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Diagnosis, prevention and treatment of haemodialysis catheter-related bloodstream infections (CRBSI): a position statement of European Renal Best Practice (ERBP)

Raymond Vanholder[1], Bernard Canaud[2], Richard Fluck[3], Michel Jadoul[4], Laura Labriola[4], A. Marti-Monros[5], J. Tordoir[6] and W. Van Biesen[1]

[1]Nephrology Section, Department of Internal Medicine, University Hospital, Gent, Belgium, [2]Nephrology, Dialysis and Intensive Care Unit, Lapeyronie University Hospital, Montpellier, France, [3]Department of Renal Medicine, Royal Derby Hospital, Derby, UK, [4]Nephrology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium, [5]Nephrology Department, Consorcio Hospital General Universitario, Valencia, Spain and [6]Vascular Surgery, Department of Surgery, Maastricht University Medical Center, Maastricht, the Netherlands

Correspondence and offprint requests to: Raymond Vanholder; E-mail: raymond.vanholder@ugent.be

In the July 2009 issue of the journal *Clinical Infectious Diseases*, the Infectious Diseases Society of America (IDSA) published an update of their 'Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection' [1]. The largest part of the IDSA text relates to non-dialysis catheters, and it is not always clear how far these general recommendations can be extrapolated to the haemodialysis condition. A specific section of the IDSA guidelines is, however, devoted to haemodialysis catheters.

In the present position statement by European Renal Best Practice (ERBP), we intend to focus on the items in these guidelines which are relevant for nephrologists and to amend them to haemodialysis conditions and/or for the European situation with regards to tunnelled catheters. ERBP is the new guidance body of the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA), replacing European Best Practice Guidelines (EBPG) since 2008.

We will discuss only those IDSA guidelines worth reflection or amendment. The corresponding IDSA guidelines will be mentioned between parentheses (). Guidelines which we did not consider for discussion, although they still might be relevant, are summarized in Table 1.

The present text has been issued in accordance with the new philosophy of ERBP to offer guidance by means of position statements commenting on documents issued by other guideline bodies or on recent relevant studies, next to *ad hoc* recommendations when not enough evidence is available [2,3]. Real guidelines are to be issued only in case of sufficient evidence. ERBP recently published two position statements along these principles [4,5].

Of note, earlier EBPG recommendations have been issued on vascular access and infectious disease in haemodialysis patients [6,7]. The current document further elaborates and updates these documents.

The IDSA guidelines are well written with a clear distinction between several subheadings, covering a general and a specific part. The same guidelines are frequently repeated, and the same items are also often covered both in the general and specific guidelines, albeit that the recommendations are not always exactly the same. The grading system is not the same as the one currently propagated by Grading of Recommendations, Assessment, Development and Evaluation (GRADE) and applied by ERBP and Kidney Disease: Improving Global Outcomes (KDIGO) [3,8,9.]: it is a nine-tiered system with three levels of evidence and three levels of strength vs two levels of evidence and four levels of strength for the three bodies mentioned above. Although the majority of IDSA guidelines are based on only one or two non-randomized trials often generated by one single research group, most of them are graded as level A.II, with only seven of 123 recommendations (5.7%) having the highest level (A.I). Although A.II gives the impression of being based on robust evidence, 'dramatic results even from uncontrolled experiments' suffice to attribute this level. The result is that, without clear notification to the readership, poorly-evidenced statements or 'parachute type' guidelines (i.e. guidelines which seem obvious but have not been or cannot be evidenced, like the recommendation of using a parachute when jumping out of a flying plane) are classified as well evidenced. However, the real evidence level of these IDSA guidelines is not high, which unfortunately is also true for most nephrological recommendations [2].

For the sake of clarity, the present position statement contains recommendations which are not based on a systematic literature review and are not supported by an evidence review team. The reader should consider them rather

Table 1. IDSA guidelines of relevance to nephrology which are not discussed in the present position statement

Overall aspects
Diagnosis: intravenous catheter cultures
Culturing of the tip is preferred to that of the subcutaneous segment (3)
Swab drainage should be performed in case of exit exudate (6)
Diagnosis: blood cultures
Samples for culturing should be obtained before antibiotic treatment and be collected in the same volumes if taken from different sites (11)(20)
Appropriate preparation with antiseptics of both skin and catheter hub is necessary (13)(14)
General management of catheter-related infections
Empirical combination coverage is necessary for multiresistant gram negatives (e.g. *Pseudomonas aeruginosa*) in severely ill patients (e.g. neutropenics[a]) (26)
Empirical coverage is needed for candidaemia in patients at risk (e.g. during or after prolonged use of broad spectrum antibiotics) (28) [b]
Unique aspects
Treating patients receiving haemodialysis
Antibiotics can be discontinued if all blood cultures are negative (55)
Suppurative thrombophlebitis
The diagnosis of suppurative thrombophlebitis requires the presence of a positive blood culture plus the demonstration of a thrombus in the affected vein by imaging (107)
Antimicrobial therapy for suppurative thrombophlebitis should last at least 3 to 4 weeks (110)
Persistent bloodstream infection and endocarditis
Trans-oesophageal endoscopic echocardiography (TEE) should be performed in case of CRBSI in association with prosthetic heart valve, pacemaker, implantable defibrillator, persistent bacteraemia or fungaemia or persistent fever >72 h after start of appropriate treatment and catheter removal and in any case of *S. aureus* CRBSI where duration of therapy less than 4 weeks is considered (112)
Unless dictated otherwise by clinical condition, TEE should be performed at the earliest 5–7 days after onset of bacteraemia or fungaemia to avoid false negative results. In case of negative results, a repeat examination should be considered when endocarditis is suspected (113)

[a]Examples given in this table and text are not exhaustive. We refer the reader to the original text [1] for the full list of examples.
[b]For details on how this should be done, please read in the text under 'Antibiotic and antimycotic treatment'.

as practical expert advice than as real 'guidelines' which are supposed to be supported by strong evidence.

IDSA only covered diagnosis and treatment, not prevention. In this ERBP monography, we will start with general aspects and prevention ('General: tunnelled vs non-tunnelled catheters' and 'Prevention of infection' sections—two aspects not covered by the IDSA), only then followed by comments and amendments of the IDSA guidelines *per se* in 'Overall aspects' and 'Unique aspects' sections.

General: tunnelled vs non-tunnelled catheters

Permanent tunnelled central vein catheters are generally considered as an ultimate resource for vascular access in maintenance haemodialysis patients. One of the major arguments for discouraging the use of tunnelled as well as non-tunnelled catheters as an access for haemodialysis is the risk of infection, which is a source of morbidity and mortality, by inducing septic complications, metastatic infectious disease, central vein thrombosis, malnutrition, inflammation and cardio-vascular damage.

Apart from their almost inevitable use in acute kidney injury requiring renal replacement therapy, non-tunnelled temporary catheters should be avoided as much as possible, since the risk of infection as compared to tunnelled catheters is even higher, reflecting the lack of a cuff to act as a barrier against inoculation from the exit site into the systemic circulation.

Although the use of permanent catheters in chronic dialysis is also generally discouraged as well [7], the proportion of patients treated with them is still growing [10], and they are a life-saving option in a substantial proportion of the currently dialysed population who have run out of native vascular access possibilities. Presumed reasons for their high prevalence, especially in the Western World, are the increased frequency of dialysis patients of older age, with cardio-vascular disease and/or with diabetes mellitus, in whom creation or repair of an autogenous fistula or graft appears technically challenging, risky or impossible.

ERBP recommendations:

- A.1.1: The use of non-tunnelled catheters, except in acute kidney injury (AKI), is undesirable. In chronic maintenance haemodialysis patients, it is recommended to remove temporary catheters as soon as possible, even without or with only minor complications, and to have them replaced preferentially by an arterio-venous fistula (AVF) or, if that is impossible, an arterio-venous graft (AVG) or, if that is impossible, a tunnelled central vein catheter (CVC).
- A.2.2: If haemodialysis catheters are required either due to need or because patients refuse an AVF, the occurrence of a catheter-related complication should be a trigger to re-evaluate options for alternative access, such as an AVF.

Prevention of infection

The IDSA guidelines do not consider recommendations on preventive measures. ERBP recommends the following.

Catheter insertion and position

Catheter insertion should be performed under strict aseptic circumstances and according to the conditions formulated by European Best Practice Guidelines [7].

Next to thrombosis, catheters inserted in the femoral position are also prone to a higher risk of infection and bacteraemia [11,12] than those in the internal jugular one and should therefore be avoided as much as possible. If the femoral site is nevertheless considered, the benefit of preserving other central veins should be balanced with this increased risk of infection. Of the remaining positions, the subclavian is discouraged for other reasons than infectious risk (stenotic complications). Among the internal jugular positions, the right one is the most convenient [7].

ERBP recommendations:

- B.1.1 Catheters should be inserted under strict aseptic conditions.
- B.1.2 The right internal jugular vein position is the preferred location for insertion, followed by the left internal jugular vein position. The use of the femoral vein position is discouraged.
- B.1.3 The use of the subclavian vein position is discouraged for reasons not related to infection (frequent stenosis).

Nursing care

Universal precautions using sterile material should be applied by caregivers whenever a central vein catheter is manipulated, connected or disconnected. The use of disposable sterile material such as masks and gowns has been suggested to protect against transmission of Staphylococci or other organisms [13,14], but, to the best of our knowledge, their protective effect has not convincingly been proven. In a collaborative intensive care unit (ICU) study, a set of five different preventive interventions including full barrier precautions was successfully implemented, but the study did not evaluate the relative importance of each of the individual interventions separately [15]. In another study, the use of surgical face masks reduced bacterial contamination of the area in front of the operator's face [16], who, however, was asked to talk during the 20-min observation period and to turn his/her head 90° every 30 s [16]. The use of precautions such as masks and gowns should not be considered as an excuse to relax on general hygienic and sterile conditions.

Branching of central vein catheters to the dialysis machines as well as their disconnection is resource intensive, and therefore sometimes two trained staff members (one nurse focusing on the catheter and one helper for the management of the dialysis machine and to assist the nurse) are deployed to enable connection and disconnection. The basic and meticulous approach to handling catheters in a reliable and sterile fashion at the time of both connection and disconnection or at any other time the catheter connection site is manipulated forms the core of the prevention of infection.

ERBP recommendation:

- B.2.1 Universal precautions, a sterile environment and aseptic technique should be applied at any occasion when a venous catheter is manipulated, connected or disconnected.

Preventive antimicrobial catheter locks and catheter surface treatment

There is increasing evidence that antimicrobial locks applied within the catheter lumen are effective at preventing catheter-related bloodstream infections (CRBSI).

Some locks may have extra antimicrobial or biofilm-removing properties [e.g. citrate, alcohol, ethylene diamine triacetic acid (EDTA)]. On the contrary, heparin tends to antagonize the bactericidal properties of certain antibiotics, e.g. the aminoglycosides [17,18]. It also promotes biofilm formation unless at very low concentrations [19].

The clinical advantages offered by citrate have been confirmed in at least two meta-analyses [20,21]. Over time, progressively lower concentrations of citrate have been applied (from 46.7 to 4%) with even in the latter case still significantly better results than with heparin [22–26]. In two studies, no benefit regarding infectious complications was observed for citrate at 4% [27,28].

Addition of antibiotics, either to heparin or to citrate solutions, has an additional beneficial effect vs vehicle alone [20].

One potential drawback of catheter locks is that some of the contents spill over to the circulation at injection and in between dialysis sessions [29,30]. A Food and Drug warning against citrate locks was issued in 2000 following a fatal accident with the 46.7% solution [31]. The reported fatal case was very likely related to abrupt hypocalcaemia followed by cardiac arrest, due to intracardiac injection of an excessive amount of 46.7% citrate, which is a potent chelator of calcium. The 46.7 and 30% concentration ranges have been considered unsafe [29]. For that reason, the low 4% concentration might be preferred, as also proposed by the American Society of Diagnostic and Interventional Nephrology (ASDIN) [32].

Of note, the capacity of citrate locks to prevent thrombus formation may be incomplete, especially at the highest concentrations. Recently, several cases of symptomatic pulmonary and cerebral embolisms were observed with hypertonic citrate locks [33]. This is probably attributable to seepage out of the lumen through the catheter side holes, a process that might be exacerbated if the solution is hyperosmolar.

For antibiotic locks, spillover may be a source of resistance [34]. This issue has not been sufficiently studied and remains a point of concern. With potentially toxic antibiotic locks such as those containing aminoglycosides, trough levels should regularly be checked.

According to ERBP, there is not enough evidence of clinical benefit of ethanol locks [35,36], although *in vitro* data, both for ethanol alone at 60% and for an ethanol 30%/citrate 4% mixture, are promising [37,38]. Also, ethylene EDTA has been proposed as an option [19,39].

For each type of lock, the corrosive or damaging potential on catheter polymers should be taken into consideration, and the manufacturer of the catheter should provide information regarding this issue.

Although findings might be influenced by differences in the definition of CRBSI, it nevertheless is of interest to note that several studies with application of locks achieve results in the treatment arm which are comparable to those obtained

in centres of excellence with dedicated care to catheters without applying locks [21]. Hence, the use of antimicrobial locks should not be used as an excuse to relax on the application of universal precautions and hygienic measures.

Several options of catheter surface modifications have been proposed to combat biofilm, fibrin sheath, thrombus or infection [40]. They essentially consist of silver sulfadiazine, heparin, Trillium^{R} [40] and/or coating with protective polymer layers preventing $BaSO_4$ release from the catheter surface [41]. Results regarding clinical impact on colonization are contradictory [42,43]. By lack of convincing clinical data, it is at present difficult to justify their additional cost.

ERBP recommendations:

- B.3.1 The preventive use of antimicrobial locks is advocated to reduce the rate of CRBSI.
- B.3.2 In view of the potential risks of spillover of the locking solution, associated risks (arrhythmias, toxicity, allergic reactions, development of resistance to antibiotics) should be balanced with the benefits in terms of prevention of infection. Citrate locks have, for the time being, most extensively been studied. The 4% solution seems to offer at present the best benefit/risk ratio.
- B.3.3 Antimicrobial lock solutions should not replace hygienic standards with regard to catheter care and handling.

Exit-site dressings

Next to skin antisepsis before placement, sterile precautions during placement and catheter site care at each dialysis session, the site should be covered with a dressing as long as the catheter is in place [44]. One meta-analysis comparing the complication profile of transparent and gauze dressings suggested a higher risk for catheter sepsis and bacteraemia with transparent dressings [45]; another more recent meta-analysis showed no differences but registered a high level of uncertainty regarding the reliability of the studies included [46]. With long-term catheters, gauze is the preferred choice. Gauze should be replaced if it is no longer dry or clean. The patient should be instructed to respect strict hygienic measures, preserving the integrity and dryness of the dressing, and should know what to do in case of disintegration or wetness.

ERBP recommendations:

- B.4.1 The catheter exit site should be covered by a dressing as long as the catheter remains in place. The exit site should be inspected at every haemodialysis session, and the exit-site dressing should be replaced on a routine basis if it is no longer clean or intact.
- B.4.2 The patient should be instructed to maintain the hygiene and integrity of the dressing.

Exit site and nasal antibiotic ointments

The use of antibiotic ointment at the insertion site has a beneficial effect on CRBSIs and exit-site infections [47–49]. Their application is especially recommended after catheter placement until the insertion site has healed [44]. Application of mupirocin might be complicated by development of resistance [50–52]. Prolonging antibiotic ointment application after site healing probably offers no advantage and has the potential to increase the risk for development of resistance [48] and for *Candida* colonization [53].

In peritoneal dialysis (PD), ointments containing gentamicin applied to the exit site have been shown to be effective [54,55]. Gentamicin ointment was superior to mupirocin in at least one study [55]. To the best of our knowledge, similar treatment protocols have not been studied with haemodialysis catheters. One study showed that honey (Medihoney) was equivalent to mupirocin in haemodialysis catheters [56]. One potential advantage of Medihoney is that the theoretical risk of resistance is lower than with mupirocin [56].

Another option is Polysporin triple ointment, containing Bacitracin, gramicidin and polymyxin B, which was shown to be superior to placebo in haemodialysis catheters when applied to the exit site [57]. Comparative data with mupirocin or other antibiotic ointment formulations are, however, lacking.

Topical application of antibiotic ointments at the exit site is also the first option in case of exit-site infection without fever (see below, 'Catheter removal and preservation of existing and future access options' section).

Although there is ample literature on nasal mupirocin ointment in peritoneal dialysis, information in haemodialysis is scanty. In PD, nasal mupirocin decreases exit-site and tunnel infection but not peritonitis [58,59]. Application is, however, also related to an increase in MIC90 and frequent recolonization [60]. According to ERBP, there is not enough evidence to propagate nasal antibiotic ointment in a haemodialysis setting.

ERBP recommendations:

- B.5.1 Application of antibiotic ointment at the exit site should be considered after catheter placement until the insertion site has healed but should be discontinued after healing.
- B.5.2 With long-term exit-site and nasal antibiotic ointment applications, especially of mupirocin, development of resistance should be taken into account as an effect counterbalancing the potential benefit on infectious complications.

Overall aspects

Diagnosis: cultures of intravenous catheter

Several IDSA guidelines refer to the approach by the bacteriological laboratory; it might be important for the nephrologist to check the approach used in the laboratory to which he/she usually sends samples. Qualitative broth cultures of catheter tips are discouraged [61] (2), whereas the roll plate technique of 5 cm of the catheter tip is recommended especially for short-term catheters (in place since less than 14 days) (7) and the quantitative broth culture (luminal flushing or sonication) for catheters which have remained

in place for a longer time. Other studies, however, showed no differences between both approaches [62]. In general, only detection of >15 colony forming units (CFU) is relevant for roll plate and $>10^2$ for quantitative broth culture (5)(90).

Although the IDSA guidelines explicitly recommend culturing of catheter tips upon removal (1), questions can be raised about the relevance of this approach. In a recent study [63] on 312 patients with a positive catheter culture and a negative blood culture, only eight patients (2.6%) subsequently developed CRBSI with the same germ as the one cultured from the tip, suggesting a low yield for this costly and time-consuming strategy.

ERBP recommendations:

- C.1.1 Preferred laboratory approaches for cultures of catheters are the semi-quantitative roll plate technique of 5 cm of the catheter tip (positive if >15 CFU are detected) or the quantitative broth culture (luminal flushing or sonication, positive if $>10^2$ CFU are detected).
- C.1.2 In general, the therapeutic relevance of culturing catheter tips in symptomatic patients with presumed CRBSI should be considered low when blood cultures are collected appropriately (see below, 'Diagnostic blood cultures') and if appropriate antibiotic treatment is instituted (see below, 'Antibiotic and antimycotic treatment').
- C.1.3 Nephrologists should be aware whether the bacteriological laboratory analysing their samples applies the appropriate techniques for culturing.

Diagnosis: blood cultures

A diagnostic test proposed in the IDSA monography not necessitating catheter withdrawal is simultaneous sampling from peripheral vein and from the catheter or from two different catheter lumens with appropriately marked bottles [64] (15), with colony count from inside the catheter or one of the two lumens being at least three times higher than for the other sample. Alternatively, cultures from the peripheral blood sample should become positive at least 2 h later than the ones from the catheter (differential time to positivity—DTP). Usefulness of DTP criteria in samples from two catheter lumens has not been clarified [65–67] (17)(18)(19).

The ERBP considers that, although such recommendations may be valid for non-dialysis catheters, it may be more difficult to implement these in haemodialysis. Firstly, in many cases, it may be impossible to puncture a peripheral vein because of unavailability or because it is deemed desirable to preserve veins for future access creation. Secondly, since many of the fever episodes necessitating blood culture sampling occur during dialysis, during which high blood flows are created through the catheter, it is likely that blood cultures collected at that moment through the haemodialysis circuit, which is then directly linked to the catheter, will offer similar results as peripheral blood, so that peripheral sampling becomes redundant [68].

Fibrin sheath or biofilm collection via endoluminal brushing has been proposed as another option [69,70] but has been criticized because of risk of arrhythmia, embolization and bacteraemia [71]. Hence, data at present are not convincing enough to propagate its use.

When the approach of intradialytic collection through the catheter is followed, a risk exists that some of the positive blood cultures relate to other infectious sources than the catheter. To minimize this bias, alternative sources should be excluded as much as possible by history taking, clinical examination, imaging and targeted laboratory testing (e.g. urine culture if possible).

ERBP recommendations:

- C.2.1 If a haemodialysis catheter is not removed, blood cultures obtained during dialysis through the dialysis circuit linked to the catheter are a more realistic and practical method to isolate an organism related to catheter-associated infection than the dual-site approach including also a peripheral vein sample, which is propagated in the general population.
- C.2.2 When the catheter remains in place, alternative sources of infection should be considered with an appropriate clinical history, examination, imaging and targeted laboratory testing (e.g. urine culture if possible).

Diagnosis: registration

To guide empiric antibiotic therapy, it is of utmost importance that each haemodialysis centre maintains a database of all suspected and proven CRBSI and episodes of bacteraemia in general, the causative organisms, their sensitivity pattern to antibiotics, the potential source (catheter related, pneumonia, urinary tract, etc.) and the outcomes after therapeutic intervention. As a consequence, each unit should be aware of the epidemiology of its catheter-related infections.

ERBP recommendation:

- C.3.1 Haemodialysis units should record all details regarding CRBSI epidemiology as well as about all episodes of bacteraemia (events, causative organisms with their susceptibility and evolution in response to therapy).

Unique aspects

Management of catheter infection in patients receiving haemodialysis

Management of catheter infection is covered in two sections of the IDSA guidelines, one on general management and one on management of haemodialysis catheters. As the aim of this ERBP position statement is to discuss only haemodialysis catheter infections, we will merge the discussion on these two topics under the present heading.

It should be noted that only catheter-related infection and/or bacteraemia are discussed in this ERBP position statement. Bacteraemia related to AVF or AVG or bacteraemia in the presence of a dialysis catheter but attributable to other causes will not be covered.

Catheter removal and preservation of existing and future access options. In the following clinical situations, the re-

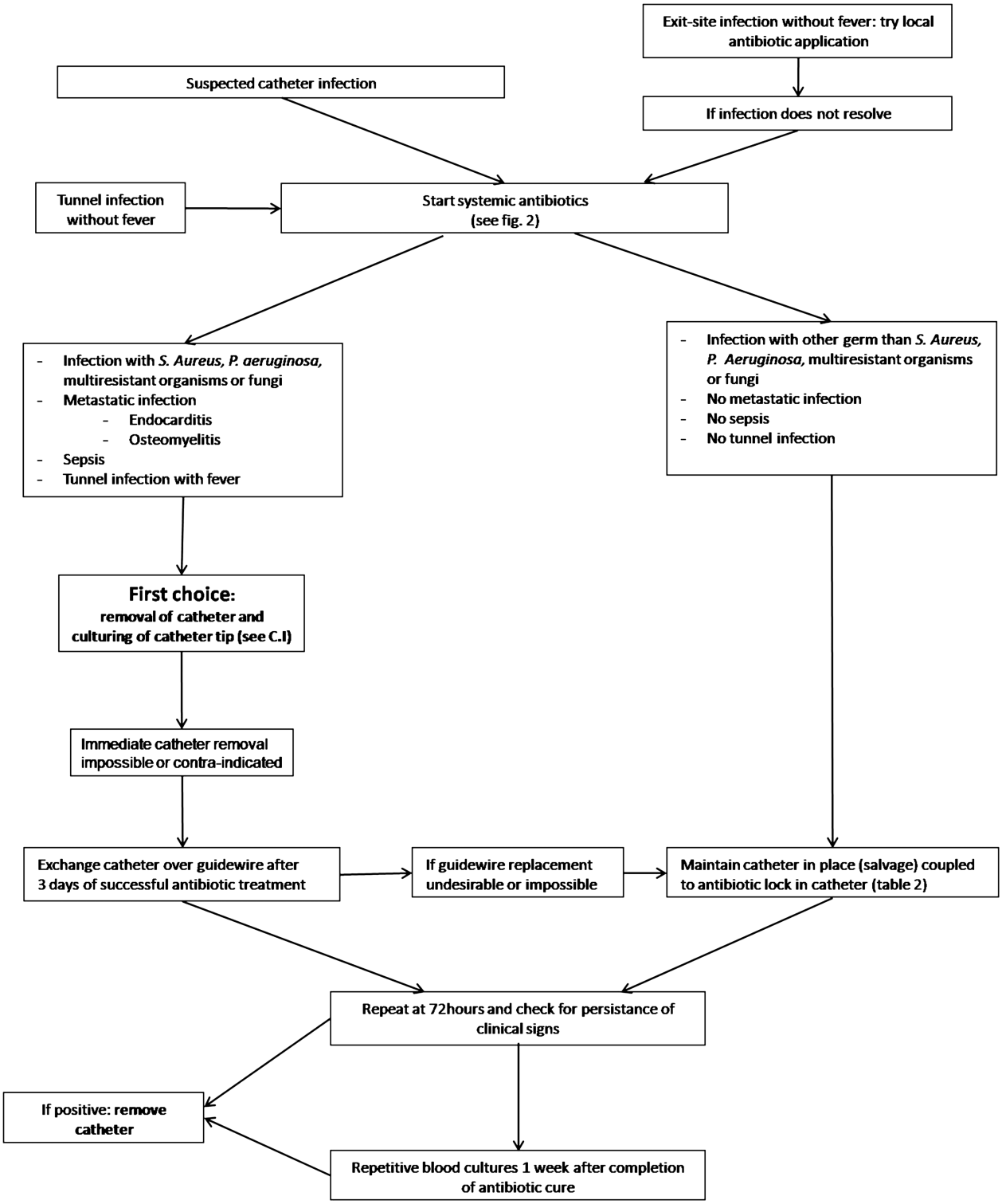

Fig. 1. Flow chart summarizing a stepwise approach in case of suspected or proven catheter-related infection, including strategies for catheter removal or preservation (salvage) of the catheter.

moval of the catheter should be considered as an additional intervention to systemic antibiotic treatment (see below, 'Antibiotic and antimycotic treatment') (Figure 1): severe complications (e.g. severe sepsis, suppurative thrombophlebitis, metastatic infection); persistent bloodstream infection or persistent clinical signs of infection in spite of 48–72 h of appropriate antimicrobial therapy; infection with *Staphylococcus aureus*, *Pseudomonas aeruginosa*, multiresistant organisms or fungi; and tunnel infection with fever. For exit-site infection without fever, topical antibiotic ap-

plication might be attempted first (see above, 'Exit site and nasal antibiotic ointments'), but if infection does not resolve, systemic antibiotic treatment should be installed (47). If systemic antibiotics also fail, the catheter should be removed (49).

ERBP recommends the insertion of a new tunnelled catheter preferably only when the patient remains afebrile for 48–72 h and shows a normalization of C-reactive protein (CRP) and negative blood cultures. If the interval needs to be prolonged for more than 48–72 h, a haemodialysis catheter could be inserted in the intermediate at another site. A strategy of placement per single dialysis session and removal immediately afterwards might be considered as an alternative to minimize the risk of colonization.

However, in patients on haemodialysis, options for access may be limited. Firstly, removal of a catheter will require another catheter to be inserted, increasing the potential risk to generate further damage to the central vein. This could have adverse consequences on the creation of an AVF in the future. Secondly, access options may already be extremely limited and further attempts at central vein cannulation impossible or risky. Of note, even in the non-dialysed population, catheter-sparing strategies have recently been employed to avoid unnecessary and wasteful removal of catheters [71]. Therefore, removal of the catheter might be considered, if clinically indicated, but the strategy for future access should be part of this consideration. For example, one should be sure that an alternative site for insertion of a new catheter is available before the original catheter is removed.

If any problems are anticipated, an alternative strategy is to exchange the catheter over a guidewire. The optimal time for guidewire-assisted replacement is after 48–72 h of appropriate and effective antibiotic treatment (59). However, guidewire-assisted replacement increases the risk of venous wall sclerosis and stenosis and is associated with a high treatment failure rate. An alternative option is to leave the catheter in place and to attempt catheter salvage instilling an antibiotic lock (see below, 'Antibiotic locks') in addition to systemic antibiotic therapy [72,73] (30)(60). In a recent study, catheter salvage after incident bacteraemia achieved a cure, defined as no recurrence or complication, in 66.1% of cases [74]. Recurrent bacteraemia was less common after catheter removal and reinsertion than after salvage (8.1 vs 33.0%) but at the expense of dramatically more complications (14.3 vs 0.9%). In this study, salvage consisted of systemic antibiotic treatment but not of antimicrobial or antibiotic locks. Both in the case of guidewire-assisted replacement and of catheter salvage, close follow-up by assessment of clinical status and repetitive blood cultures is imperative, and if persistent clinical signs of infection and bacteraemia are found after 48–72 h, the catheter should still be removed and replaced (33).

Surveillance blood cultures should be obtained 1 week after completion of antibiotic treatment for CRBSI if the catheter has not been removed. If these cultures are positive, the catheter should still be removed (67).

In order to preserve future access options, the practice of peripheral blood culture sampling from vessels that potentially could be used in the future for creation of vascular access should be limited or avoided [7] (53).

Antibiotic and antimycotic treatment (Figure 2). In all circumstances, systemic antibiotic therapy should be administered.

For the approach in the general population, instructions in the IDSA Guidelines are given separately for gram-positive and gram-negative bacteria. According to ERBP, empiric coverage should be inspired by the recorded infections in the unit (see above, 'Diagnosis: registration'). If the registry indicates that current catheter infections are regularly caused by both gram positives and gram negatives, coverage for both classes of organisms should be provided when empiric antibiotic therapy is started for CRBSI, with eventual refinement of the antibiotic regime once the responsible organism has been isolated and sensitivities are known.

Although the choice of antibiotic treatment may depend on individual preference, local or regional patterns, and/or recommendations from hospitals and organizations, according to ERBP, preference should be given to antibiotics with a pharmacokinetic profile allowing administration after each dialysis session only; this is the case for vancomycin, teicoplanin, cefazolin, ceftazidime and daptomycin. Although the same is correct for aminoglycosides, it might be impossible to reach appropriate trough levels as pursued in the general population with simple post-dialysis administration, hence increasing the risk for ototoxicity, loss of residual renal function, treatment failure and development of resistance. Nevertheless, in view of their rapid bactericidal effect, a single shot of aminoglycosides might be considered useful. If no alternative is available, a longer therapeutic course might be considered; in that case, administration 1 h before dialysis followed by a highly efficient dialysis procedure is probably the most efficient approach to mimic pharmacokinetics and pharmacodynamics observed in the general population.

In settings where methicillin-resistant *S. aureus* (MRSA) is highly prevalent, vancomycin or teicoplanin is the first choice for empirical treatment of gram-positive germs (23).

In patients on empirical vancomycin or teicoplanin in whom infection with methicillin-sensitive *S. aureus* appears, antibiotic treatment should be switched to cefazolin (62). Potential advantages of cefazolin are its broader spectrum; its favourable pharmacokinetics necessitating only IV administration in direct relation to dialysis compared to a need for additional interdialytic IV or PO administrations for the methicillin group; and compared to vancomycin, a bactericidal instead of a bacteriostatic activity. Continued treatment with vancomycin in case of methicillin sensitivity substantially increases the risk of treatment failure [75].

When minimum inhibitory concentration (MIC) for vancomycin exceeds 2 μg/mL, alternative antibiotics should be used such as daptomycin [76] (23). Daptomycin has also the advantage of being cleared by the kidneys, which allows long intervals between administrations. In haemodialysis patients, post-dialysis administration of one dose (4 to 6 mg/kg depending on the seriousness of the infection) is considered sufficient. Daptomycin is, however, not yet available in all European countries (e.g. not in Belgium). Linezolid should not be used for empirical treatment (24). For candidaemia, echinocandin should preferably be used,

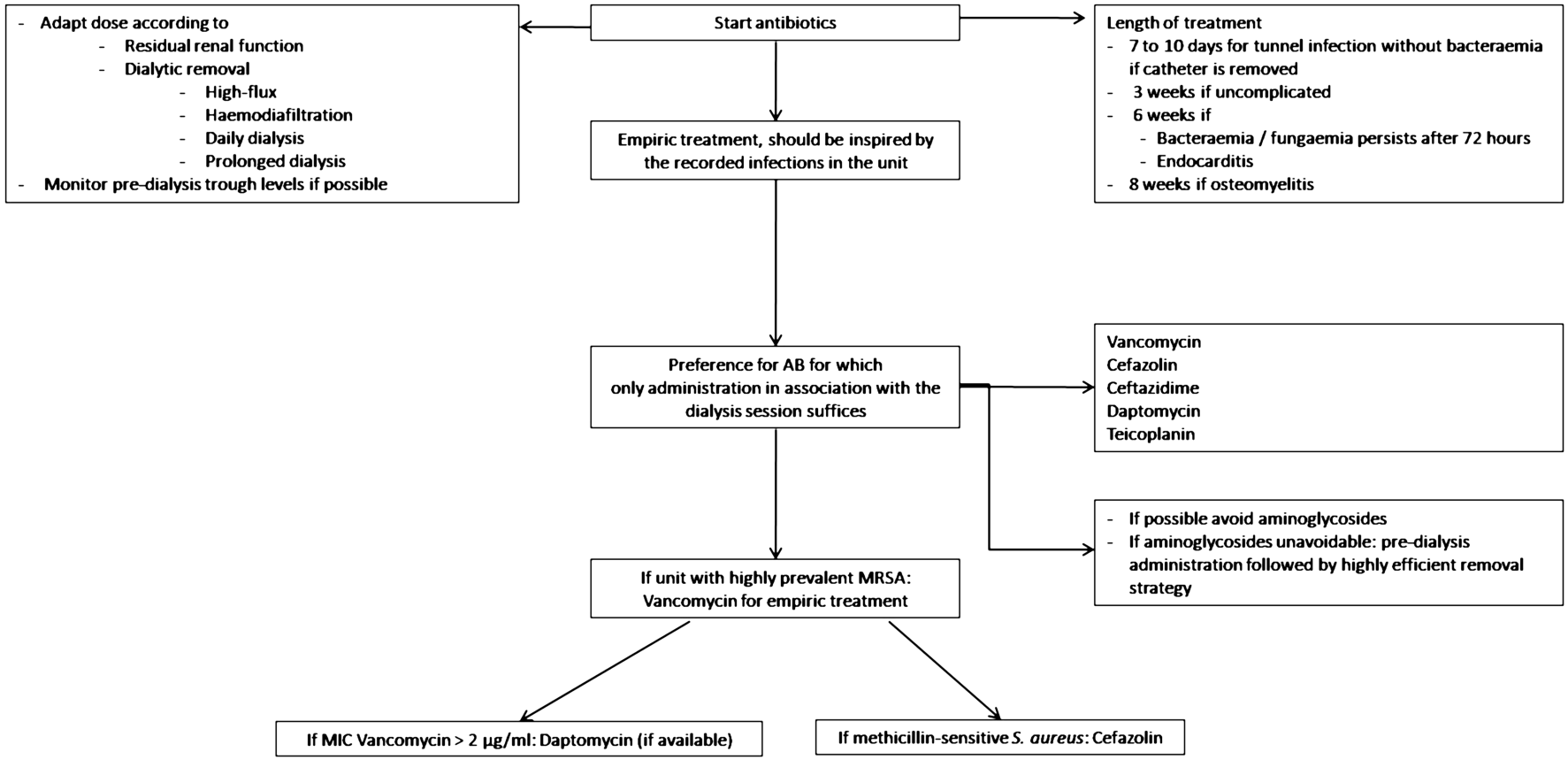

Fig. 2. Flow chart summarizing approaches for systemic antibiotic treatment.

with fluconazole only for selected cases (e.g. if risk of *Candida krusei* or *Candida glabrata* is low) [77] (29). Candida infection is, however, rare in haemodialysis catheters, probably reflecting a different immune predisposition as compared to other populations at risk (e.g. HIV, long-term antibiotic treatment). Candida catheter infection is associated with a high rate of treatment failure or early recurrence, so that catheter removal is a first-line therapeutic option.

Usual length of treatment for uncomplicated cases is 3 weeks. For tunnel infection without bacteraemia or fungaemia and if the catheter has been removed, 7 to 10 days is sufficient. Prolonged (6 weeks) antibiotic treatment should be administered if fungaemia or bacteraemia persists 48–72 h after catheter removal, since very likely serious metastatic complications such as endocarditis are present; 6-week treatment should be installed as well in case of a definite diagnosis of metastatic infection (31). For osteomyelitis, antibiotic treatment should be prolonged to 8 weeks.

For uncomplicated infections with other organisms than those mentioned above, antibiotic treatment without catheter removal should be attempted first (both systemic and lock), because catheter reinsertion is not free of risk (35). With a single positive blood culture of coagulase-negative *Staphylococci*, a careful clinical evaluation and additional positive cultures should have been obtained before therapy and/or catheter removal [78] (38).

For antibiotics with substantial removal via the kidneys, such as vancomycin, residual renal function should be taken into account when determining the dose and frequency of administration. Highly efficient dialysis strategies (high-flux haemodialysis, haemodiafiltration, daily dialysis, prolonged dialysis sessions such as in nocturnal dialysis) can equally remove substantial amounts of antibiotic [79], and also in these cases the dose should be adapted accordingly. To guide treatment, pre-dialysis trough levels are the optimal approach.

ERBP recommendations:

- D.1.1 Systemic antibiotic treatment should be always administered as part of the therapy of catheter infection.
- D.1.2 Catheter removal is the first therapeutic option in case of severe complications and metastatic infections; infection with *S. aureus*, *P. aeruginosa*, multiresistant organisms or fungi; and tunnel infection with fever.
- D.1.3 The therapeutic advantages of catheter removal should be balanced against the risk of reinsertion, and removal might not be appropriate, if an alternative insertion site is not available or if reinsertion of a catheter is associated with excess risk. In this scenario, the catheter could be replaced over a guidewire, preferably 3 days after appropriate and effective antibiotic treatment.
- D.1.4 If guidewire-assisted exchange is also impossible or too risky, a valid option is to keep the catheter *in situ* and to combine this with a treatment consisting of systemic antibiotics and antibiotic locks (catheter salvage).
- D.1.5 With either guidewire-assisted exchange or if the original catheter is left in place for salvage and if the clinical picture is not improving or if blood cultures remain positive after 48–72 h, the option to remove the catheter should be re-evaluated as indicated under D.1.2.
- D.1.6 If a catheter is not removed, blood cultures should be checked 1 week after completion of antibiotic treatment, and if those cultures remain positive, the catheter should be removed.
- D.1.7 For exit-site infection without fever, topical antibiotic application can be considered as an alternative. If infection does not resolve, systemic antibiotics should be administered. For tunnel infection without fever, systemic antibiotics are the preferred option, although peroral treatment may be sufficient. If these treatments fail, the catheter should be removed.
- D.1.8 When haemodialysis catheter infection is suspected, primary antibiotic approach should be inspired by the previously recorded responsible organisms in the unit. If both gram-positive and gram-negative organisms are registered on a regular basis, both types should be covered with eventual refining of the antibiotic regime once the organisms and their sensitivities are known.
- D.1.9 In general, antibiotics necessitating administration post-dialysis only (vancomycin, teicoplanin, cefazolin, ceftazidime, daptomycin) should be preferred.
- D.1.10 Vancomycin or teicoplanin is the first choice for empirical therapy of gram positives in settings where MRSA is highly prevalent.
- D.1.11 For methicillin-sensitive *S. aureus*, haemodialysis patients should receive cefazolin.
- D.1.12 Doses of antibiotics of which the active concentration is affected by residual renal function and/or dialysis adequacy should be adapted accordingly. If possible, pre-dialysis trough levels should be obtained to guide therapy.

Antibiotic locks

Recommendations for removal (either with catheter-free interval or over a guidewire) should be applied as detailed above ('Catheter removal and preservation of existing and future access options'). If removal is deemed unnecessary, undesirable or impossible, antibiotic lock is an important therapeutic option (71). Antibiotic lock should not be used alone but always in conjunction with systemic antibiotics for the recommended periods (see above, 'Antibiotic and antimycotic treatment') (69). Although dwell times generally should not exceed 48 h and even 24 h for ambulatory patients with femoral catheters, for haemodialysis lock renewal after every dialysis session is considered sufficient (70). For vancomycin, the concentration in the lock should at least be 1000 times higher than the MIC of the micro-organism involved [80] (73). For all other antibiotics, at least 100-fold greater than therapeutic plasma concentrations should be pursued [68]. Antibiotic concentrations as they are reported in the literature are summarized in Table 2.

The success rate of salvage in case of *S. aureus* is low (approximately 40%) [81] and therefore should be considered only in problematic cases. Success rate for *Enterococcus* is approximately 60% [82]. For all other organisms, success rates are substantially higher [68].

Table 2. Antibiotic concentrations applied in locks[a]

Antibiotic	Concentration (mg/mL)
Vancomycin	2.5–25
Gentamycin	4–40[b]
Tobramycin	5
Minocycline	3
Cefazolin	10
Ceftazidime	10

[a]May be diluted 1/1 or 2/1 in another vehicle such as citrate or heparin solution.
[b]The preferred concentration is 4 mg/mL because of risk for ototoxicity with spillover at higher concentrations; sources: Yahav *et al*. [20], Onder *et al*. [73] and Allon [68].

Antibiotic locks can be dissolved in different vehicles. Some of these might have extra antimicrobial or biofilm removing properties (see above, 'Preventive antimicrobial catheter locks and catheter surface treatment'). Urokinase and other thrombolytic locks are not recommended as adjunctive therapy for patients with CRBSI (37).

ERBP recommendations:

- D.2.1 When catheter salvage is attempted, the combination of an antibiotic lock and systemic antibiotic therapy should be applied.
- D.2.2 Salvage of the catheter in case of *S. aureus* infection should only be considered when catheter removal and replacement are expected to be problematic.
- D.2.3 Urokinase and other thrombolytic locks are not recommended. The use of heparin locks alone in case of CRBSI is discouraged.

Diagnosis and management of an outbreak of CRBSI

Criteria defining the exposed patients should be established (117). A root cause analysis or case control study should be undertaken to elucidate the potential aetiology of contamination (118). Micro-organism patterns should be evaluated by studying antibiotic sensibility and molecular fingerprinting to understand recurrence and relapsing episodes (119).

ERBP recommendation:

- D.3.1 Outbreaks of CRBSI should be scrupulously checked by case definition, case control studies and root cause analysis.

Standard care

Centres should establish standard care protocols around prevention and treatment and a quality improvement program. In case of an outbreak of CRBSI, the root cause analysis should assess compliance with these protocols. If compliance is below expectation, retraining and eventually reorganization of care should be considered. If compliance with the protocol is deemed appropriate, modification of the protocol could be considered and the process of care re-audited.

ERBP recommendation:

- D.4.1 Standard protocols detailing all aspects of preventive care (catheter manipulation and exit-site care), diagnosis, treatment and follow-up should be established in each centre. These protocols should include hygienic measures for catheter manipulation (see above, 'Nursing care' and 'Exit-site dressings') and should be assessed by quality control and quality improvement strategies, in conjunction with clinical audit. In case of an outbreak, adherence to those protocols should be improved if it is considered inappropriate. If adherence is appropriate, modification of the protocols should be considered in function of the findings.

Research recommendations

Studies of outcome (or surrogate endpoints like CRP) with central vein catheters for haemodialysis compared to other access methods, if optimum prevention against CRBSI is applied

International multicentric registry of frequency of access infection, type of organism, resistance profile, recurrence profile

Evaluation whether wearing a mask (doctor, nurse, patient) during catheter insertion/manipulation protects against catheter infection

In vivo studies comparing citrate with alternative lock vehicle solutions such as EDTA, ethanol, urokinase

Head-to-head comparisons of lock solutions with different citrate concentrations

Studies on the effect of spillover of antibiotics from preventive antibiotic locks on antibiotic resistance and on the impact of citrate spillover on symptoms and side effects

Studies on the impact of lock solutions on catheter polymers

Comparison of topical applications of gentamicin, Medihoney or Polysporin Triple ointments in the prevention of infection, as compared to mupirocin ointment

Studies on application of hypertonic saline solutions at exit site as preventive measure

To evaluate the laboratory strategies for culturing dialysis catheters in Europe

To check the concordance between blood cultures taken from the dialyser blood lines and peripheral blood samples

Studies of protocols optimizing aminoglycoside pharmacokinetics in haemodialysed patients

Studies comparing the impact on catheter infection of broad catheter salvage (including systemic antibiotics as well as antibiotic and antimicrobial locks) vs removal and reinsertion

Studies on the usefulness of antibiotic locks in infections with other organisms than *S. aureus*, *P. aeruginosa* when catheters are left in place

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Disclaimer. The present text is based upon the information available to the work group at the moment of the preparation of this publication. It has been designed to provide information and assist decision making but is not intended to define a standard of care or to improve an exclusive course of diagnosis, prevention or treatment. Individual decision making is essential in the approach to any disease and thus also CRBSI.

Variations in practice are inevitable when physicians take into account individual patient needs, available resources and limitations specific for a geographic area, country, institution or type of practice. In addition, evidence may change over time as new information becomes available, so that practice may be modified subsequently. Every practicioner using this text is responsible for its application to any particular clinical situation. The work group members involved in the development of the present text have disclosed all actual and potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional or business interest.

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