CRBSI [49–51]. A recent report suggested that for diagnosis of *Candida* spp. CRBSI a DTP of ≥120 minutes is the optimal cut-off point (85% sensitivity and 82% specificity), except for *Candida glabrata* [51]. However, Bouza et al [49] in a catheter-related candidaemia (CRC) study including mainly *Candida albicans* and *Candida parapsilosis,* found that a DTP of ≥120 minutes had high sensitivity (94.7%) but a low specificity (40%). In general, the accuracy of DTP method requires accurate tracking of the source of blood cultures (central venous catheter vs. peripheral vein), as well as simultaneous placement of the cultures in the automated machine [46].

For suspected CRBSI, detection of the identical microorganism in blood cultures obtained by peripheral venipuncture and through the suspected catheter has been recently been evaluated as a means of diagnosing CRBSI without catheter removal. Although most laboratories use antimicrobial susceptibility testing and biochemical identification without molecular technology to establish identity, and this seems the most practical way to compare isolates, the possibility of a polyclonal infection should always be considered, as several studies have demonstrated that polyclonal infections are probably more common than previously suspected [52–54].

Recommendation:

- For the diagnosis of CRBSI, positivity of blood cultures obtained through the catheter ≥120 minutes earlier than those from a peripheral vein with the same microorganism is highly suggestive. It has not been stablished an optimal DTP cut-off for the diagnosis of catheter-related Candidemia. (A-II).
- The interpretation of DTP should consider the adherence to the technique of the procedure and the type of microorganism (A-II).

- Rapid microbial identification by MALDI-TOF MS from positive blood cultures reduces significantly the time to identification of microorganisms and has clinical impact on the management of patients with suspected bloodstream infection (A-II).

How should quantitative blood cultures be taken and interpreted?

Quantitative methodology is based on the lysis of blood with different detergents, centrifugation (i.e., lysis-centrifugation or pour-plate method) and inoculation of the sediment onto different culture media and different atmospheres [55,56]. This system has shown better results in detection time and specificity than conventional methods, but it is relatively complex and requires processing of the sample in less than 20-30 minutes since blood inoculation in the tube [26,27]. No specific guidelines exist for the procedure of taking blood cultures, so recommendations for conventional blood cultures mentioned above should be applied for quantitative blood cultures [15,16,25–27,32], except for inoculation in the bottle: in the lysis-centrifugation system 10 ml of blood are inoculated in the lysis tube, which contains the specific amount of detergent for this volume. After inoculation, blood and detergent need to be mixed gently, and then centrifugation is performed.

The number of required blood cultures is similar to conventional blood cultures. For the diagnosis of CRBSI, several authors have demonstrated that a greater colony count (5 to 10 times) in blood obtained through the intravascular catheter than in blood obtained through a peripheral vein is considered to be indicative of CRBI [42,57–60]. In a meta-analysis performed by Safdar et al [61], differential quantitative blood culture (DQBC) was the best approach to diagnose CRBSI without catheter removal, with a pooled sensitivity of 0.79 (95% CI: 0.74, 0.84), and a pooled specificity of 0.99 (95% CI: 0.98, 1.0). There is some controversy regarding the cut-off point of DQBC. A study that evaluated different cut-off points for paired quantitative blood cultures for the diagnosis of CRBSI showed that DQBC was not useful for short-term central venous catheters (CVCs). However, in long-term CVCs, DQBCs at ≥2:1 or ≥5:1 were sensitive but associated with low specificity and positive predictive value [60].

Quantitative blood cultures are labor intensive and expensive; therefore, this method is less practicable for routine use.

Recommendation:

- For the diagnosis of CRBSI, quantitative blood cultures with a ≥ 3:1 fold higher colony count in the sample drawn through the catheter than the sample from the peripheral vein support a diagnosis of CRBSI (A-II). This method is less practicable for routine use.

What particularities should be considered in the diagnosis of a CRBSI in patients on hemodialysis?

Central venous catheters (CVC) have become an acceptable form of vascular access for hemodialysis (HD) in patients without functioning vascular access, although their clinical usefulness is severely limited by infectious complications [62–64]. The relative risk of CVC causing CRBSI in HD patients has been estimated to be approximately 10 times higher than the risk of bacteremia in patients with arteriovenous fistulas or grafts [62,64,65].

Among HD patients, particularly in the outpatient setting, the standard microbiological criteria to confirm diagnosis of CRBSI by paired quantitative blood cultures and differential time to positivity are difficult to meet. Limitations of classic diagnostic criteria for CRBSI include the following:

1. Obtaining peripheral blood cultures may not be possible in up to 40% of HD patients, either because their peripheral veins have been exhausted or because of the need to avoid venipuncture in veins intended for future creation of a dialysis fistula or graft [25,65–68].

2. If the blood cultures are drawn during the dialysis session, when systemic blood is circulating through the catheter, there is no difference between peripheral and catheter blood culture results, so that peripheral sampling can be omitted [66–68].

3. In the absence of concurrent blood cultures from the catheter and a peripheral vein, a risk exist that the positive blood culture relate to other infectious source than the catheter [66,67].

4. In the outpatient setting a long pre-incubation period due to excessive transport time may lead to false-negative DTP [25,68] .

Recommendations:

- Whenever possible, paired blood samples from the CVC and a peripheral vein should be obtained for CRBSI diagnosis in haemodyalisis patients (A-II).
- Peripheral blood samples should be obtained from veins that are not intended for future creation of a dialysis fistula or graft. Hand vein in outpatients and hand or femoral vein in hospital inpatients should be used to obtain peripheral blood cultures (A-III).
- If a blood sample cannot be drawn from a peripheral vein, two separate samples drawn, 10 to 15 minutes apart, through the CVC or from the dialysis circuit linked to the catheter should be obtained (B-II).

What other conservative techniques may be used for diagnosis of CRBSI?

Conservative methods, such as endoluminal brushing, superficial cultures of skin surrounding the insertion site and catheter hubs, and Gram staining and the acridine orange leukocyte cytospin (AOLC) test have been proposed to diagnose CRBSI [42,43,69–71]. Endoluminal brushing, a method of sampling the internal catheter surface, showed a high sensitivity (95% to 100%) and specificity (84% to 89%) in two studies[71,72]. The procedure, however, is impractical and unreliable, and important side-effects such as cardiac arrhythmias, embolization, and subsequent bacteraemia were reported [56]. Superficial cultures (semiquantitative cultures of skin surrounding the catheter insertion site and catheter hubs) have also been proposed for the diagnosis of CRBSI [43] based on a sensitivity and specificity of 78% and 92%, respectively. It has therefore been suggested to combine superficial and peripheral blood cultures to screen for CRBSI, reserving DQBC as a confirmatory and more specific technique. Other authors have also reported on the use of Gram stain and AOLC test as a rapid method for the diagnosis of CRBSI [69]. This method requires two 50 µL samples of catheter blood. After several steps, including the use of cytospin technology, a monolayer of leucocytes and microorganisms are

placed on two slides, then stained with either acridine orange or Gram stain, and viewed by ultraviolet and light microscopy, respectively. The authors reported a sensitivity of 96% and a specificity of 92% [69]. In the meta-analysis of Safdar et al [61], the overall sensitivity and specificity of the AOLC test were 72% and 91%, respectively. In general, these methods have not been validated by other authors, and their use has not been generalized in clinical laboratories. A brief summary of these conservative methods and those methods requiring catheter removal is shown in Table 2.

What is the current value of molecular techniques for the diagnosis of CRBSI?

Most molecular techniques for the diagnosis of CRBSI without catheter withdrawal are those performed directly in blood samples drawn through the catheter. Different molecular methods have been applied in different patient populations. 16S rDNA analysis at blood drawn through vascular access devices in haematological patients had a 100% positive predictive value for CRBI [73,74]. Other authors have tested the pulsed-field gel electrophoresis (PFGE) to confirm CRBSI caused by coagulase-negative staphylococci (CoNS) in patients with neutropenia [75]. Most studies are based on real-time PCR, such as LightCycler® Septi*Fast* or Gene Xpert®, which have demonstrated to be a complementary diagnostic tool for blood cultures, specially in patients receiving antibiotics [76–79]. Data of the use of molecular techniques in samples other than blood to confirm an episode of CRBI are scarce[80].

Although direct detection of microorganisms in blood and other samples by molecular testing to streamline the diagnosis of CRBSI is a promising approach to improve patient management and outcome, it is currently not able to replace traditional cultures and these methods are still expensive and time-consuming[81,82].

Recommendations:

- At the present moment, there is not enough information to recommend the implementation of these techniques in the clinical practice for CRBSI diagnosis (C-II).

3.3. Diagnosis of CRBI with catheter withdrawal

When should a catheter tip be sent for culture?

Diagnosis of CRBSI requires establishing the presence of a bloodstream infection (see section 3.2: How should blood cultures be taken?), and demonstrating that the infection is related to the catheter. As a general recommendation, catheters should be done only when a CRBSI is suspected [83] thus, avoiding unnecessary cultures. Determining whether the catheter should be removed should take several factors into consideration: the type of catheter, the ease of a new catheter insertion, the immune status, the severity of the underlying illness of the patient, and the presence and severity of sepsis [84–87].

Recommendations:

- Culture of catheters should be done only when catheter-related bloodstream infection is suspected (A II).

How should a catheter be sent and processed in the Microbiology Laboratory?

After pulling the catheter, its tip should be cut to a length of approximately 5 cm under sterile conditions, avoiding contact with the patient´s skin, and placed in a sterile dry container for transport. The catheter tip should be stored at 4-8ºC [27] while transport to the laboratory is arranged.

The most widely used laboratory technique is the Maki's semi quantitative method, in which the catheter segment is rolled over the surface of a blood agar plate using sterile forceps, and colony-forming units (cfu) are counted after overnight incubation [88] . A limitation of this method is that mainly detects colonization of the external surface of the catheter. This concern is higherin long-term catheters in which luminal colonization more frequently leads to bloodstream infections [56,89]. To improve the detection of microorganisms progressing inside the catheter lumen, a quantitative culturing system was

described in 1980 by Cleri [90]. Quantitative endoluminal cultures are obtained by introducing the catheter segment into 2-10 ml of thrypticase soy broth (TSB) and flushing the catheter three times with a syringe. The broth is serially diluted 100-fold and 0.1 ml of each dilution is streaked onto sheep blood agar, counting the number of cfu after incubation [90].

Brun-Bruisson *et al* [91] simplified Cleri's technique by introducing the catheter segment into a test tube with 1 ml of sterile distilled water and, after vortexing it for 1 minute, 0.1 ml of the suspension is plated on a blood agar plate. Other modifications to quantitative endoluminal cultures includes a quantitative sonication method [92]: the catheter tip is immersed in 10 ml of TSB and sonicated for 1 min. 0.1 ml from both the broth and its dilution 1:100 plated on blood agar plates for counting the number of colony forming unit (cfu).

To distinguish internal from external catheter surface colonization, Liñares *et al* [89] reported culturing catheters by the semiquantitative method [88] and after, by a modified quantitative method, flushing the catheter lumen with 2 ml of TSB, which is then serially diluted and plated.

All quantitative methods are time-consuming, whereas the simplicity of semiquantitative techniques has contributed to their widespread use in clinical microbiology laboratories [43,93]. Several prospective studies have compared Maki's semiquantitative technique and the quantitative methods (sonication and vortexing) for the detection of CRBSI. These studies concluded that these three methods exhibit similar reliability but Maki's semiquantitative technique has a greater simplicity. [94,95]

The predictive values of quantitative or semiquantitative methods may vary depending on the type and location of the catheter, the culture methodology used, and the source of catheter colonization [96]. For example, recently inserted catheters would be more likely colonized by a skin microorganism along the external surface of the catheter, thus the Maki's semiquantitative method will be very sensitive in the identification of such colonization. In contrast, catheters in place in for more than a week could become colonized via intraluminally from the hub, rendering the roll plate method less sensitive. In this case methods that obtain samples of both the internal and external surfaces for culture are more sensitive [94]

Recommendations:

- Semiquantitative (roll plate) or quantitative (vortex or sonication methods) catheter culture techniques are the most reliable diagnostic methodologies (A-II).
- Qualitative cultures (culture of the catheter tip by broth immersion) are unreliable to distinguish contamination from infection and therefore not suited for the diagnosis of CRBSI (A-II).

How should the results of catheter cultures be interpreted?

Semiquantitative catheter cultures discriminate between catheters causing infection and non-significant colonization. If the culture of the tip of the catheter grows ≥15 the catheter is considered to be the source of infection, whereas <15 cfu without associated clinical signs is considered catheter colonization[88]. This cut-off point was based on a significant association with clinical signs and bacteremia for ≥15 cfu with a specificity of 76%[88]. Subsequent studies have validated the semiquantitative culture technique for the evaluation of catheter-related infections [97,98]. There is no established cut-off point for mycobacteria and fungi.

For quantitative catheter cultures (flushing internal surface and vortexing), the cut-off point has been established at 10^3 cfu/segment, again based on its association with bacteremia in CRBSI. Counts below 10^3 cfu are considered as intermediate, possible contamination or early stages of colonization [90,91]. For quantitative cultures based on sonication, a cut-off point of $>10^2$ cfu was established to discriminate between catheter infection and catheter colonization [92]. In general, semiquantitative and quantitative cultures gave comparable results, but the semiquantitative procedure proved to be easier and faster [27,99].

Recommendations:

- The presence of 15 or more cfu per plate by semiquantitative culture (roll-plate) is indicative of significant catheter colonization (A-II).

- For quantitative culture methods based on vortexing or flushing internal surface, counts above 10^3 cfu/segment reflect significant catheter colonization (A-II).
- For quantitative culture methods based on sonication, counts above 10^2 cfu/segment indicate significant catheter colonization (A-II).

How should a subcutaneous reservoir be processed?

Venous access devices (VADs) are widely used for long-term access to the vascular system, mainly in oncologic patients. The diagnosis and management of CRBSI includes the recommendation to perform qualitative culture of the port reservoir contents in addition to the semiquantitative catheter tip in suspected VAD-related bloodstream infection (VAD-RBSI). This has been thoroughly studied in patients with suspected VAD-RBSI by comparing VAD cultures with blood cultures obtained before removal. In all studies the catheter tip failed to detect several VAD-RBSI episodes, whereas cultures of the endoluminal content (thrombotic material) had a better predictive value[100–103].

Bouza et al. assessed the validity values of cultures from different sites of 223 VADs which were withdrawn for any reason. They confirmed that VAD colonization rate improved when they combined not only cultures from the catheter tip and the inside of the port, but also from the sonication fluid used to obtained microorganisms from the external port surface [104]. Besides, del Pozo et al. assessed the yield of sonication in the septum of 240 VAPs. This procedure showed the highest sensitivity and specificity for the diagnosis of VAD colonization with a cut-off of 110 cfu/ml (78% and 93%, respectively) [105].

These recent findings will probably impact on the routine laboratory processing of pulled VADs, as confirmation of VAD-RBSI requires performing cultures of the catheter tip and of the inner and the outer surfaces of the port. A consensus statement for thresholds for VAD cultures does not exist.

Recommendations:

- Venous access devices removed for suspected CRBI, should be sent to the microbiology laboratory. Routine processing should include a

combination of cultures from different parts of the VAD, including culture after septum sonication and semiquantitative catheter tip culture (B-II).

What is the current value of molecular techniques for the diagnosis of CRBSI after catheter removal?

The diagnosis of CRBSI requires confirmation that the microorganisms isolated from catheter tip and blood cultures are phenotypically identical. A recent study using quantitative PCR for detection of CoNS suggest that the role of the catheter as a source of bacteremia may be overestimated [106]. Actually, conventional routine microbiological practice performed poorly in diagnosing CoNS CRBSI when evaluated by PFGE on different morphotypes of CoNS isolated from catheter tip and blood cultures[107]. In contrast, using microsatellite markers, genotypes of *Candida* isolates recovered from blood cultures matched in 91% with those recovered from catheter tips[108].

16S rRNA polymerase chain reaction (PCR) does not seem to be able to replace conventional culture, due to its low sensitivity. Also, presently, there are not data available about application of molecular methods in non-tunneled catheters. In contrast, 16S rRNA PCR of endoluminal samples was able to increase the detection of VAD-PRBSI by 21.1% in patients undergoing antibiotic therapy [109].

In summary, molecular methods have the potential to improve diagnosis of CRBSI in patients undergoing antibiotic therapy, although these techniques have not been standardized

Recommendation:

- 16S rRNA PCR could be performed in the septum sonication fluid to rule out or confirm VAD-RBSI in patients under antibiotic therapy (C-III).

3.4. Diagnosis of local signs of infection

What samples should be taken and how should they be interpreted when an insertion site infection is suspected?

Insertion site infections are characterized by inflammatory signs, including induration, erythema, warmth, and pain or tenderness within 2 cm of the catheter insertion site. They may also be associated with other signs and symptoms of infection, such as fever or purulent discharge from the insertion site with or without a concomitant bloodstream infection [6,110]. Microbiologically documented insertion site infection is defined by an exudate at catheter insertion with a positive culture [6,110]. The sensitivity and positive predictive value of local inflammation for the diagnosis of CRBSI has been shown to be very low [111]. When catheter infection is suspected and catheter insertion site exudate is evidenced, the exudate should be sent for Gram stain, routine culture, and additional culture for fungi as indicated, when assessing immunocompromised patients [25].In addition, blood cultures should be drawn [6,110,111].

In the absence of local signs of infection, the results of several studies suggest that semi-quantitative cultures of swabs taken of skin surrounding the insertion site as well as from the internal surface of catheter hubs (surface cultures) may be useful for rule out catheter colonization and infection, avoiding unnecessary catheter withdrawals [43,80,112–114]. For skin samples, a dry cotton swab should be rubbed over a 2 cm^2 area around the insertion site. For hub samples a small (alginate) swab should be introduced in each hub and rubbed repeatedly on the inner surface [43,112]. Semi-quantitative growth of < 15 UFC from both the insertion site and the catheter hub allow to rule out CRBSI [43,112], although, surface cultures have shown very low specificity and positive predictive value. The combination of the semiquantitative culture of the subcutaneous tract and culture of the hub swab improves specificity and positive predictive values [115].

VAD-related infection should be suspected if a patient exhibits local signs of infection, such as pain or erythema, at the site of implantation [103]. Local complicated infection has been defined as infection of the tunnel or pocket with extended erythema or induration (more than 2 cm), purulent collection, skin necrosis, and spontaneous rupture and drainage. Clinical signs of local infection, such as erythema or purulent exudate, have high specificity but low

sensitivity [100,103]. A recent study showed that 23% of patients with VAD-related infection had local signs of infection [116]. In these cases, culture of purulent fluid and/or necrotic tissue surrounding the port is mandatory. Blood culture from peripheral vein should also be performed in order to rule out CRBSI.

Recommendations:

- When catheter infection is suspected and there is a catheter insertion site exudate, it should be sent for Gram stain and culture. In addition, blood cultures should be drawn (A-III).
- In patients with a suspected catheter-related infection but negative superficial cultures (growth of < 15 CFU from both the insertion site culture and the catheter hubs culture) the possibility of infection may be reasonably ruled out (B-II).

4. Catheter related bloodstream infection treatment.

Main antimicrobial drugs dosages that should be used for CRBSI are shown in Table 3.

In which situations can a catheter be retained until blood cultures are available?

Two studies found no differences in outcome comparing early CVC removal with watchful waiting strategy for suspected CRBSI in patients with non-tunnelled catheters [117–119]. These studies excluded patients with neutropenia, solid or haematological tumour, immunosuppressive or radiation therapy, organ transplantation, intravascular foreign body, haemodynamic instability, suppuration or frank erythema/induration at the insertion site, as well as bacteremia or fungemia. One of these ICU studies was a randomized single-center clinical trial[117], the other was prospective, observational, and multicenter [118]. CRBSI was confirmed in only 12% of patients in the multicenter study, and there was no difference in mortality between immediate and late CVC removal. Another randomized trial demonstrated

that in critically ill patients, DTP allows for a watchful waiting strategy up to definitive diagnosis of CRBSI [120]. It should be noted that catheter exchange is not absent of risks and severe complications, although fortunately uncommon, may occur [121].

Recommendation:

- In patients with hemodynamic stability, without immunosuppressive disease or therapy, intravascular foreign body or organ transplantation, and without suppuration at the insertion site or bacteremia/fungemia, immediate CVC removal is not routinely recommended when a CRBSI is suspected (A-I).

When is it safe to perform an exchange of catheter over guidewire?

Replacement of CVcs can be achieved by a new-site percutaneous venipuncture or by using the Seldinger technique to change the catheter over a guidewire. A meta-analysis including 12 RCTs [122] found nonsignificant differences between guidewire exchange to prevent CRBSI compared to inserting a new catheter: fewer mechanical complications (8 RCTs, relative risk = 0.48, 95% confidence interval = 0.12 to 1.91), increased frequency of catheter colonization (9 RCTs, relative risk = 1.26, 95% confidence interval = 0.87 to 1.84), catheter exit-site infection (5 RCTS, relative risk = 1.52, 95% confidence interval = 0.34 to 6.73), and catheter-related bacteremia (9 RCTs, relative risk = 1.72, 95% confidence interval = 0.89 to 3.33) [122]. A study of 1,598 CVC in critically ill patients showed that exchange over a guidewire was associated with development of CRBSI [123]. On the contrary, elective guidewire exchange of non-tunnelled hemodialysis catheters was not associated with a higher incidence of catheter infections and preserved venous access in these high-risk patients [124].

Guidewire exchange is not indicated in patients with documented infected catheter or in CRBI [125]. Guidewire-assisted catheter exchange is an option to replace a malfunctioning catheter if there is no evidence of infection at the catheter site and a new percutaneous venipuncture is not recommended for high risk of complications (difficult venous accesses, bleeding diathesis).

Recommendations:

- Routinely guidewire exchange of CVCs is not recommended because this strategy is associated with a higher risk of infectious complications. (B-II)
- Guidewire exchange of CVCs is contraindicated in patients with a documented catheter infection. (A-II)
- Guidewire exchange should be restricted to patients with very difficult venous access (i.e. extensive burns, morbid obesity, or severe coagulopathy) without documented catheter infection (B-II). In this case, a meticulous aseptic technique and the catheter tip culture are mandatory. (A-III)
- If catheter tip culture is positive, the new line, inserted over guidewire, should be replaced using a new direct venipuncture. (C-III)

How should be done if culture of the catheter tip is positive but blood cultures are negative?

Only limited data are available about clinical implications of a positive CVC tip culture with negative blood cultures taken at the time of cather removal.

Two retrospective studies [126,127] concluded that *S. aureus* colonization of intravascular catheters is a risk factor for subsequent *S. aureus* CRBSI. Furthermore, antibiotic therapy initiated within 24 hours of catheter removal significantly reduced the risk for subsequent *S. aureus* bacteremia (SAB).

Another retrospective multicenter study showed that the incidence of septic complications after the removal of a colonized catheter was lower in patients with early antibiotic treatment (13% vs. 4%) (OR 4.2; 95% CI 1.1-15.6). In this study, the presence of exit-site infection was also a risk factor for the development of *S. aureus* CRBSI (OR 3.39; 95% CI 1.19-9.34) [126]. A meta-analysis of four retrospective studies yielded a pooled OR of 5.8 (95% CI, 2.6-13.2) for SAB when antibiotic therapy was not initiated. The number needed to treat to prevent 1 episode of SAB was 7.4 [128]. Conversely, a more recent retrospective study concluded that the administration of early anti-staphylococcal therapy had no impact on the outcome, defined as *S. aureus*

infection within 3 months after catheter withdrawal or death with no obvious cause. The only factor independently associated with a poor outcome was the presence of clinical signs of sepsis at the time of catheter removal (OR 20.8; 95% CI 2.0-206.1) [129,130]

A retrospective study in patients with *Candida* spp. CVC colonization, observed that the incidence of subsequent candidaemia (SC) was only 1.7% and multivariate analysis of risk factors for poor prognosis showed that antifungal therapy was not a protective in this setting (OR 0.82; 95% CI 0.27-2.47) [131]. A more recent study showed an incidence of SC of 2.5%, and that antifungals, administered in 55% of patients, were not protective[132]. However, another study showed that the risk of infectious complications after catheter removal was higher in the case of *Candida* spp. (7.7%) than in the case of bacterial infection (1.8%), and it was suggested to start antifungal therapy for all patients with positive catheter tip and culture negative blood cultures.

No clear recommendations can be given if the catheter is colonized with other microorganisms. The decision should be individualized but antimicrobial therapy would be justified only in patients with septic shock and no other evident explanation of the clinical picture.

Recommendations:

- Antibiotic treatment (i.e., 5-7 days) should be given to patients with a positive catheter tip culture for *S. aureus* and negative blood cultures if the patient shows systemic signs of infection or signs of local infection. (B- II).
- In non-neutropenic patients or in patients with valvular heart disease, the presence of a *Candida* spp. positive catheter tip culture and negative or unavalialable blood cultures should be assessed on an individual basis before starting systematic antifungal treatment. In patients without systemic signs of infection, antifungal treatment should not be prescribed (B-II).
- No clear recommendations can be given for catheters colonized with other microorganisms (C-III).

4.2. Empirical antimicrobial therapy

What is the empirical antimicrobial therapy of a CRBSI?

The initial antimicrobial choice should be based on assessment of the risk for infection, the severity of the clinical picture and the likely pathogens associated with the specific intravascular device. Figure 1 summarizes the recommended empirical approach for a patient with high suspicion of CRBSI.

Patients with *S. aureus* CRBS are at high risk of hematogenous metastatic complications, specially when the catheter cannot be removed and/or antibiotic treatment is not appropriate [133]. As most CoNS are methicillin-resistant, choice of empirical therapy should include antibiotics with activity against these strains. Vancomycin is the most commonly prescribed antimicrobial for CoNS and methicillin-resistant *S. aureus* (MRSA) bacteremia over the last decades. Studies comparing the efficacy and safety of glycopeptides (i.e.,vancomycin vs teicoplanin) for *Staphylococcus* spp (including MRSA) bacteremia have not observed significant differences [134,135], although clinical isolates of *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* with reduced susceptibility to teicoplanin have been reported[136].

Vancomycin is associated with a lower clinical success rate in treating MRSA bacteremia with MIC ≥ 1.5 mg/L (measured by E-test) [137,138]. In a case-control study focused on cases of bacteremia caused by MRSA with a vancomycin MIC ≥ 1.5 mg/L (measured by E-test), a higher survival rate was observed in the group of patients treated with daptomycin [139]. Multivariate analysis of this study confirmed that renal impairment and previous therapy with vancomycin were associated with a significantly higher clinical failure. The impact on outcome of bacteremia caused by CoNS with a vancomycin MIC ≥ 1.5 mg/L (measured by E-test) is an unsolved issue.

Previous studies indicated that vancomycin is suboptimal when compared to beta-lactams (i.e., cefazolin or oxacillin) for the treatment of methicillin-susceptible *Staphylococcus aureus* (MSSA) bloodstream infections [140–142]. This issue could justify the inclusion of a beta-lactam in the empirical treatment of any suspected CRBSI. A recent study compared beta-lactams with vancomycin for empiric and definitive therapy in 5787 patients from 122 hospitals with MSSA bloodstream infections [143]. Patients who received definitive therapy with a beta-lactam had 35% lower mortality compared with patients who

received vancomycin (HR, 0.65; 95% CI, 0.52–0.80) after controlling for other factors [143].

Daptomycin is a lypopeptide antibiotic with *in vitro* activity against Gram-positive bacteria, which is more bactericidal than vancomycin [144,145]. The only randomized trial comparing daptomycin with vancomycin or a β-lactam concluded that daptomycin was non-inferior to vancomycin [146]. In a recent cohort study including 579 episodes of bacteremia caused by MRSA, no significant differences were observed regarding the mortality of patients treated with vancomycin or daptomycin (OR 1.42 [95%CI 0.83-2.44]) [147]. However, a recent study analyzing the efficacy of daptomycin in 40 oncologic patients treated for Gram-positive CRBSI (including *S. aureus*) compared to a historical control group of 40 patients treated with vancomycin confirmed a faster bacteriological and clinical resolution in the daptomycin group [148].

In a randomized clinical trial in skin-structure infection and CRBSI with *S. aureus*, including MRSA, linezolid showed similar efficacy as comparators for CRBSI [149]. A meta-analysis of 5 randomized controlled trials of MRSA bacteremia, observed that linezolid was non-inferior to vancomycin [150].

Recommendations:

- If a CRBI is suspected, antimicrobial therapy with a bactericidal agent active against *S. aureus* and CoNS must be started as soon as possible, specially if associated with sepsis or septic shock (B-II).
- Vancomycin is recommended for empirical therapy in patients with suspected CRBSI (B-II). Teicoplainin is not recommended as empirical therapy given the existence of coagulase-negative staphylococci with reduced susceptibility to teicoplanin (C-III).
- Daptomycin could be administered in cases of CRBSI with septic shock (C-III), with acute kindey injury (B-III), in patients with recent exposure to vancomycin (> 1 week in the past 3 months) (C-III) or if the local prevalence of *S. aureus* isolates with vancomycin MIC ≥ 2.0 μg/ml is high (C-III). The level of local prevalence of *S. aureus* isolates with vancomycin MIC ≥ 1.5 μg/ml supporting routine empirical use of daptomycin remains undefined.

- Linezolid should only be used in patients with contraindications for the previous agents (B-II).

When should empirical coverage of Gram-negative bacilli or fungi be added?

The incidence of Gram-negative bacilli (GN)-CRBSI has been reported to be 17% to 25% of all episodes of CRBSI [151,152]. GN-CRBSI is particularly relevant during outbreaks and in patients with special conditions such as spinal cord injuries, femoral catheters, neutropenia and hematological malignancy, gastrointestinal colonization, prolonged ICU stay, post-operative status or diabetes [153–155]. In some centers, the predominance of GN-CRBSI has been related to an increase in transplantations (solid organ or hematological bone marrow) [155] and the implementation of a CRBI prevention bundled including the use of silver sulphadiazine-chlorhexidine impregnated catheters, which preferentially prevented Gram-positive CRBSI [156]. In a recent report, solid organ transplantation, prior use of penicillin and hospital stay longer than 11 days were independently associated with a significantly higher risk of GN-CRBSI, whereas, cirrhosis, diabetes and use of quinolones were associated with a higher risk of Gram-positive CRBSI [152]. Femoral catheters are associated with a higher incidence of CRBSI due to Gram-negative bacilli than other anatomic sites. Therefore, empirical antibiotic coverage for Gram-negative bacilii has been suggested when a CRBSI is suspected in a patient with a femoral access [157]. No clinical trial has validated the benefit of a specific drug in the management of GN-CRBSI and empirical coverage should be based on local antimicrobial susceptibility data and the severity of disease [156].

The rate of *Candida* spp. CRBS was significantly higher for femoral catheter, than in the other catheter sites (16.67% vs 1.92%; p =0.035) in a prospective study of risk factors for yeast bacteremia. A recent study, however, only identified solid tumors (OR, 3.11; 95% CI, 1.75-5.53), total parental nutrition (OR, 2.65; 95% CI, 1.39-5.06), and administration of anti-anaerobic agents (OR, 2.22; 95% CI, 1.03-4.79) as independent variables for candidal CRBSIs. In this study, the (1,3)-β-D-glucan (BDG) test was positive in 94.6% (35/37) of *Candida* spp. CRBI patients and 9.4% (10/106) of non-candidal

CRBSI cases [158]. In ICU patients, multivariate logistic regression analysis identified severity of illness on the day of candidaemia (as assessed by SOFA score) as the only potential risk factors for CRBSI caused by *Candida* spp [159].

Recommendations:

- Patients with suspected CRBSI should receive (in addition to coverage for gram-positive pathogens) empirical antibiotic therapy to cover gram-negative bacilli under any of the following circumstances: hemodynamic instability (septic shock), neutropenia or hematological malignancy, solid organ or bone marrow transplantation, femoral catheter in place, a high index of colonization by gram-negative bacilli or a prolonged ICU admission (C-III).
- Antimicrobial therapy should be adapted to local epidemiology, and must include an antipseudomonal agent (piperacillin-tazobactam, carbapenems, a fourth-generation cephalosporin, aztreonam, quinolones or aminoglycosides) (A-II). Aztreonam and cephalosporins must be avoided in patients with colonization or at risk for extended-spectrum β-lactamases infections (A-I).
- The need for empirical antifungal therapy in a patient with suspected catheter-related candidemia should be evaluated in combination with the possibility of catheter removal (A-III).
- Empirical therapy for suspected catheter-related candidemia could be considered in patients with hemodynamic instability and one or more of the following conditions: total parenteral nutrition, prolonged use of broad-spectrum antibiotics, malignancy, femoral catheterization, colonization due to *Candida* species at multiple sites or intense previous anti-anaerobic therapy (C-III).
- The use of biomarkers (like B-D-Glucan) might be useful when considering initiation of empirical treatment (B-III).

What particularities should be considered in the empirical treatment of a CRBSI in patients on hemodialysis?

Vascular catheters are the leading source of bacteremia in HD patients [160,161]. Usually bacteremia develops when the catheter is in use. Catheter salvage should be a priority in these patients.

Conservative management is associated with a higher success rate if a combination of systemic antibiotics and catheter antibiotic-lock is used [162–165].

Microorganisms causing CRBSI in hemodialysis patients are similar to those observed in other patient populations, although a higher proportion of *S. aureus* is usually found in most series [166–169]. *S. aureus* CRBSI is one of most difficult microorganisms to treat while maintaining the catheter in place due to their propensity to cause septic complications, treatment failures and relapses [170,171]. *S. epidermidis* CRBSI, however, has shown excellent results when treated conservatively combining systemic and local antibiotics inter-dialysis periods[164].

Alternatively, if retaining a catheter is not possible, exchange of the catheter over guidewirew has been shown to be safe. This approach could lead to a higher cure rate than treatment based on antibiotic-lock therapy in *S. aureus* infections [164]. Systemic antibiotics need to be administered considering PK/PD characteristics of end stage of renal disease and hemodialysis for each particular drug.

Recommendation

- Conservative management of CRBSI should be attempted in hemodialysis patients. Combining systemic and local intracatheter antibiotics is associated with imporoved results compared to systemic antibiotics alone (A-I).
- In patients with tunneled hemodialysis catheters, guidewire exchange is an alternative specially when catheter removal is not feasible. (C-III).

4.3. Targeted antimicrobial therapy

Pathogen-specific directed management of confirmed CRBS is summarized in Figure 2.

What is the recommended directed therapy and its optimal duration in CRBSI due to *Staphylococcus aureus*?

Methicillin-susceptible *S. aureus* (MSSA) CRBSI.

The treatment of choice is high-dose intravenous isoxazolic penicillin, (i.e. cloxacillin). Cefazolin is an adequate alternative [172–174]. Treatment with other beta-lactams, including second and third generation cephalosporins has been associated with an increased mortality [174]. Likewise, *in vitro* activity and clinical results of vancomycin therapy for MSSA have repeatedly shown to be significantly worse [140–142,175]. The use of intravenous daptomycin as could be the case in patients with beta-lactam allergy, yields comparable results to cloxacillin [146]. Infections caused by methicillin susceptible *S. aureus* (MSSA) strains with reduced susceptibility to vancomycin (MIC ≥ 1.5 mg/L, measured by E-test), in spite of being treated with cloxacillin, have been associated with worse outcome [176].

Duration of uncomplicated MSSA CRBSI treatment should be 14 days, including patients with intravenous prosthetic devices and negative transesophageal cardiac ultrasound findings [177]. Blood cultures should be obtained at 72 hours of antibiotic therapy [178]. The management for patients with persistent positive blood cultures and/or no clinical improvement after catheter removal is outlined elsewhere [177]. Treatment length for these episodes of complicated CRBSI should be 4 to 6 weeks.

Methicillin-resistant *S. aureus* (MRSA) CRBSI: Vancomycin is the treatment of choice for MRSA-CRBSI [177]. Doses of vancomycin should be adjusted to maintain trough levels between 15 and 20 mg/L in order to achieve the parameter of efficacy of this antibiotic in MRSA bacteremia (i.e., AUC/MIC >400) [179]. Teicoplanin is a suitable alternative to vancomycin probably

associated with less side effects. However, serum level concentrations cannot be measured in clinical practice and the optimal dose is not well defined [180]. If the vancomycin MIC is ≥1.5 mg/L [181,182], alternative antibiotics like daptomycin should be considered although no randomized studies are available. Combination therapies for complicated MRSA bacteremia have been reported, like daptomycin with beta-lactam (i.e., cloxacillin), daptomycin with fosfomycin, and imipenem with fosfomycin). For further information, this panel recommends a guideline recently released by the SEIMC [177]. Duration of treatment in uncomplicated and complicated MRSA CRBSI is the same as for MSSA.

Recommendations:

- Treatment of choice of an episode of CRBI caused by MSSA is cloxacillin or cefazoline (B-I).
- Patients with beta-lactam allergy should be treated with daptomycin (A-I) or a glycopeptide (B-II).
- The best antimicrobial treatment in episodes caused by a strain of MSSA with reduced susceptibility to vancomycin (MIC ≥ 1.5 mg/L measured by E-test) has not been elucidated. This panel suggests using a combination of cloxacillin and daptomycin when blood cultures remain positive and/or clinical improvement is not evident after catheter removal (C-III).
- Vancomycin is the treatment of choice for CRBSI caused by MRSA (B-II). Teicoplanin may be a valid alternative especially in case of serious side effects associated with the use of vancomycin. (C-III)
- Alternatively, patients may be treated with daptomycin, specifically if MIC measured by E-test is ≥1.5 mg/L (A-I).
- Linezolid should only be used in patients in whom the previous agents are contraindicated (C-III).
- In both MSSA and MRSA CRBSI, blood cultures should be obtained after 72 hours of antibiotic therapy (C-III).

What is the recommended directed therapy and its optimal duration in CRBSI due to coagulase-negative *Staphylococcus* (CoNS)?

CoNS-CRBSI is associated with a significant increase in length of stay although without attributable mortality [183–185]. As these infections may resolve just with catheter removal, some authors suggest that no antibiotic therapy is needed in immunocompetent patients without signs of infection and no foreign body. If the catheter is removed, uncomplicated CRBSI can be treated with a short course of 5 to 7 days of antibiotics. In the infrequent case of a strain susceptible to methicillin, a penicillinase-resistant penicillin (i.e. cloxacillin 2 g/4 hours) or cefazolin are the recommended antibiotics. For MR-CoNS CRBSI, vancomycin is the treatment of choice. Teicoplanin is also a suitable alternative in the directed therapy [186].

In patients with intravascular devices, biomedical devices or in whom inflammatory markers persist after catheter removal therapy, antibiotic therapy for 10–14 days is recommended, although no clinical study has addressed this issue. If for some reason the catheter needs to be retained, additionally, antibiotic lock therapy is a reasonable alternative[187].

Staphylococcus lugdunensis can cause severe infection with an aggressive clinical course similar to *Staphylococcus aureus* infection. For this reason, management of *S. lugdunensis* CRBSI should be as for *S. aureus* bloodstream infection [188]

Recommendations:

- Cloxacillin or cefazolin are the treatments of choice for an episode of CRBSI caused by CoNS susceptible to methicillin (B-I).
- For CoNS resistant to methicillin, a glycopeptide is the treatment of choice for directed therapy (B-II). Teicoplanin is recommeded in case of serious side effects associated with vancomycin. (C-III).
- The optimal trough concentration of vancomycin for treatment of CoNS CRBSI is an unsolved issue and this panel cannot issue a specific recommendation (C-III).

- Management of *S. lugdunensis* CRBSI should be carried out as *S aureus* CRBSI (C-III).

What is the recommended directed therapy and its optimal duration in CRBSI due to *Enterococcus* spp.?

Enterococcus spp is increasing as a cause of CRBSI and represents the fourth leading cause of CRBSI [189]. For susceptible isolates, ampicillin is the drug of choice. After adjusting for confounders, glycopeptide use is associated with increased mortality in patients with *Enterococcus faecalis* bacteraemia compared to β-lactam treatment[190]. There is no information supporting the superiority of combination therapy (a beta-lactam plus an aminoglycoside) instead of a β-lactam monotherapy for uncomplicated CRBSI [187]. For other species of *Enterococcus*, particularly *E. faecium*, with a high rate of resistance to ampicillin, vancomycin is the drug of choice. For *Enterococcus faecium* isolates resistant to vancomycin, linezolid seems to be superior to daptomycin [191,192]. Duration of treatment is unresolved issue but may range from 7 to 14 days.

It is worth mentioning that a recent retrospective cohort study of adults with enterococcal CRBSI showed a lower in-hospital mortality rate in patients in whom CVCs were removed (18.3% versus 37.9%; p=0.03). In the multivariate analysis, catheter retention was an independent predictor of mortality (OR 3.34 [95% CI 1.21 to 9.26]) [193].

Recommendations:

- Enterococcal CRBSI should be treated with catheter withdrawal and one active antimicrobial (A-III).
- Ampicillin is the drug of choice for susceptible isolates (A-II). Vancomycin should be reserved for isolates resistant to amplicillin or in case of beta-lactams allergy. For vancomycin-resistant isolates or in case of severe adverse effects, linezolid is preferred to daptomycin (B-III).
- There is no evidence that association of drugs is necessary if IE has been properly ruled out (A-III).

- Despite data suggesting that length of treatment may me shorter, the classic 7-14 days regimen continues to be recommended (A-III).

What is the recommended directed therapy and its optimal duration in CRBSI due to Gram-negative bacilli?

As stated in the empirical therapy section, no clinical trial has assessed specific antibiotic drugs in the management of GN-CRBSI. The choice for targeted therapy should be based on susceptibility results and aiming at the narrowest spectrum. The principles of antimicrobial stewardship should be wisely applied in this clinical scenario [194]. No study has evaluated the length of antimicrobial therapy in patients with GN-CRBSI. Duration of therapy should be individualized considering clinical factors such as resolution of symptoms or immunological status. It is usually recommended to treat for no less than 7 days.

Recommendations:

- Directed therapy for GN-CRBSI must be chosen based on the susceptibility results (C-III).
- The proper length of antimicrobial therapy has not been elucidated but a recommendation to continue therapy for at least 7 days is given (C-II).

What is the recommended directed therapy and its optimal duration in CRBSI due to *Candida* spp.?

Currently echinocandins are recommended for empirical therapy in candidemic patients with severe infections [195,196]. The decision of continuing with an echinocandin or step-down to an agent with narrower spectrum (i.e. fluconazole) should be based on several factors: a) Catheter removal; b) fluconazole susceptible strain c) Good clinical response with hemodynamic stability d) negativization of blood cultures. An open-label, non-comparative study has documented that de-escalation from anidulafungin to fluconazole is a safe strategy in patients with candidaemia [197]. In critically ill patients with

invasive candidiasis, an observational study confirmed that de-escalation within 5 days was not related to increased day-28 mortality [198]. No study has specifically assessed the impact of de-escalation of antifungal therapy in CRBSI caused by *Candida* spp. Combination therapy is not recommended for Candida-CRBI [195,196]. In addition, removal of the intravenous catheter was an independent determinant of survival in patients with candidaemia, specially if the catheter is the source of *Candida* bloodstream infection or is associated with septic shock [119,199–201].

Biofilm formation is relevant in the pathogenis of CRBSI and differences in activity of antifungals on *Candida* growth in biofilms should guide for the choice of the most appropriate treatment. Liposomal amphotericin B and echinocandins are active against *Candida* cells in biofilms, while the activity of amphotericin B deoxycholate and azoles is poor [202]. A potential situation in certain types of patients is that the catheter cannot be removed for whatever reason and remains in place. If this occurs, it is wise to use an antifungal agent with high activity against the biofilm [203–206].

Based on the study protocol of the relevant clinical trials, two weeks (14 days) after the first negative blood culture is the recommended duration of therapy. Therefore, follow-up blood cultures every other day until demonstration of the negativization of blood cultures are helpful to establish the appropriate duration of antifungal therapy.

Recommendations:

- In patients with *Candida* spp CRBSI, this panel advocates for de-escalation from an echinocandin or a lipid formulation of amphotericin B to fluconazole for susceptible isolates in clinical stable patients in whom the catheter has been removed (B-II).
- Recommended duration of therapy for candidemia without obvious metastatic complications is two weeks after the first negative blood culture set (B-III).

- In candidemia all intravascular catheters should be removed if at all feasible (B-II), particularly in patients with septic shock in whom Candida CRBSI is suspected (B-III).
- If a catheter that is the source of a Candida bloodstream infection cannot be removed for whatever reason and remains in place, an antifungal agent with high activity against the biofilm should be used (i.e. an echinocandin or liposomal amphotericin B) (A-II).

What is the recommended directed therapy and its optimal duration in CRBSI due to nontuberculous mycobacteria?

CRBSI and/or sepsis is the most common health care-associated type of infection due to the pathogenic rapidly growing mycobacterium (RGM) in both immunosuppressed and immunocompetent patients. The organisms not only may cause mycobacteremia but also may present as local wound exudate from an exit site or tunnel infection. The most commonly recovered RGM species or groups include *M. fortuitum*, *M. abscessus*, and the *M. mucogenicum* group[207–209]. Both short and long-term catheters should be removed in CRBSI due to mycobacteria. Likewise, long-term catheters should be removed in the setting of CRBI due to mycobacteria.

The duration of treatment for NTM CRBSI varies, but is usually at least 6 to 12 weeks to prevent relapse [211,212]. In leukemic children, recent studies suggest that systemic infections with mycobacteria may require up to 2 years of therapy, even if the catheter was removed. Prognosis is excellent if catheters are pulled in addition to systemic antibiotic therapy over extended periods of time.

Recommendations:

- Treatment for CRBSI caused by NTM involves the removal of the infected catheter (B-II) followed by combined antimicrobial treatment appropriate for the species involved (B-III).
- The duration of treatment for NTM CRBSI should last 6 to 12 weeks to prevent a relapse of infection and development of septic metastasis (B-III).

Should antimicrobials for CRSBI administered intravenously for the entire treatment course?

Efficaccy of the treatment of CRBSI depends on the following variables: a) Early or prompt removal of the catheter; b) Documentation of the bacteremia and identification of the causative organism and its susceptibility pattern; c) Clinical response over the first 48-72 hours of empiric treatment; and d) Development of complications. All patients with CRBSI require initially intravenous antimicrobial therapy. The aforermentioned variables should determine the duration of treatment and the decision to resort to sequential treatments or swith to the oral route. A randomized open trial compared an oral combination therapy with a fluoroquinolone and rifampicin (iv for 24 h, but switched to oral route as soon as possible) to standard parenteral therapy (flucloxacillin or vancomycin) for bacteremia or deep-seated infections caused by *S. aureus* or catheter-related bacteremia due to drug-susceptible CoNS. Approximately, 40% of the infections were CRBSI, two-thirds caused by *S aureus* and the rest by CoNS. Clinical and bacteriological cure rates were similar in both groups, although the median length of hospital stay was significantly shorter in the oral group [215]. A recent study demonstrated that oral linezolid in monotherapy or in combination therapy, mostly with rifampin, is a valid alternative to intravenous therapy for patients with Gram-positive infections, although the number of CRBSI was low. Interestingly, none of the patients with CRBSI required hospital readmission due to the infection or restart of intravenous antibiotic treatment [216].

Clinical trials evaluating echinocandins allowed swift to oral fluconazole after 7-10 days of intravenous therapy, although specific analyses of outcome of the subgroup of Candida-CRBSI are not available [217–219]. A recent non-comparative trial in candidemia showed that an early step-down strategy from intravenous anidulafungin to oral azole therapy after 5 days, with approximately 50% of the episodes being CRBSI, is effective and safe and shortens the duration of the intravenous treatment [197].

No specific information about the use of oral therapy in Gram-negative CRBSI is available. Sequential oral therapy can be considered in clinically

stable patients, with no metastatic complications and with negative blood cultures after the onset of treatment and the removal of the intravenous line.

Recommendations:

- Sequential oral therapy could be considered in clinically stable patients, with no metastatic complications, with negative blood cultures after the onset of treatment and the removal of the intravenous line, and if a therapeutic option with high oral biodisponiblility is available (A-II).
- In non-complicated CRBSI caused by fluoroquinolone-susceptible staphylococci the initial intravenous antibiotic treatment may be switched to high-dose oral fluoroquinolones plus rifampin to complete the duration of antibiotic therapy in clinically stable patients in whom clearance of bacteremia is documented. Linezolid could be an option if the involved microorganism is fluorquinolone resistant (A-II).
- In non-complicated CRBSI caused by fluoroquinolone-susceptible Gram-negative bacilli, the initial intravenous antibiotic treatment may be switched to high-dose oral fluoroquinolones to complete the duration of antibiotic therapy in clinically stable patients in whom clearance of bacteremia is documented (A-II).
- Step-down from an echinocandin or a lipid formulation of amphotericin B to oral fluconazole is safe and effective (C-III).

4.4. Conservative treatment. Antibiotic lock therapy

When is conservative management with antibiotic lock therapy recommended?

Whenever a conservative treatment is chosen, antibiotic-lock therapy should be combined with a systemic antimicrobial. In addition, the patient should be in a stable condition and the causal microorganism be considered of low virulence, i.e. CoNS. Metastatic or local septic complications should be excluded before a conservative treatment is initiated. Table 4 summarizes indications for catheter removal imposibiliting antibiotic lock therapy. Lock therapy consists of filling the catheter lumen with a mixture of an anticoagulant agent and high concentrations of antimicrobial or antiseptic substances, and

stopping temporarily of flushing the catheter. There´s currently no fully agreement about the choice of drugs and the duration of each lock period and of local treatment [220]. The first randomized, placebo-controlled trial [221] included tunneled or totally implanted long-term VAD and compared a lock solution containing vancomycin and ceftazidime to placebo, combined with parenteral antimicrobial treatment in both arms. 174 patients developed bacteremia, of which 85 were catheter-related and 44 patients met the criteria for the modified intention to treat analysis. Failure to cure the CRBSI occurred in 33% of the patients in the antibiotic lock arm and 57% in the placebo group (HR 0.55 P=0.10). The study failed to show statistically significant differences and had to be prematurely stopped due to difficulties in enrollment. A retrospective and prospective, open, non-comparative study, lock therapy with vancomycin plus ciprofloxacin or amikacin, for 7-16 days showed a cure rate of 82% [170]. A prospective, non-comparative study in tunneled hemodialysis catheters causing bacteremia, combining systemic antimicrobial therapy with lock-therapy cured 40 of 79 patients [222]. Compared to the author´s own historical series of patients treated with systemic antibiotics and immediate catheter withdrawal, salvage therapy was not associated with increased complications or long term differences in survival.

Recommendation:

- Conservative treatment should not be prescribed to patients with metastatic or local septic complications (A-II).
- The use of lock-therapy, added to systemic antimicrobial agents, is recommended systematically for infected catheters that fulfill criteria of retaining the catheter: the patient in a stable condition and the involved microorganism is considered of low virulence (i.e., CoNS). (A-I)
- In stable patient without local or systemic complications, conservative treatment may be also attempted for enterococci, corynebacterium (except *Corynebacterium jeikeium*) and Gram-negatives (consultation with an ID expert is suggested in these cases) (C-III)
- The use of an antibiotic lock does not preclude the need for systemic antimicrobial therapy (A-I).

What antibiotics and concentrations of antibiotic lock solutions are recommended?

Ideal antibiotics used for the conservative treatment CRBSI should meet the following characteristics: 1) high activity against biofilms (ability to penetrate and disrupt the biofilm); 2) achieve high concentrations (100-1,000 times the MIC of planktonic cells); 3) stability at room temperature for several days (allows storage of prepared solutions and replacement of antibiotic-lock every 24h-72h); 4) compatibility with anticoagulants; 5) safety; 6) low potential for resistance; and 7) affordable cost [223–225] .

There are no randomized studies comparing the effectiveness of different antibiotics used for antimicrobial lock-therapy (ALT). Data derive from very heterogeneous observational studies. Here, the published evidence of the most commonly used is summarized.

Vancomycin is probably the most widely used antibiotic for ALT, at concentrations ranging from 2,000 to 20,000 mg/L, with 2,000 mg/L being the most commonly used [223,226], because the drug precipitates at 10,000 mg/L. Vancomycin 2,000 mg/L is stable at 37ºC [170], and may be combined with heparin at 20-100 IU/mL and 4% sodium citrate [227,228], as well as with other antibiotics such as ciprofloxacin, gentamicin, amikacin and ceftazidime, which facilitates the treatment of polymicrobial infections. In terms of efficacy, vancomycin 2,000 mg/L has shown to cure 77%-93% cure in infections caused by CoNS [170,226,229] .

Teicoplanin has been used at concentrations between 5,000 and 20,000 mg/L, the most commonly used being 10,000 mg/L [170]. It remains stable for 96 hours with and without associated heparin [230]. It may combined with heparin 100 IU/mL [226] and amikacin and gentamicin for polymicrobial infections [231]. Compared with vancomycin 2,000 mg/L, teicoplanin 10,000 mg/L has shown superior efficacy [226].

Daptomycin has been used at concentrations between 3,500 and 5,000 mg/L [226,232]. Ringer lactate should be added to solution. The solution remains stable with and without heparin for 96h [230] and may be combined with heparin 100, 400 and 5,000 IU/mL and 4% sodium citrate (daptomycin 5,000 mg/L), as well as ethanol 25% [233]. In a study of 13 cases, daptomycin 5,000 mg/L achieved an 85% rate of cure [234].

Ciprofloxacin has been used at 2,000 mg/L for the treatment of infections caused by Gram-negative bacilli, including *Pseudomonas* spp. [170,229,235] reaching success rates of 95% in selected populations [223]. The solution remains stable at 37ºC for 10 days. It precipitates with heparin [231] but maintains its efficacy [170]. *Amikacin* has been broadly used at concentrations between 1,500 and 60,000 mg/L, the most frequently used being 2,000 mg/L [223]. It can be administered with heparin and its efficacy is high, above 90%[223] .
Other antibiotics used as ALT for the conservative treatment of CRBSI are gentamicin (2,000-5,000 mg/L), cefazolin (5,000-10,000 mg/L), and ceftazidime (500-10,000 mg/L) [223,224].

Recommendation:

- The most frequently used antibiotics for ALT as part of the conservative treatment of CRBSI are vancomycin 2,000 mg/L, teicoplanin 10,000 mg/L, daptomycin 5,000 mg/L, ciprofloxacin 2,000 mg/L, and amikacin 2,000 mg/L (B-I).

How should antibiotic lock therapy be performed?

Lock solutions described in the literature with potential use in clinical practice have been depicted in Table 5. Although many published studies on the effectiveness of ALT are available, few describe the methos of the technique in detail [103,223–225].

ALT preparation and storage. The solution should be prepared under sterile conditions, ideally, in a Pharmacy Service. These solutions have prolonged stability and may be prepared every 3-7 days and stored at 4ºC until use (Table 6).

Volume of the lock solution. Most studies use between 2 and 3 mL in tunneled catheters and 3 to 5 mL in totally implantable ports [170,235–240]. However, considering the great variability of catheters used, the exact catheter volume, according to data provided by the manufacturer, should be instilled [235,237,241].

Replacement of ALT solutions. Before using the catheter or replacing the ALT solution, the previous ALT should be removed [170,222,238,241–244], thus avoiding the risk of adverse events associated with rapid infusion of antibiotics at high concentrations and cleaning of the catheter lumen occurs by entrainment.

Length of ALT. The optional duration of ALT is not known. In most of the recent studies, ALT was given for 10-14 days [170,221,229,234,235,239,243–245], although shorter treatment duration may be efficatious, specially for Gram-negative infections [170,245].

Frequency of ALT. The frequency of ALT replacement has not been established. It is usually performed every 24-72h and adapted to the needs of use of the infected line. In hemodialysis patients ALT is replaced after each hemodialysis session [170,234–236,241,246] . If a more frequent use of the catheter is needed, the lock is replaced every 24h [221,229,245].

Catheter use. Ideally, the catheter should not be used while the ALT solution is in place. However, in patients receiving parenteral nutrition or those with few or no other venous access options, ALT and catheter may be alternated. In these cases a minimum of 8-12h a day is recommended [221,229,235,245,247]. If the catheter has more than one lumen, all should be treated.

Systemic treatment. Bacteriemic patients should be treated with systemic antibiotics for a period of 7-14 days [170,229,235,237,243,245,247]. This time can be reduced in infections with CoNS[25].

Recommendation:

- ALT solutions should be prepared under sterile conditions. They should be infused after removing the previous dose and the exact volume of the catheter lumen should be infused. Duration of ALT of 10 to 14 days are recommended. ALT solution should be replaced every 24-72h and must remain in the catheter lumen a minimum of 12h a day (B-I).

What non-antibiotic substances could be used for lock therapy?

Besides the previously described antibiotics, other non-antibiotic substances have been used for lock therapy.

Ethanol (with activity against bacteria and fungi) has been used for the prevention of CRBSI in long-term CVCs. Compared to saline or heparin solutions, a 70% ethanol lock has shown a significant decrease in the rate of CRBSI in several therapeutic randomized trials [165,248–251]. It is important to note that these studies also reported on severe adverse events, like flushing, dizziness, liver enzyme doubling, catheter rupture or thrombosis, leading to interruption of therapy in some patients [251]. In two retrospective and one randomized studies including more than 100 patients that used 70% ethanol lock for the treatment of CRBSI cure rates were reported in 62%-91% of cases with no significant adverse events [165,252,253] .

Taurolidine, as 70% ethanol, has been evaluated in several large randomized studies in the prevention of CRBSI. Compared, mostly to heparin, taurolidine was associated with significant reductions in the rate of bloodstream infections. In a retrospective study of treatment of CRBSI with taurolidine lock in 11 oncology patients, only three relapsed, but were eventually cured with repeated taurolidine lock [254] .

EDTA and citrate. These two chelators disrupt biofilm, thus increasing antimicrobial activity. Several in vitro studies have proven the anti-biofilm effect of EDTA alone or in combination with gentamicin or minocycline-25% ethanol [103,223]. Further clinical studies are needed to establish the role of these two substances[255].

Recommendations:

- 70% ethanol and taurolidine locks may also be used for the conservative treatment of CRBSI. There is no evidence to advocate for its routine use. (B-I).

Which are the criteria for failure of the conservative management?

Criteria for failure of conservative treatment of CRBSI is based on worsening clinical condition of the patient, persistence of the infection and catheter dysfunction or removal [84,164,170,229,256–258].

Performance of randomized clinical trials about retaining infected catheters in certain critical clinical conditions seem unethical. Also, catheter dysfunction requiring its replacement is considered conservative treatment failure. In most reports, catheters were removed for ongoing sepsis, defined as persistent fever or bacteremia after 48-72 hours of adecuate therapy, if metastatic septic complications, like endocarditis or osteomyelitis, or if local complications, such as venous thrombosis, septic phlebitis or tunnelitis occur. Some of these complications are those that contraindicate a conservative management. They should be followed by sequential blood cultures drawn both from a peripheral vein and through the catheter to monitor the clinical course of CRBSI [229,256].

The definition of efficacy or failure of conservative management in clinical studies or in clinical practice sometimes includes late relapses of infection [258].

Recommendation:

- Any clinical condition or catheter dysfunction prompting to catheter removal should be considered a failure of conservative management (A-I).

4.5. Management of local complications

How should insertion-site infection be managed?

Short-term catheters (peripheral venous, non-tunnelled CVCs and arterial catheters) with erythema, pain, warmth, induration and/or purulent drainage within 2 cm of the catheter exit site should be removed despite absence of concomitant bacteremia [25,259]. Any exudate at the insertion site should be submitted for Gram staining, routine culture, and fungal culture when assessing immunocompromised patients [25].

In uncomplicated exit–site infections of long-term catheters (tunneled CVCs, hemodialysis), defined as absence of fever, positive blood cultures or purulence, cultures of any drainage from the exit site and peripheral blood

cultures should be obtained [260]. Under these circunstances, topical application of antibiotic ointments at the insertion site may be considered based on exit site culture results. If the infection does not resolve or purulent exudate develops, systemic antibiotics should be administered. If clinical signs of infection persist after 48-72 hours of appropriate antimicrobial therapy, the catheter should be removed [25,260] Topical application of antibiotics ointments to the insertion site after catheter removal is not recommended [261].

Recommendations:

- The presence of local pain, induration, erythema or exudate for peripheral venous catheters mandates catheter removal (A-I).
- For non-tunneled CVC the presence of erythema or purulence at the catheter insertion site requires immediate catheter removal (B-II).
- For uncomplicated exit–site infections in long-term catheters a conservative approach with topical antimicrobial agents should first be attempted. In case of topical treatment failure, systemic antibiotics should be administered (B-III).
- Persistence of clinical signs of infection beyond 72 hours of conservative management requires removal of the catheter (B-II).

How should tunnellitis be managed?

A tunnel infection in long-term catheters other than hemodialysis catheters should be managed with catheter removal, drainage and incision, if indicated, and 7-10 days of systemic antibiotic therapy in the absence of concomitant bacteremia or candidemia [25,262], if systemic antibiotics fail, the catheter should be removed. In the setting of a tunnel infection with fever catheter removal is the first choice, together with adequate antibiotic therapy [67,263].

Failures rates higher than 50% with a conservative approach have been reported and, in this case, are associated with increased cost and work load [223,264].

Recommendations:

- Patients with tunnel infection not associated with hemodialysis catheters require catheter removal, incision and drainage, if indicated, and 7-10 days of systemic antimicrobial therapy in the absence of concomitant bacteremia or candidemia (A-II).
- For tunnellitis without fever in hemodialysis catheters, systemic antibiotic therapy may be attempted first (A-II). In tunnel infection with fever, however, catheter removal is the first therapeutic option in combination with systemic antimicrobial therapy (A-II).
- In tunnellitis, conservative management is associated with increased failure rates (B-II)

How should a port reservoir local infection be managed?

A complicated local infection of a venous access device is defined as infection of the tunnel or port pocket with erythema or induration (more than 2 cm), purulent collection, skin necrosis and spontaneous rupture and drainage. A stitch abscess is a focal area of purulence or erythema surrounding a suture. The single offending stitch can usually be removed without further consequence and should not be confused with a port infection [264]. Management of a port reservoir requires port removal, drainage of the affected tissue and administration of antibiotic therapy for 7-10 days, in the absence of concomitant bacteremia or fungemia [25,223,225.] Depending of the severity of the infection, the insertion wound may either be sutured after remoival the port, or, if there is significant drainage of exudate or pus, the wound should be left open and packed with iodoform gauze to heal by second intention [264]. Removal of a surgical venous access port is frequently a management challenge and, therefore, avoided initially. Alternatively, port salvage by conservative treatment may be attempted for halting the use of the device and initiating a combination of antibiotic lock and systemic antibiotic treatment [103]. Most infections are associated with intraluminal colonization and, therefore, administration of high concentration of antimicrobial solution is necessary to attempt to sterilize the

device [265].

Recommendations:

- The presence of local inflammatory signs in a port reservoir mandates the removal of the port, draining the affected tissue and starting systemic antibiotic therapy (A-II).
- If a conservative strategy is the only option, a combination of systemic antibiotic and antibiotic lock therapy should be prescribed, bearing in mind that this approach is associated with a high failure rate (B-II)

4.6. Patient follow-up

In which patients and when should a follow-up blood culture be taken?

Persistence bloodstream infection is defined as the presence of viable pathogens in the blood after 3 days of appropriate antimicrobial treatment. Persistent bacteremia with certain pathogens has been associated with the development of complications and a worse outcome[266] . Patients with persistent bacteremia due to *Staphylococcus aureus* presented higher rates of relapse and related mortality within 12 weeks of bacteremia [267]. The most robust predictor of complicated *S. aureus* bacteremia was the positivity of follow-up blood cultures at 48 to 96 hours from the first positive blood culture [268]. In a study taking blood cultures every 3 days after a positive blood culture for *S. aureus,* a <3 days duration of bacteremia was with a rate of septic metastasis of 5%, whereas the rate increased to 25% for patients with ≥10 days of documented bacteremia [269] .

Persistent candidemia has also been associated with a high mortality rate. Kim et al, reported that persistent candidemia increased the mortality risk with an adjusted hazard ratio of 2.5 (95% CI 1.33-4.72). As antifungal therapy should be continued until 14 days after the first negative blood culture, follow-up blood cultures should be obtained daily until the first negative blood culture[270].

Recommendations:

- Follow-up blood cultures should be taken in all patients with *S. aureus* or *Candida* spp CRBSI (A-II).
- In patients with S. aureus CRBSI, our recommendation is that follow-up blood cultures should be obtained every 72 hours until the first negative result (A-II).
- Control blood cultures in CRSB by Candida spp should be obtained every 48 hours until the first negative blood culture.(A-II).
- For other microorganims causing CRBSI and if catheter salvage is attempted, follow-up blood cultures should be obtained after 72 hours of starting appropriate antibiotic therapy. If persistent bacteremia is documented catheter removal is mandatory (B-II).
- It is not necessary to routinely perform follow-up blood cultures in patients with CRBSI due to microorganisms other than *S. aureus* or *Candida* spp if catheter withdrawal has been performed (A-II).

When should echocardiography be performed?

The risk of underlying infective endocarditis in bacteremic patients depends mainly on the etiologic causing bacteremia and the predisposing conditions of the patient. Patients wih *S. aureus* bacteremia has a high risk for IE that frequently is not clinically evident or suspected.

The absence of valvular risk (no valvular disease, neither previous nor diagnosed at the moment of SAB), along with a clinical and microbiological response (negative blood cultures) to therapy within the first 72 h of after the catheter removal and start onset of adequate antibiotics are associated with a favorable outcome (absence of complications or relapse) in more than 95% of patients receiving treatment for at least 14 days after negative blood cultures. A recent systematic review [271] of 9 observational studies with sample sizes ranging from 98 to 877 patients[272,273] reported an incidence of 2 to 14% detected by transthoracic echocardiography (TTE) and 14% to 25% by transesophageal echocardiography (TEE). Clinical findings and TTE were poorly predictive of subsequent TEE findings. In a high proportion of cases IE is

not suspected on clinical grounds and 15% of the cases were reclassified on the basis of the TEE [274].

Currently, 6 studies [275–280] suggest that TEE can be avoided safely in patients without any of the following risk factors due to very low risk for IE: prolonged bacteremia, hemodialysis, community-acquisition, metastatic foci of infection, immunologic or embolic phenomena, intravenous drug abuse (IVDA), implantable CVC, intracardiac device, prosthetic valve, previous IE or cardiac structural abnormality.

In patients with proven enterococcal CRBSI the requeriment of systematically ruling out endocarditis is currently under discussion. Estimates of endocardial involvement vary and are not well addressed in the medical literature. In a recent study on 1515 patients with enterococcal –BSI, 65 (4.29%) had endocarditis, representing 16.7% of those who underwent TTE and 35.5% who underwent TEE. A bedside predictive score totalling of 12 points for enterococcal endocarditis the NOVA score includes the number of positive blood cultures, the origin of the bacteremia, previous valve disease and auscultation of a heart murmur. A NOVA score below 5 points, 14 to 27% of patients with enterococcal bacteremia, identifies a subgroup at very low risk for enterococcal endocarditis in whom TEE could be avoided [281].

The incidence of endocarditis in patients with candidaemia has been assessed less frequently. In a recently study, endocarditis was detected in 2.9 % of patients with candidaemia using TTE and in 11.5% undergoing TEE [282].

Recommendations:

- In the large majority of patients with *Staphylococcus aureus* bacteremia TEE should be performed. A TEE is not needed or may be delayed in patients without the following risk factors: prolonged bacteremia, hemodialysis, metastatic foci of infection, IVDA, implantable CVC, intracardiac device, prosthetic valve, previous IE or cardiac structural abnormality. (A-II)
- The need of a TEE in episodes of CRBI caused by other pathogens should be individualized. This panel considers that IE should be ruled out in all patients with persistent bacteremia (or fungemia) (C-III).

Enterococcus spp or *Candida* spp are pathogens associated with high risk of developing endocarditis.

What is the diagnosis and management of suppurative thrombophlebitis?

Suppurative thrombophlebitis refers to venous thrombosis associated with infection and bacteremia. The pathogenesis of catheter related thrombosis results from activation of coagulation pathways by the foreign material and from vascular endothelial damage and endothelial cell activation [25,283]. Infection may also stimulate thrombus formation by aggravating coagulation abnormalities. The presence of a thrombus mass around the catheter increases the risk for microbial colonisation and bacteraemia [284]. Therefore, CRBSI and thrombosis have a bidirectional relationship.

Suppurative thrombophlebitis combines signs and symptoms of infection and from thrombosis together with the dysfunction of the involved catheter. Microbiological and radiologic tests are necessary to confirm the diagnosis. Thrombosis should be confirmed by means of ultrasonography (70-100% sensitivity and 93% specificity), high resolution computed tomography or flebography. Limited experience with magnetic resonance imaging suggests that it may also be useful in the diagnosis of thrombophlebitis [25,285]. Recent data indicates that a proactive search for thrombosis in the setting of suspected CRBSI is a safe and effective strategy allowing preservation of the catheter in neutropenic patients if tromosis is ruled out [285].

Thrombophlebitis management mandates catheter removal, prolonged antimicrobial treatment of at least 4-6 weeks, surgery (abscess drainage and/or venous resection) if a collection is detected or if clinical response is not achieved, and thrombus treatment (anticoagulation or even thrombolysis) [284]. Venous resection has not demonstrated to be superiot to conservative management (including involvement of superficial veins). There is insufficient clinical evidence available supporting the use of systemic anticoagulacion and systemic thrombolysis has been used only in specific cases [286–288].

Follow-up of thrombophlebitis should include clinical data, sequential ultrasonography and eventually biomarkers. Procalcitonina (PCT) will probably will be more effective in the detection of non-responding CRBSI, potentially due to associated thrombophlebitis, where urgent catheter removal would be

required[289].

Recommendation

- Suppurative thrombophlebitis should be ruled out in all episodes of CRBSI with persistent bacteremia (A-II).
- Confirmed diagnosis, mainly by ultrasonography, should be followed by catheter withdrawal, prolonged antibiotic treatment and individualized assessment of the need for anticoagulation (A-II).

When can a new catheter be inserted?

There is no scientific evidence indicating how long it should wait before a new catheter can be safely inserted after an episode of CRBSI. The placement of a new catheter will obviously be conditioned by the need for vascular accesss. Short-term catheters for continuous infusion of vital drugs usually require immediate insertion of a new catheter. If waiting is feasible, PCT may be useful for monitoring the response to therapy. In a small prospective study including 26 patients with CRBSI, serum PCT concentrations >1.5 ng/ml on day 3 of therapy was associated with lack of response to therapy (sensitivity 70%, specificity 68.7%; p = 0.028). Moreover, a decrease in serum PCT concentration from day 1 to day 2 and from day 2 to day 3 of at least 1.00 ng/ml and 0.30 ng/ml, respectively, indicated response to therapy (p = 0.037 and 0.017 respectively) [289].

The clinical situation of patients with long-term catheters, implantable venous access ports (IVAC) or tunneled catheters may allow for a time interval before a new catheter is placed. Experts recommend to wait for resolution of clinical signs and even for microbiological eradication (negative blood cultures). The only available study is a small case-control evaluation did not show differences between removal with simultaneous reimplantation in 13 patients and delayed reimplantation (mean 14 days) in 21. Reinfection occurred in two patients in the simultaneous reimplantation group (15.4%) and in one patient in the delayed re-implantation group (4.8%) [290]. Non-randomized studies in haemodialysis-associated CRBSI have shown heterogeneous results [164].

Recommendation

- Although there is a clear lack of scientific evidence, it seems advisable to wait, if feasible, before placement of a new catheter after an episode of CRBSI. The waiting time period should be determined by the resolution of signs and symptoms. If a patient urgently needs vascular access, a catheter should be inserted without delay (C-III)
- The insertion of a new catheter after the diagnosis of a CRBSI is always possible if the patient´s clinical condition dictates the need for a new vascular access (A-III)

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Table 1. Strength of recommendation and quality of evidence.

Category / grade Strength of recommendation	**Definition**
A	Strongly supports a recommendation for use
B	Moderately supports a recommendation for use
C	Marginally supports a recommendation for use
D	Supports a recommendation against use
Quality of evidence	
I	Evidence from at least one properly designed randomized, controlled trial
II	Evidence from at least one 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 of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

Table 2. Summary of Main Diagnostic Methods for Catheter-Related bloodstream infections.

	Criteria for positivity	Interpretation	Comments	Recommendation
Diagnosis without catheter withdrawal				
Paired quantitative blood cultures	Ratio ≥3:1	Both sets are positive for the same microorganism and the set obtained through the catheter has ≥5:1 fold-higher colony count than the peripheral culture	Sensitivity ≈ 79% Specificity ≈ 99% Labor intensive and expensive	A-II
Paired blood cultures for differential time to positivity (DTP)	≥120 minutes	Both sets are positive for the same microorganism and the set obtained through the catheter becomes positive ≥120 minutes earlier	Sensitivity: 72% to 96% Specificity: 90% to 95% Less specificity for long-term catheters The interpretation of DTP should take into account the adherence to the technical procedure and the type of microorganism	A-II
Endoluminal brushing	>100 CFU	Indicative of CRBI	Sensitivity: 95% to 100% Specificity: 84% to 89% It may underestimate CRBI in short-term catheters Risk of pathogen dissemination and thrombotic complications.	C-III
Superficial cultures (semiquantitative cultures of skin surrounding the	≥15 CFU per plate	Indicative of CRBI	Sensitivity: 78% Specificity: 92% It is necessary to combine with peripheral blood culture	B-II

portal entry and catheter hubs)				
Gram stain and Acridine orange leukocyte cytospin of catheter blood	Presence of any microorganisms in a minimum of 100 high-power fields	Indicative of CRBI	Sensitivity: ≈79% Specificity: ≈87% It is a simple and rapid technique, but it requires cytospin technology	B-II
Diagnosis with catheter withdrawal				
Semiquantitative catheter culture	≥15 CFU	The same microorganism in at least one percutaneous blood culture and the catheter tip	Sensitivity ≈ 84% Specificity ≈ 86% This method mainly detects colonization of the external surface	A-II
Quantitative catheter segment culture (vortexing or flushing internal surface)	$\geq 10^3$ CFU	The same microorganism in at least one percutaneous blood culture and the catheter tip	Sensitivity ≈ 83% Specificity ≈ 91% All quantitative methods are time consuming	A-II
Quantitative catheter segment culture (sonication)	$\geq 10^2$ CFU	The same microorganism in at least one percutaneous blood culture and the catheter tip	Sensitivity ≈ 83% Specificity ≈ 91% All quantitative methods are time consuming	A-II

Table 4. Indications for catheter removal in patients with CRBSI

CRBSI presenting with septic shock
CRBSI caused by certain pathogens: S. aureus, Non-fermenting gram-negative bacilli, Candida spp. or Mycobacterium
Metastatic complications (endocarditis, Thrombophlebitis or septic lung emboli)
Bacteremia (or candidemia) persisting after 72 h of correct treatment
Evident pus at the insertion site.
Signs of infection at the subcutaneous tunnel.
No possibility of antibiotic lock therapy

Table 3. Main antimicrobial drugs dosages that could be used for catheter related infections. Note that doses of the drugs are not adjusted to renal or hepatic function.

Antimicrobial	Dosage
Antibacterials	
Amikacin	Loading dose: 25-30 mg/kg IV followed by 15-20 mg/kg/d IV
Amoxicillin-clavulanate	2g/200-500 mg every 6-8 h IV
Ampicillin	2 g every 6-8 h IV
Aztreonam	1-2 g/6-8 h IV
Cefazolin	2 g every 8 h IV
Cefepime	2 g/8-12 h IV
Ceftaroline	600 mg/12h IV
Ceftazidime	2 g/8-12h IV
Ceftriaxone	1 g every 12 h
Cefotaxime	1-2 g/6-8 h IV
Ciprofloxacin	500 mg/12h IV VO
Cloxacillin	2 g every 4 h IV
Colistin	7-9 MU load, then 4.5 MU every 12 h IV
Dalbavancin	1000 mg IV, 500 mg IV one week apart
Daptomycin	8–10 mg/kg/d IV
Ertapenem	1 g every 24 h IV
Fosfomycin	4 g/6-8 h IV
Gentamycin	5-7 mg/kg/d IV
Imipenem-cilastatin	500 mg every 6 h IV
Levofloxacin	750 mg daily 750 mg daily
Linezolid	600 mg every 12 h
Meropenem	1 g every 8 h IV

Piperacillin-tazobactam	4/0.5 g every 6–8 h
SMX-TMP	160–800 mg bid 5–10 mg/kg/day of TMP
Tedizolid	200 mg/d
Teicoplanin	6 mg/k/12 h (3 doses), 6 mg/k/d IV
Tobramycin	5-7 mg/k/d IV
Vancomycin	Loading dose: 25-30 mg/kg IV then 15-20 mg/kg/8-12h IV
Antifungals	
Anidulafungin	200 mg loading dose, 100 mg/d IV
Caspofungin	70 mg loading dose, 50 mg/k/d
Fluconazole	800 mg loading dose, then 400 mg daily
Liposomal amphotericin B	3–5 mg/kg/d
Micafungin	100 mg/d IV
Voriconazole	400 mg bid × 2 doses, then 200 mg every 12 h 6 mg/kg IV every 12 h for 2 doses, followed by 4 mg/kg IV every 12 h

Table 5. Lock solutions described in the literature with potential use in clinical practice. This table is not intended to be an exhaustive compendium and there are no clinical trials to provide evidence level to use so only they reflect the opinion of experts. Although there is no scientific evidence to make a recommendation regarding the optimal time duration and replacement of lock solutions, we recommend to extend it for 14 days. We also recommend drawing a blood culture through all catheter lumens 72 hours after completion of therapy. We further recall that the antimicrobial lock therapy is necessary but not sufficient. Any antimicrobial lock therapy must be accompanied by a systemic antibiotic treatment that will last over time depending on the pathogen involved.

MICROORGANISM	ANTIMICROBIAL	CONCENTRATION	NOTES
Staphylococci[1]	Daptomycin	5 mg/ml	Solve in Ringer lactato (calcio)
	Vancomycin	2 mg/ml	Incompatible with heparin > 5 mg/ml
	Teicoplanin	10 mg/ml	
Enterococci[2]	Vancomycin + Gentamycin	Both 2 mg/ml	
Gran-negative bacilli[3]	Levofloxacin	5 mg/ml	Precipitates with heparin
	Ciprofloxacin	2 mg/ml	Precipitates with heparin
	Amikacin	2-10 mg/ml	
	Piperacillin-tazobactan	10 mg/ml	
Candida species[4]	Equinocandin	5 mg/ml	
	Liposomal Anfotericin B	1-5 mg/ml	

[1] A conservative treatment is recommended only in the case of coagulase-negative staphylococci. Catheter removal is recommended if S. aureus is involved.
[2] There is insufficient experience to recommend conservative treatment. However, if the patient is stable and is uncomplicated bacteremia conservative treatment might be assessed
[3] In the case of *Pseudomonas aeruginosa* and other non-fermenting Gram-negative bacilli (*Acinetobacter* spp , *Stenotrophomonas* spp , ...) there is no clear recommendation for a conservative treatment
[4] In the case of catheter-related candidemia it is recommended to remove the catheter. If it is not possible to withdraw or withdrawal is postponed, catheter should be locked.

Table 6. Preparation of the most common antibiotic solutions for lock therapy.

Vancomycin 2,000 mg/L plus sodium heparin 20 IU/mL	250 mL of 0.9% saline or 5% glucose + 500 mg of vancomycin + 5 mL of 1% sodium heparin (1 mL heparin = 1.000 IU)
Teicoplanin 10,000 mg/L plus sodium heparin 125 IU/mL	1. Reconstitute 400 mg of teicoplanin with 3 mL of sterile water for injection 2. Remove 18 mL from a bag of 50 mL of 0.9% saline 3. Add 3 mL of reconstituted teicoplanin to saline bag 4. Add 5 mL of 1% sodium heparin to saline bag
Daptomycin 5,000 mg/L plus sodium heparin 100 IU/mL	1. Reconstitute 350 mg of daptomycin with 7mL of sterile water for injection 2. With a 1 mL syringe, take 1 mL of reconstituted daptomycin 3. With the same syringe, take 1 mL of 1% sodium heparin 4. With the same syringe, take 8 mL of Ringer lactate
Ciprofloxacin 2,000 mg/L plus sodium heparin 20 IU/mL	1. Add 4 mL of 1% sodium heparin in a bag of 400 mg of ciprofloxacin 2. Stir for a minute before taking the required amount of solution
Amikacin 2,000 mg/L plus sodium heparin 20 IU/mL	250 mL of 0.9% saline or 5% glucose + 500 mg of amikacin + 5 mL of 1% sodium heparin

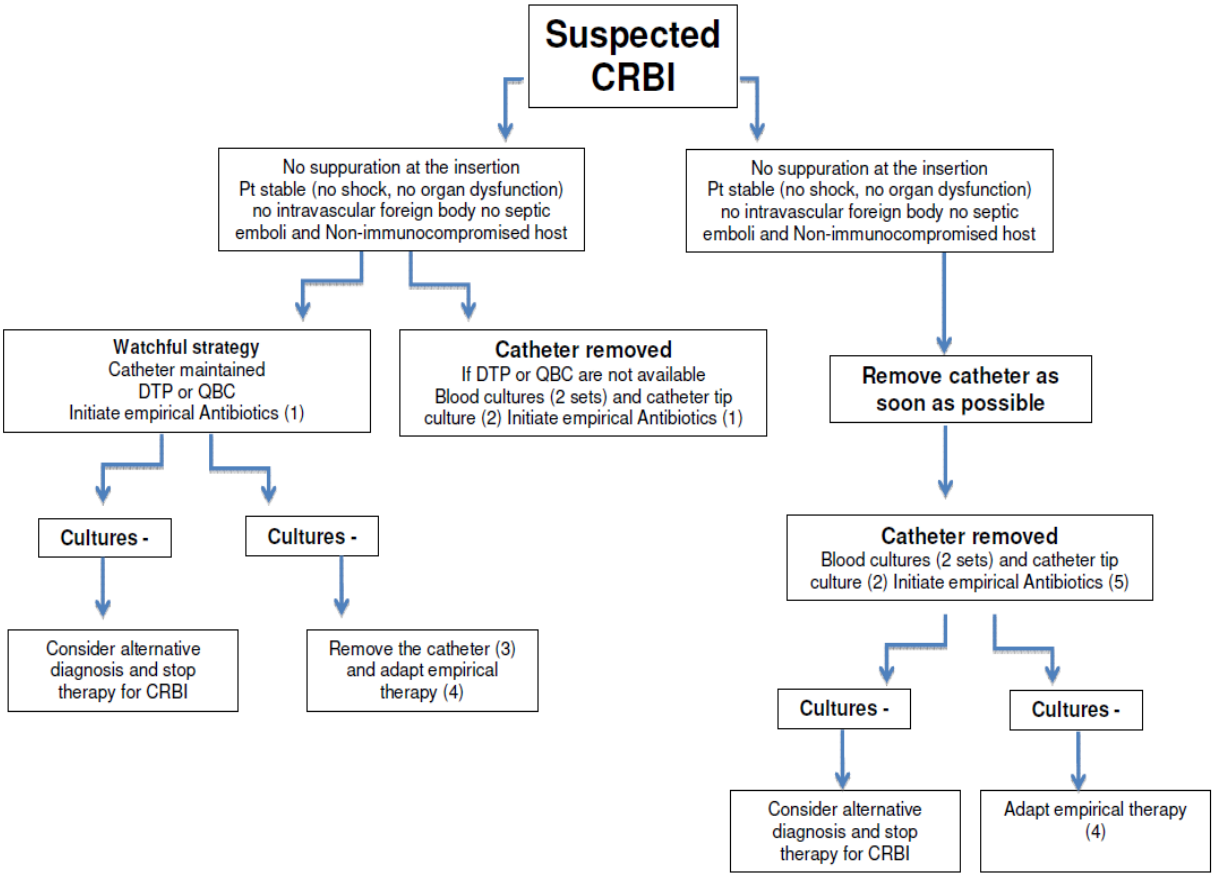

FIGURE 1. Approach to the management of a patient with suspicion of CRBI.

(1) Vancomycin (Alternative daptomycin; see text for specific recommendations of this agent) plus antibiotic therapy to cover gram-negative bacilli if: femoral catheter in place, a known focus of gram-negative infection, a high index of colonization by gram-negative bacilli or a prolonged admission in ICU. As the patient is clinically stable, consider antifungal therapy (fluconazole) in patients with total parenteral nutrition, prolonged use of broad-spectrum antibiotics, malignancy, femoral catheterization, colonization due to Candida species at multiple sites or previous anti-anaerobic therapy.
(2) Semicuantitative or quantitative tip culture.
(3) Catheter can be maintained only in patients without septic shock secondary to CRBI, without intravascular devices, and if the culprit pathogen is a CoNS (except *Stahphylococcus lugdunensis*) or a Gram-negative bacilli if the isolate is susceptible to antibiotics that are available for ALT. See Figure 2 for management.
(4) See text and Figure 2 for choosing targeted treatment, duration of therapy, and need of Echocardiography.
(5) Vancomycin (Alternative daptomycin; see text for specific recommendations of this agent) plus antibiotic therapy to cover gram-negative bacilli plus an antifungal agent in patients with septic shock or in other patients if: total parenteral nutrition, prolonged use of broad-spectrum antibiotics, malignancy, femoral catheterization, colonization due to Candida species at multiple sites or intense previous anti-anaerobic therapy. Echinocandins or alternatively liposomal amphotericin B should be used only in patients with septic shock. Fluconazole is the drug of choice in the rest of situations excepts in patients colonized by fluconazole-resistant *Candida* spp. Patients with Suppuration at the insertion site but without the other conditions should not receive antibiotic therapy active against gram-negative bacilli and antifungal agent.

DTP: differential time to positivity
QBC: Quantitative blood culture

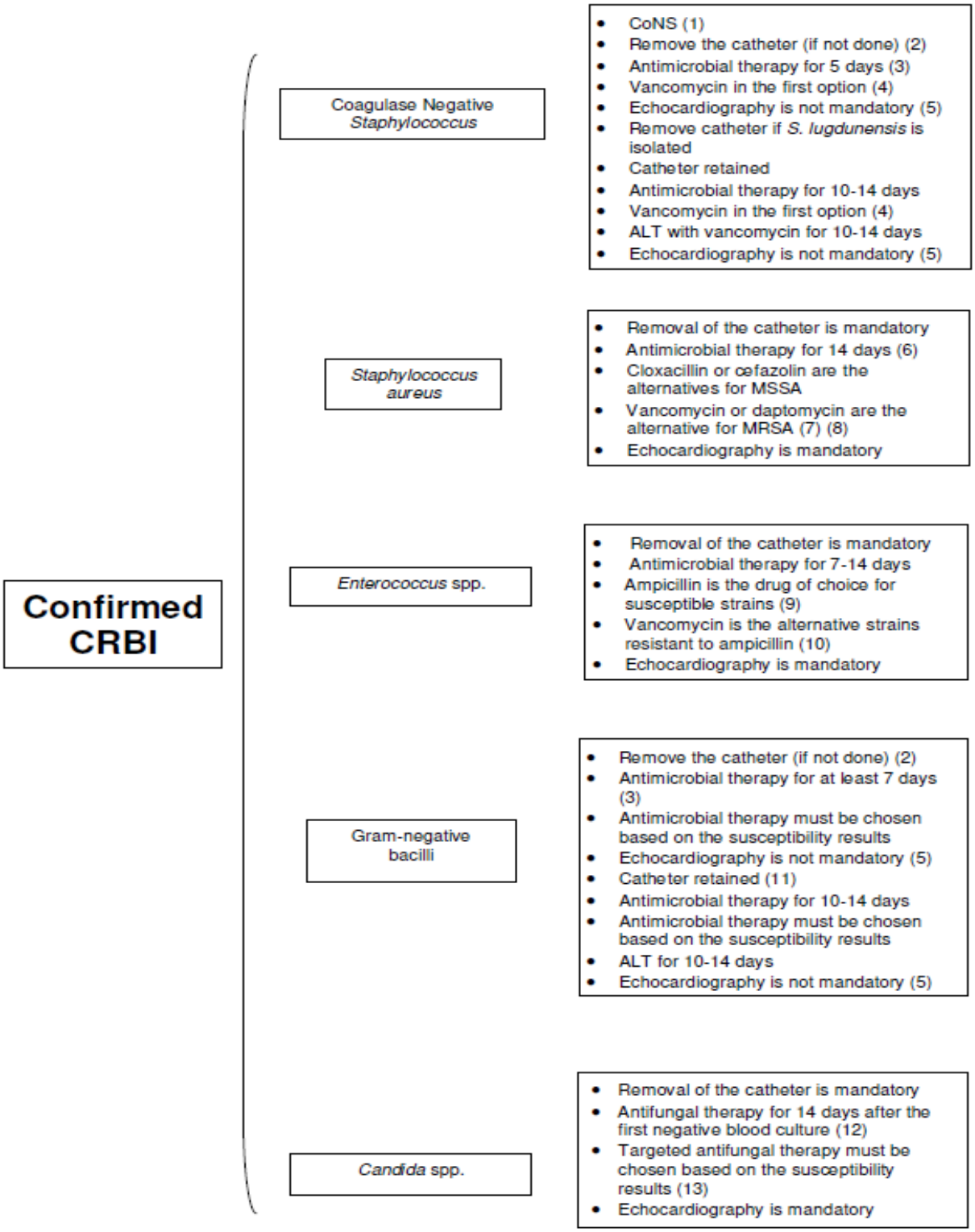
Confirmed CRBI
Coagulase Negative Staphylococcus
CoNS (1)
Remove the catheter (if not done) (2)
Antimicrobial therapy for 5 days (3)
Vancomycin in the first option (4)
Echocardiography is not mandatory (5)
Remove catheter if S. lugdunensis is isolated
Catheter retained
Antimicrobial therapy for 10-14 days
Vancomycin in the first option (4)
ALT with vancomycin for 10-14 days
Echocardiography is not mandatory (5)
Staphylococcus aureus
Removal of the catheter is mandatory
Antimicrobial therapy for 14 days (6)
Cloxacillin or cefazolin are the alternatives for MSSA
Vancomycin or daptomycin are the alternative for MRSA (7) (8)
Echocardiography is mandatory
Enterococcus spp.
Removal of the catheter is mandatory
Antimicrobial therapy for 7-14 days
Ampicillin is the drug of choice for susceptible strains (9)
Vancomycin is the alternative strains resistant to ampicillin (10)
Echocardiography is mandatory
Gram-negative bacilli
Remove the catheter (if not done) (2)
Antimicrobial therapy for at least 7 days (3)
Antimicrobial therapy must be chosen based on the susceptibility results
Echocardiography is not mandatory (5)
Catheter retained (11)
Antimicrobial therapy for 10-14 days
Antimicrobial therapy must be chosen based on the susceptibility results
ALT for 10-14 days
Echocardiography is not mandatory (5)
Candida spp.
Removal of the catheter is mandatory
Antifungal therapy for 14 days after the first negative blood culture (12)
Targeted antifungal therapy must be chosen based on the susceptibility results (13)
Echocardiography is mandatory

FIGURE 2. Approach to the treatment of a patient with confirmed CRBI.

(1) With the exception of Stahphylococcus lugdunensis that should be managed as *S. aureus*.
(2) Catheter must be removed in patients with septic shock secondary to CRBI or in patients with intravascular devices,
(3) In patients with intravascular devices, foreign body (such as articular prosthesis) or in whom inflammatory markers persist after catheter removal therapy, antibiotic therapy for 10–14 days is recommended.
(4) Cloxacillin or cefazolin are the alternatives in methicillin susceptible strains. Optimal trough levels of vancomycin for CoNS are not defined.
(5) Echocardiography should be done in patients with valvular diseases or in case or persistent bacteremia despite appropriate therapy.
(6) Complicated episodes require longer therapy courses (4-6 weeks).
(7) Trough levels of vancomycin should be15-20 mg/L
(8) Daptomycin is preferred for isolates with MIC for vancomycin > 1.5 mg/L.
(9) Combined therapy with an aminoglycoside is discouraged for *Enterococcus* spp CRBI.
(10) Optimal trough levels of vancomycin for Enterococcus spp CRBI are not defined.
(11) Only in immunocompetent patients, without septic shock and the isolate is susceptible to antibiotics that are available for ALT.
(12) If metastatic complications has been ruled out.
(13) De-escalation from an echinocandin or a lipid formulation of amphotericin B to fluconazole is highly recommended in patients who have isolates susceptible to fluconazole, who are clinically stable, and catheter has been removed.