



Management of infections related to totally implantable venous-access ports: challenges and perspectives

David Lebeaux, Nuria Fernández-Hidalgo, Ashwini Chauhan, Samuel Lee, Jean-Marc Ghigo, Benito Almirante, Christophe Beloin

► To cite this version:

David Lebeaux, Nuria Fernández-Hidalgo, Ashwini Chauhan, Samuel Lee, Jean-Marc Ghigo, et al.. Management of infections related to totally implantable venous-access ports: challenges and perspectives. The Lancet Infectious Diseases, 2014, 14 (2), pp.146 - 159. 10.1016/S1473-3099(13)70266-4 . pasteur-01381818v1

HAL Id: pasteur-01381818

<https://pasteur.hal.science/pasteur-01381818v1>

Submitted on 14 Oct 2016 (v1), last revised 5 May 2021 (v2)

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - ShareAlike 4.0 International License

Review

Management of totally implantable venous access port-related infections: challenges and perspectives

David Lebeaux, Nuria Fernández-Hidalgo, Ashwini Chauhan, Samuel Lee, Jean-Marc Ghigo, Benito Almirante, Christophe Beloin

Institut Pasteur, Unité de Génétique des Biofilms. Paris, France (David Lebeaux, M.D., Ashwini Chauhan, Ph.D., Jean-Marc Ghigo, Ph.D., Christophe Beloin, Ph.D.).

Servei de Malalties Infeccioses, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona. Barcelona, Spain. (Nuria Fernández-Hidalgo, M.D., Benito Almirante, M.D.).

New Mexico Veterans Healthcare System and University of New Mexico, Albuquerque, USA. (Samuel Lee, M.D.)

Correspondance to:

Christophe Beloin. Institut Pasteur, Unité de Génétique des Biofilms. 25 rue du Dr. Roux, 75724 Paris cedex 15 France. E-mail address: cbeloin@pasteur.fr
Tel: 33 01 44 38 95 97; Fax: 33 01 45 68 80 07

Benito Almirante. Servei de Malalties Infeccioses, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona. Barcelona, Spain. E-mail address: benitoalmirante@gmail.com
Tel: 34 93 2746090; Fax: 34 93 4894091

Summary

Use of totally implantable venous access ports (TIVAP) is a standard clinical practice, in particular for patients with solid cancers, hematologic malignancies and chronic digestive diseases. Use of TIVAPs allows long-term administration of veinotoxic compounds, improves patient quality of life and reduces risk of infection. However, microbial contamination, formation of pathogenic biofilm in TIVAPs and subsequent infection are associated with morbidity, mortality and increased healthcare costs. In case of TIVAP-related infection, local and systemic complications, or infection related to specific pathogens may constitute indications for device removal. Alternatively, conservative treatment can be proposed with the combination of systemic antibiotics and antibiotic lock therapy. In light of recent *in vitro* and *in vivo* fundamental or clinical research addressing epidemiology, diagnosis and prevention of TIVAP-related infections, with a particular focus on antibiotic lock therapy, this review presents current challenges and promising strategies to improve the management of TIVAP-related infections even if some of them are still at an early developmental stage and need clinical validation.

Search strategy and selection criteria

References for this review were identified through searches of PubMed for articles published in English between January 1980 and July 2013 including totally implantable venous access port (TIVAP)-related infections for any indication of TIVAP insertion. We restricted studies by use of the terms: “Totally implantable venous access”, “Totally Implantable port”, “Port-a-cath”, “Catheters, Indwelling”, “Central venous catheter”, “Port-a-cath infection”, “Port-pocket infection”, “Catheter-Related Infections”, “Bloodstream infections”, “Bacteremia” and “Infection”. We focused on studies assessing TIVAP-related infections epidemiology, risk factors, microbiology, diagnosis, prevention, treatment and prognosis. Regarding treatment, we also included the following key-words: “Sepsis/prevention & control”, “Catheter-Related Infections/drug therapy”, “Bacteremia/drug therapy”, “antibiotic lock therapy”, “ethanol lock”, “antibiotic lock technique”, “antifungal lock therapy”. For epidemiologic or therapeutic studies including different types of long-term intravascular catheters (LTIVC), we retained them if specific data about TIVAP were described. Articles resulting from these searches and relevant references cited in these articles were reviewed.

1 **Introduction**

2 Patients may require long-term administration of potentially veinotoxic compounds due to
3 chronic conditions such as solid tumors, hematologic malignancies, digestive diseases, cystic
4 fibrosis (CF) or infection with human immunodeficiency virus (HIV).^{1,2} Long-term
5 intravascular catheters (LTIVC) were developed to reduce the associated toxicity and risk of
6 bacterial or fungal colonization due to the subcutaneous route or “tunnel” that impedes the
7 migration of microorganisms present on the surface of the skin.^{3,4} In the early 80’s, an initial
8 report described the use of a new type of LTIVC called a totally implantable venous access
9 port (TIVAP).⁵ TIVAP is composed of a subcutaneously implanted port (or reservoir)
10 connected to a central venous catheter, most frequently inserted into the internal jugular,
11 subclavian or cephalic vein.² Use of TIVAPs is now a standard clinical practice and has
12 significantly increased patients’ comfort and quality of life, as compared to other LTIVCs.²
13 TIVAPs are inserted for the administration of antineoplastic chemotherapy, parenteral
14 nutrition, blood products and for prolonged antimicrobial treatment in CF.^{2,6,7} The number of
15 implanted TIVAPs is increasing and more than 400,000 of them are sold each year in the
16 USA.⁸ Despite a reduction of the risk of microbial contamination due to total implantation
17 under the skin, 3 to 10% of TIVAP carriers experience a related infection which is the most
18 common indication for TIVAP removal, illustrating the impact of this complication on patient
19 care and the necessity for focused research in this area.⁹⁻¹⁴
20 This review aims to provide insights into challenges associated with TIVAP-related
21 infections, including diagnosis, prevention, and novel approaches that may improve patients’
22 management.

Epidemiology reflects risk factors and routes of colonization

Depending on the indication for TIVAP insertion, patients are exposed to different risk factors and therefore exhibit different infection rates. For instance, if TIVAP is inserted for antineoplastic chemotherapy or in CF patients, the incidence density of infection ranges from 0·11 to 0·37/1,000 catheter-days.^{6,9,10,13-17} In cancer patients, the risk of TIVAP-related infection appears to remain unchanged with incidence densities of 0·21 and 0·20/1,000 catheter-days reported in 1993 and 2011, respectively.^{9,13}

If TIVAP is used for total parenteral nutrition (TPN), incidence density of infection is higher and is comprised between 0·33 and 3·2/1000 catheter-days with heterogeneous data depending on the indication for TPN.^{7,18,19} In HIV-infected patients, incidence density ranges from 1·5 to 3·81/1,000 catheter-days, probably because when a LTIVC is required, these patients combine most of the risk factors of infection identified so far.^{20,21} The reported time to infection from TIVAP insertion ranges from 80 to 192 days with extreme values of 2 and 1406 days.^{10,13,20,21}

These discrepancies between patient groups probably reflect exposure towards different risk factors and TIVAP handling frequency. Indeed, a prospective study demonstrated that the frequency of LTIVC handling (including about 50% of TIVAP) was associated with infection incidence.²¹ Additional risk factors are described in Panel 1.

Since frequency of TIVAP handling is one of the major risk factor identified, it is not surprising to observe that coagulase-negative staphylococci (CoNS), which are frequent colonizers of the human skin and mucosal flora, are one of the leading pathogens responsible for TIVAP-related infections.²² For instance, among 29 cases of TIVAP-related infections, a majority of infections (57%) were caused by CoNS, other microorganisms being Gram-negative rods (GNR) (20%), *S. aureus* (7%) and *C. albicans* (3%).¹³ More recent studies described a higher rate of GNR (up to 40%) and yeasts (up to 23%).^{10,20,23} This shift may be explained by different factors such as antineoplastic chemotherapy intensification with more sustained neutropenia allowing translocation of microorganisms from the gut to bloodstream, besides more frequent use of TPN and broad-spectrum antibiotics.¹⁰ To note, early TIVAP-related infections (≤ 30 days) are more frequently caused by *S. aureus* than late infections (50% vs. 12%, respectively).²⁴

Regarding antibiotic resistance, a French cohort of cancer patients reported that 58% of CoNS and 25% of *S. aureus* were methicillin-resistant (MR).²⁴ MR is more frequent in the USA as suggested by data reported by the National Healthcare Safety Network and also in a study of

1 *S. aureus* catheter-related bloodstream infection (CRBSI) in cancer patients, with 37 to 55%
2 of *S. aureus* being MR.^{25,26}

3 As TIVAPs are totally implanted, risk of extraluminal colonization is low and mostly occurs
4 during TIVAP insertion, resulting in surgical site infection. Once the device is inserted,
5 contamination may occur during repeated punctures with Huber needles, if the skin has not
6 been completely cleaned, therefore leading to an intraluminal colonization that can spread
7 from the port to the catheter tip.²⁷⁻²⁹ In case of BSI coming from another focus of infection,
8 bacteria may adhere on the catheter tip, therefore defining a hematogenous route of
9 colonization, which is rare except in case of *S. aureus*. After device contamination, bacteria
10 adhere to the internal or external surface of TIVAP, depending on the source of
11 contamination, using proteinaceous stalks called adhesins.³⁰

12 Bacterial adhesion is influenced by the type of catheter material, bacterial characteristics or by
13 the presence of a layer of blood components. Indeed, once an indwelling device is inserted, a
14 conditioning film made of host components like fibrin or platelets covers it.^{27,31} These
15 deposits may enhance or inhibit bacterial adhesion besides reducing the efficacy of any
16 antibiotic-releasing surface. After several days, all catheters get covered by a fibrin sheath.³²
17 Following adhesion, bacteria multiply and constitute a surface-associated microbial
18 community called a biofilm, which is embedded in a matrix of extracellular polymeric
19 substances produced by both bacteria and the host.^{11,30} Biofilm bacteria exhibit tolerance
20 defined as the ability to survive high concentrations of antibiotics.³³ Thus, systemic
21 antibiotics can cure TIVAP-related BSI but the source of infection cannot be eradicated
22 unless the device is removed or intraluminal treatment used. This high tolerance is
23 responsible for infection relapse with the same pathogen. Preventive approaches are therefore
24 pivotal in order to avoid any microbial contamination and subsequent biofilm formation.

Preventive strategies to reduce risks of colonization

Because of a reduced risk of infection, TIVAPs are favored over other LTIVCs for use in treatment of solid tumor and pediatric hematology patients.^{13,23,34} In case of prolonged TPN, due to a higher risk of infection associated with TIVAPs, a tunnelled catheter may be preferred if daily vascular access is required.^{1,7} If TIVAP is chosen in oncology or hematology patients, it should be inserted as early as possible, due to increased risk of infection in case of neutropenia.^{35,36} Then, preventive strategies must be applied during and after TIVAP insertion.

Preventive measures during TIVAP insertion

Trained personnel with maximum sterile barrier precautions, including sterile gloves, cap, mask, sterile gown and a sterile full body drape, must perform TIVAP insertion.^{2,37,38} For skin preparation, alcohol-based chlorhexidine or alcohol-based povidone-iodine should be used at least 30 seconds and left to dry, as suggested by recent Infectious Diseases Society of America (IDSA) guidelines.³⁸ Chlorhexidine concentration should be >0.5% (usually 2% in clinical trials) with alcohol. Although recommended in France, skin cleaning (or scrubbing) before antiseptic application is still debated.³⁹ Furthermore, no randomized, prospective clinical trial has directly compared the two alcohol-based antiseptic solutions, therefore advocating a comparative study.³⁹

The choice of venipuncture site is not associated with different infection rates as demonstrated by a prospective study of 403 patients randomly allocated to an internal jugular vein or subclavian vein insertion, or a surgical cut-down through the cephalic vein.⁴⁰ If the superior vena cava is not accessible - for instance due to thrombosis - TIVAP can be inserted in the femoral vein with an infection incidence of 0.69/1,000 catheter-days, as reported among 20 cancer patients.⁴¹ Use of ultrasound guidance for catheter insertion has not been shown to reduce the rate of TIVAP-related infections but significantly reduces the number of attempts and increases patient comfort.^{40,42} Systemic antibiotic prophylaxis has no demonstrated benefit during TIVAP insertion and is not indicated.⁴³⁻⁴⁵

Preventive measures after TIVAP insertion

Training of patients, nursing teams and physicians is mandatory to minimize the risk of bacterial contamination.⁷ The Huber needle used to access the TIVAP must be inserted by trained nurses and requires that operators wear a facial mask, a cap and use sterile gloves. Skin disinfection must be performed with an alcoholic antiseptic, prior to each needle

insertion (see above).³⁸ The Huber needle can be changed every seven days if vascular access is maintained continuously.¹⁰ During needle withdrawal, an experimental study suggested that positive pressure using saline injection reduces the risk of blood reflux, therefore preventing catheter tip occlusion.⁴⁶ It is now recommended that heparin lock or flush after TIVAP use should not be performed, as sterile saline locks are equally efficient to prevent functional or infectious complications.^{38,47} Even if different studies demonstrated the benefits of chlorhexidine-impregnated sponges or dressings for the prevention of CRBSI in intensive care units, no studies including TIVAP have been published.

Lock solutions and coatings to prevent TIVAP-related infections

The principle of preventive antibiotic lock therapy (ALT) is to inject highly concentrated antibiotic solution inside the TIVAP lumen. This solution dwells for extended time periods in order to eradicate any bacteria that might get injected inside TIVAP due to incomplete skin antisepsis. Preventive ALT can thus only prevent intraluminal contamination. The chosen volume must allow coverage of the whole internal surface and therefore depends on the type of device. A meta-analysis demonstrated that ALT or antibiotic flush made of vancomycin reduced the risk of CRBSI.⁴⁸ Other groups have assessed the combination of antibiotic (minocycline) and a chelator such as ethylene diamine tetra-acetic acid (EDTA).⁴⁹ Two studies in the pediatric oncology setting have shown that minocycline-EDTA ALT was more effective than heparin for the prevention of CRBSI.^{50,51} Nevertheless, systematic use of ALT could lead to increased antibiotic resistance.^{31,52} Thus, recent IDSA guidelines recommend to restrict the use of preventive ALT to patients with LTIVC who experienced multiple CRBSI despite optimal aseptic techniques.³⁸

Limited data are available for non-antibiotic lock solutions, such as ethanol- or taurolidine-locks. One preliminary pediatric study using ethanol locks including 12 patients with TIVAP was interrupted as 3 patients experienced TIVAP occlusion.⁵³ A meta-analysis showed that ethanol lock therapy reduces the incidence of CRBSI in pediatric TPN with tunnelled catheters but increases the risk of thrombosis.⁵⁴ Therefore, ethanol lock could be proposed in cases of high-risk TPN patients with tunnelled catheters.⁵⁵ Mild and self-limited adverse effects have been reported, especially after flushing the lock, such as dizziness, nausea, headaches, facial flushing and, eventually, an alcohol taste in the mouth.^{56,57}

Taurolidine, a derivative from of the amino acid taurine, was proposed as a lock therapy in 1993 because of its antimicrobial effect against a broad range of microorganisms *in vitro*.⁵⁸⁻⁶⁰ Although studies conducted in hemodialysis patients are encouraging, data supporting its use

1 as a lock in TIVAP are limited.^{61,62} In pediatric cancer patients, an initial study showed no
2 significant reduction of CRBSI with taurolidine/citrate as compared to heparin, with ~75% of
3 TIVAP patients amongst LTIVC.⁶³ A more recent study in pediatric hematology patients
4 showed a significant reduction of CRBSI with taurolidine/citrate as compared to heparin but
5 included only tunnelled catheters.⁵⁹ A randomized study in TPN patients demonstrated that
6 taurolidine/citrate reduced the rate of CRBSI when initiated after the first episode of
7 infection, as compared with heparin (TIVAP represented ~ 40% of LTIVC).⁶⁴ Based on these
8 results, larger comparative studies with TIVAP are needed to define the precise role and
9 indications of ethanol or taurolidine as preventive locks.

10 The use of CVC coatings has been extensively studied in case of short-term CVC, leading to a
11 significant reduction of the risk of CRBSI.^{65,66} As LTIVCs dwell for a longer time in the
12 blood flow, the formation of the conditioning film reduces the antimicrobial action of the
13 coating.²⁷ Furthermore, in case of antibiotic-releasing surfaces, the effect will stop once the
14 device is exhausted. A single study assessed LTIVC coated with minocycline/rifampin but
15 with a relatively short catheterization time period (mean duration of 66±31 days) and reported
16 a significant reduction of CRBSI.⁶⁷ Clinically significant drug delivery was maintained at
17 least 35 days post catheter insertion. Thus, developing an efficient surface modification or
18 antibiotic coating that would help preventing colonization is still a major challenge (see
19 “Future Treatments” section).

1 **Diagnosis of TIVAP-related infections**

2 TIVAP-related infection is easily suspected if the patient exhibits local signs such as pain or
3 erythema at the site of TIVAP implantation. However, diagnosis is more difficult in case of
4 isolated fever, chills or severe sepsis. Recent IDSA guidelines have proposed three classes of
5 TIVAP-related infections:⁶⁸

6 -Local complicated infections, defined as a tunnel or port-pocket infection with extended
7 erythema or induration (more than two cm), purulent collection, skin necrosis and
8 spontaneous rupture and drainage (Figure 1A).⁶⁸

9 -TIVAP-related BSI, defined as a positive blood culture drawn from a peripheral vein
10 associated with evidence that the BSI originates from the TIVAP using paired blood cultures
11 or culture of a component of the removed TIVAP (see below). TIVAP-related BSI can
12 therefore be defined with or without device removal.⁶⁸

13 -Catheter-related infection, defined by the association of local or general signs of infection
14 and a positive culture of the catheter tip.⁶⁸

15 Based on these criteria, a diagnostic algorithm including clinical signs and microbiological
16 workup can be proposed (Figure 2).

18 *Diagnosis of local infection*

19 Clinical signs of local infection such as erythema or purulent exudate at the site of TIVAP
20 implantation has high specificity, but little sensitivity for the diagnosis of TIVAP-related
21 infection.⁶⁸ Indeed, local signs are reported in only 7 to 12% of TIVAP-related BSI and as
22 local infections are caused by extraluminal contamination, they can occur without any
23 concomitant BSI.^{24,69,70} Erythema can also be caused by non-infectious factors such as
24 allergy. To confirm local infection, a positive culture of aseptically removed material
25 surrounding the port such as purulent fluid, skin necrosis or swabbing of the port surface is
26 mandatory.^{24,71} Peripheral blood cultures should also be performed to rule out an associated
27 BSI (Figure 2).

29 *Diagnosis of TIVAP-related BSI without device removal*

30 This diagnosis relies on the identification of the same microorganism in paired blood
31 cultures.⁶⁸ Correct interpretation of the test requires blood samples to be performed
32 consecutively, with the same volume of blood drawn from a peripheral vein and from the
33 TIVAP through a Huber needle, ideally before the initiation of antimicrobials.^{68,72,73} Another
34 critical point is to precisely label the origin of each blood culture bottle.⁶⁸ The two most

commonly used methods for diagnosing CRBSI are simultaneous quantitative blood cultures and the differential time to positivity (DTP) of qualitative blood cultures.^{72,74-76} If TIVAP is the source of BSI, the inoculum will be higher in the blood drawn from TIVAP, as compared with peripheral vein, therefore leading to a shorter time to positivity (difference $\geq$ two hours) or a higher bacterial quantification ($\geq$ four-fold).^{68,72,73,75,76} When used for the diagnosis of LTIVC-related BSI, these two methods have sensitivity above 90% and specificity close to 100% and between 75% and 91% for quantitative paired blood cultures and DTP, respectively.^{72,75,76} They are nevertheless considered equivalent in recent guidelines and the choice of a technique will mostly rely on local equipment and training.⁶⁸

To reduce the risk of contamination when blood is drawn from TIVAP, a rigorous skin disinfection is mandatory before sampling (see “Prevention” section).⁶⁸

Diagnosis of TIVAP-related BSI after device removal

The demonstration that a BSI originates from a TIVAP relies on the identification of the same microorganism in a TIVAP component and peripheral blood cultures. The catheter tip (four-cm distal part) can be cultured using the semiquantitative or quantitative methods with thresholds defining a significant colonization of >15 CFU and $\geq 10^3$ CFU/mL, respectively (Figures 3A and B).^{77,78} Both methods can be equally used but are associated with sensitivity below 50% for the diagnosis of TIVAP colonization, stressing the importance of using other techniques.^{68,69,71,79} For instance, it has been proposed to perform quantitative culture of the TIVAP septum using an adapted Brun-Buisson method (Figures 3A and C).⁶⁹ With a threshold of 10^3 CFU/mL, this method was associated with 93% sensitivity and 100% specificity for the diagnosis of TIVAP-related BSI.⁶⁹ Furthermore, after septum removal, if macroscopic debris or clots are present, they can be sampled and cultured with a sensitivity and specificity of 100% in case of TIVAP-related BSI.⁷¹ The main limitations of port septum and port deposit cultures are lack of technical standardization and absence of a consensus threshold.⁶⁸ Therefore, performing both catheter tip culture and a culture of a component of the port reservoir is advisable.⁶⁸ Careful handling of explanted materials will reduce the risk of contamination in the clinical microbiology laboratory.

Diagnosis of fungal TIVAP-related BSI

Without TIVAP removal, such a diagnosis is challenging as studies assessing paired blood cultures infrequently included study of fungal infections.^{72,74,75,80} Some authors have proposed to use the time taken to detect *Candida* spp. growth in peripheral blood as a diagnostic tool,

1 since time to positivity is shorter in case of catheter-related (CR) candidemia (17 ± 2 h) than
2 candidemia from another source (38 ± 3 h).⁸¹ The objective of this approach would be to rule
3 out the catheter as the source of candidemia if time to positivity is above 30 hours. In case of
4 TIVAP removal, microbiological methods and thresholds are the same, and culture on blood
5 agar is sensitive enough for the growth of fungi involved in TIVAP-related infections, even if
6 they may require a longer incubation time than bacteria (24-72h).⁸²

7 8 *Workup to rule out complications*

9 When TIVAP-related BSI is suspected, clinicians should look for infectious complications
10 such as severe sepsis, endocarditis, or other hematogenous complications (Figures 1B, C and
11 D).²⁴ Recent guidelines recommend systematic transesophageal echocardiography in case of
12 *S. aureus* TIVAP-related BSI.⁶⁸ Nevertheless, it is very likely that in selected patients without
13 intracardiac devices and with rapid clearance of BSI, a transthoracic echocardiography
14 performed at least 5 days after BSI onset can safely rule out infective endocarditis.⁸³⁻⁸⁷ In case
15 of clinical signs of thrombophlebitis or persistent BSI despite appropriate systemic
16 antimicrobial therapy, venous ultrasonographic examination should be performed, especially
17 in case of *S. aureus* TIVAP-related BSI (Figure 1B).^{68,88}

18 Whatever the microorganism, persistent BSI after 3 days of adequate antimicrobials should
19 prompt a complete workup including echocardiography and, venous ultrasonographic
20 examination with or without a computed tomography (CT)-scan.⁶⁸

Treatment: should TIVAP be removed or retained?

In the case of CRBSI, the treatment of choice is systemic antimicrobial therapy in conjunction with removal of the colonized device.⁴ However, in case of TIVAPs, reduced venous access, potential presence of coagulation disorders, the need for a new procedure and its cost, all argue in favor of attempting a catheter salvage, if the clinical situation allows it.⁶⁸

TIVAP removal is mandatory, regardless of the microbial etiology, in case of complicated TIVAP-related infection defined by tunnel or port-pocket infections, severe sepsis or septic shock, endocarditis, septic thrombophlebitis, osteomyelitis or other hematogenous seeding, as suggested by IDSA guidelines (Figure 1 and 4).⁶⁸ Furthermore, infections caused by *S. aureus* or *Candida* spp. warrant TIVAP removal, except in exceptional circumstances (see below) (Figure 4).^{68,89} If a conservative strategy is decided upon, the TIVAP should be removed in case of persistent positive blood cultures 72 hours after the initiation of antibiotics.⁶⁸

In case of uncomplicated TIVAP-related BSI not caused by *S. aureus* or *Candida* spp., a conservative treatment using a combination of systemic antimicrobials and ALT can be considered.⁶⁸ Indeed, as most of LTIVC-related infections are associated with intraluminal colonization, instillation of high concentrations of antimicrobial solution filling the entire volume of the lumen and dwelling for an extended period of time may allow sterilization of the device.⁹⁰⁻⁹² Despite several limitations, there is a growing body of evidence favoring the use of ALT. For instance, a randomized, placebo-controlled study showed that ALT plus systemic antimicrobial therapy is more effective than systemic antimicrobial therapy alone for treating LTIVC-related BSI, although not reaching statistical significance due to the small sample size.⁷⁰ In addition, large uncontrolled studies demonstrated high cure rates in patients with uncomplicated LTIVC-related BSI due to CoNS (89%) or GNR (95%) (Table 1).^{89,91,93}

How to perform ALT?

No clinical trials have compared one drug to another and some *in vitro* studies have given conflicting results with mitigated clinical relevance.^{94,95} As described in Table 1, more frequently used antibiotics are glycopeptides, aminoglycosides or fluoroquinolones and their use has been associated with high rates of therapeutic success. The chosen antibiotic must be active *in vitro* against the identified microorganism. Ideally, antimicrobials should be administered at a concentration at least 1000-fold above the minimal inhibitory concentration (MIC) (frequently between 1 and 5 mg/mL) with a volume that fills the entire TIVAP lumen. In most studies, ALT is prescribed for 10 to 14 days (Table 1) and the lock solution is usually replaced every 12 to 24 hours, depending on the necessity for vascular access.⁶⁸ Replacing the

solution every 48 or 72 hours has also been performed safely.⁹³ In case of TIVAP-related BSI, systemic antimicrobials should always be administered for 10 to 14 days.⁶⁸ Addition of heparin in ALT has been proposed to avoid thrombosis of the catheter but no comparative data support its use and adverse effects have been reported such as bleeding or the enhancement of *S. aureus* biofilm formation *in vitro*.^{96,97} Therefore, ALT can be performed in saline or heparin, at 10 to 100 IU/mL (Table 1).⁶⁸ In case of conservative treatment, close follow-up is mandatory to detect treatment failure and includes, at least, blood cultures performed 3 days after the beginning of the treatment and 2-4 weeks after the end of the treatment (Figure 4).

Adapting treatment to the identified microorganism (Figure 4)

In case of uncomplicated CoNS infection, the cure rate of ALT is high (>80%), and failures are mainly due to relapses during the first month of follow-up.^{89,91} In case of treatment failure or recurrence of infection, TIVAP removal should be considered. Glycopeptides for 10 to 14 days have been extensively used and a prospective uncontrolled study identified a trend toward a higher success rate with teicoplanin as compared to vancomycin.^{89,91} Additionally, daptomycin can be considered as a possible alternative (see below).^{94,95}

Conservative treatment of GNR TIVAP-related BSI is associated with a cure rate between 87% and 95%, when local or distant complications are excluded.^{89,93} Although recent guidelines suggest TIVAP removal in the case of *P. aeruginosa* infection, *Pseudomonas* spp. have also been included in clinical ALT studies, with the same success rates as *Enterobacteriaceae*. Fluoroquinolones and aminoglycosides are the antimicrobials most commonly used for these infections.^{89,93}

S. aureus TIVAP-related BSI should lead to catheter removal due to the high failure rates of ALT (45% to 60%), with some cases of related mortality.^{89,98} ALT can nevertheless be considered in exceptional circumstances after having excluded local or distant complications, such as infective endocarditis with transesophageal echocardiography.⁶⁸ Cefazolin and vancomycin are the antimicrobials most frequently used in this setting and the efficacy of other antimicrobials such as aminoglycosides or daptomycin should be evaluated in clinical studies.^{89,95,98,99}

Infections due to *Candida* spp. should lead to catheter removal, and conservative treatment should only be considered in limited situations after ruling out local or distant complications (see below). Although optimal antifungal-lock therapy has not been established in this unusual situation, amphotericin B (liposomal or deoxycholate) and ethanol are the most

commonly used compounds.¹⁰⁰ In case of catheter retention, a systemic antifungal with activity against *Candida* biofilms should be favored such as lipid-based amphotericin B or echinocandins (see Panel 2).¹⁰¹

In case of polymicrobial infections, ALT can be proposed if two criteria are met: i) none of the involved microorganisms is *S. aureus* or *Candida* spp. and ii) a single antimicrobial can be used to treat them all or a stable association of antimicrobials can be used.^{93,102}

Recently developed locks

Aside from commonly used antimicrobials in ALT, 70% ethanol and daptomycin have been more recently used as ALT for conservative treatment. Regarding ethanol, no comparative studies have been published and most uncontrolled studies have been conducted in pediatric patients, with a less accurate diagnosis due to lack of peripheral blood cultures.¹⁰³⁻¹⁰⁵ For instance, a retrospective study of 51 patients treated with 70% ethanol dwelling for five days reported a cure rate of 100% but recurrences in 10% of cases.¹⁰⁵ More recently, daptomycin has been proposed as lock therapy because of its potent *in vitro* effect against biofilms.^{106,107} A phase II clinical study was conducted using daptomycin ALT in 13 patients with LTIVC-related infections caused by CoNS or *E. faecalis*, half of them occurring on TIVAP.⁹⁴ After a mean of 14 days of treatment, cure rate was 85% (11/13 patients).⁹⁴ Comparative clinical studies are now expected to determine if ethanol or daptomycin are more efficient or more quickly effective than already used antibiotics.

Future treatments and needs

Considering limitations of currently proposed diagnostic, preventive or therapeutic measures, many questions still need to be addressed in the field of TIVAP-related infections.

Improving diagnosis

Despite their help in diagnosing TIVAP-related BSI without device removal, paired blood cultures are not foolproof as both methods give false-positive and false-negative results.^{69,73,80,108,109} Therefore, different investigators have tried to develop molecular biology tools for the diagnosis of TIVAP-related infections. For example, amplification and sequencing of bacterial DNA (16S ribosomal RNA gene) has been performed on blood drawn from CVCs in cases of CRBSI or after TIVAP removal, on port sonication fluid and biofilms from the internal surface of the port.^{110,111} Whereas these methods are more sensitive than cultures in case of previous antibiotic administration, their reduced specificity of ~80% due to false-positive results (external DNA contamination during procedure) leads to other diagnostic challenges. Other groups have tried to identify biomarkers of biofilm formation inside the port that would allow an earlier diagnosis of colonization before the onset of BSI. For instance, certain LPS modifications are only occurring within Gram-negative bacterial biofilms.¹¹²

Regarding fungal infections, the use of selective blood culture bottles, polymerase chain reaction or antigen detection on blood samples could allow faster and/or more sensitive diagnosis but these methods still need to be assessed in the setting of TIVAP.^{113,114}

Prevention

Improvement of hygiene measures should always be attempted through definition and implementation of local clinical bundles for TIVAP insertion and handling.^{4,38,68} Dedicated infusion therapy teams could be involved in the education of healthcare workers and patients.⁴ Other preventive strategies are limited by the long-term implantation of TIVAP leading to coverage by host blood components of any modified surface, and reduction of the effect of antibiotic-coated catheters over time. One possible solution would be to use anti-adhesive compounds inhibiting the deposition of blood components or inhibiting local thrombosis that would delay or reduce the risk of formation of the protein film. For instance, a surface modification using nonleaching polymeric sulfobetaine (polySB) is associated with a significant reduction of adherence and activation of platelets and white blood cells.¹¹⁵ This scaffold retains water on the catheter surface and not only reduces proteins, host cells and

microbial adhesion but also thrombus formation *in vitro* and *in vivo*.¹¹⁵ Although this and other approaches provided encouraging results, they need to be assessed in long-term settings.¹¹⁶

Biofilm eradication inside TIVAP

Currently used antibiotics as lock therapy have drawbacks, such as possible treatment failure or a long treatment duration.⁶⁸ Several investigators have attempted to develop more efficient and faster ALT to face these challenges. *In vitro* and *in vivo* studies identified several potential lock candidates and, for instance, ethanol or daptomycin are now being clinically assessed.^{94,103} Another approach is to use an adjuvant to increase antibiotic efficiency against biofilms. For example, the association of an antibiotic and a chelator such as EDTA or citrate has been proposed, since divalent cations play a key-role in maintaining biofilm matrix stability.¹¹⁷ Addition of chelators destabilize the matrix and therefore increase antimicrobial activity.¹¹⁸ Many *in vitro* studies have reported an antibiofilm effect of EDTA alone and a synergistic effect when combined with gentamicin or minocycline/25% ethanol.^{119,120} *In vivo*, the combination of gentamicin and EDTA led to complete eradication of biofilms of Gram-positive as well as Gram-negative bacteria formed inside TIVAP implanted in rats, therefore paving the way to clinical studies.¹²¹

Fundamental research also led to the identification of compounds exhibiting promising effects. Even though none of them have been assessed as ALT *per se*, their effect should be examined in this perspective:

It has been demonstrated that the association of an aminoglycoside and a sugar such as mannitol or fructose could increase antibiotic uptake in the most tolerant bacteria inside biofilms called persister cells. Killing of persisters may lead to a more efficient treatment of *in vivo* biofilms.¹²² Such an approach could easily be converted to an ALT composed of an aminoglycoside plus sugar.

As quorum sensing (QS) is a key component of biofilm communication, many investigators have speculated that interfering with QS signals might alter biofilm maturation thereby leading to easier eradication. For instance, RNAIII inhibiting peptide (RIP), a compound interfering with *S. aureus* QS efficiently prevented CVC-related infection *in vivo*.¹²³

Another approach would be to favor bacterial biofilm dispersion as biofilm bacteria lose most of their antibiotic tolerance when they return to a planktonic state.³³ However, the dispersal approach needs to be associated with systemic and local antibiotics as released bacteria from the biofilm into the bloodstream may express virulence genes and lead to severe sepsis.¹²⁴

1 Many compounds such as dispersin B, DNase I or autoinducing peptides have been described
2 to favor biofilm dispersion *in vitro*, and to a lesser extent *in vivo*.^{125,126}
3 Many other compounds or strategies are currently being investigated and developed such as
4 vaccination, bacteriophages or association of antibiotics with non antibiotic compounds
5 through the screening of chemical libraries, but substantial research is still required before
6 reaching clinical studies.^{31,127-130}
7
8

1 **Conclusion**

2 Thirty years of intense study of TIVAP-related infection epidemiology has led to an improved
3 delineation of patients at risk of infection, which is of key importance with regard to the
4 increasing number of inserted TIVAPs. Although ALT has proven to be a pivotal strategy for
5 the conservative treatment of selected uncomplicated TIVAP-related BSI, there is still much
6 work to be done, especially in light of recent experimental progresses made on reduction of
7 antimicrobial tolerance in TIVAP-associated infections using combinations of antibiotics and
8 antibiofilm compounds. It is also to be foreseen that preventive approaches will benefit from
9 device development specifically conceived to reduce microbial colonization and infection, for
10 instance using surface modifications with anti-adhesion properties. Finally, while the
11 diagnosis of TIVAP infections remains challenging, there are indications that infection and
12 biofilm biomarkers could be developed in a near future to assist clinicians in taking
13 appropriate preventive or curative decisions at early stages of TIVAP colonization. Such
14 timely therapeutic actions could significantly reduce the rate of device removal and
15 fundamentally change our current view of TIVAP management.

Panel 1. Risk factors of TIVAP-related infections. When available, odd-ratios (OR) are expressed with 95% confidence interval [95% CI].

Modifiable risk factors

-Frequency of TIVAP handling with an OR of 1·15 [1·03-1·3] for each 10% increase of the frequency of LTIVC handling, especially among HIV-infected patients.²¹

-Use of total parenteral nutrition, because of a more frequent access to TIVAP, and because of fluids such as lipid products that can increase microbial growth.⁷ OR=28·5 [4·2-200].¹³¹

-Difficulties during insertion (*i.e.* when several punctures are required) through formation of local thrombus or hematoma that increase the risk of bacterial colonization. OR=25·6 [4·2-106].¹³¹

Non-modifiable risk factors

-Age with a threshold depending on each study. <7 year-old,¹³ < 10 year-old (OR=18·4 [1·9-106·7]);¹³¹ < 40 year-old.¹⁰

-Chemotherapy for hematologic malignancies rather than solid tumors.^{13,132} OR=5·1 [1·5-17·5].¹³³

-Hematopoietic stem cell transplantation, OR=1·74 [1·1-2·4].²³

-Reduced autonomy, as expressed by a Karnofsky performance status $\leq$ 80%, in cancer patients, OR=5·3 [1·5-19·3].²¹

-Presence of metastases in cancer patients, OR=4·1 [0·9-19·5].²¹

-Bacterial infection within the prior month, OR=2·1 [1·1-3·8] in HIV-infected patients and OR=5·4 [1·2-25·3] in cancer patients.²¹

-Neutropenia among HIV-infected patients, OR=1·8 [1·1-3·1]²¹ and patients with hematological malignancies, OR=15·1 [2·6-86·5].³⁶

-Diabetes in CF-patients.⁶

To note, no study identified a specific class of antineoplastic chemotherapy or radiation therapy as being risk factors of TIVAP-related infection.

Panel 2. Future challenges regarding TIVAP and candidemia.

All published international guidelines so far strongly recommend the early removal of any central venous catheter (CVC) in case of candidemia whether or not it is catheter-related (CR).^{68,101,134} Two situations should be distinguished. On one hand, if the candidemia is not CR, it is plausible that catheter retention does not influence outcome, especially if an antifungal efficient against *Candida* biofilms is used.¹³⁵ A comparative study is needed to definitively answer this question. On the other hand, if the candidemia is CR, it is very likely that catheter removal is required. For instance, a retrospective study including 404 patients with cancer, CVC and candidemia identified after multivariate analysis that early catheter removal improved response to antifungal therapy only among patients with CR candidemia.¹³⁶ In this context, one major issue is that the diagnosis of fungal CRBSI without catheter removal is still challenging due to poor clinical evaluation of paired blood cultures in this setting.^{72,74,75}

In case of CR candidemia, even if catheter removal is recommended, many patients cannot afford a CVC replacement because of their general condition. Therefore, antifungal lock therapy has been proposed to increase the likelihood of biofilm eradication, based on the same principles as ALT.¹⁰⁰ *In vitro* and *in vivo* studies reveal that against *Candida* biofilms: i) azoles have poor activity; ii) lipid formulations of amphotericin B are more effective than amphotericin B deoxycholate; and iii) echinocandins have excellent *in vitro* activity.¹⁰⁰ Non-antifungal lock therapy against *Candida* biofilms have also been proposed such as EDTA in combination with antifungals or minocycline, ethanol, heparin and even highly concentrated antibiotics like doxycycline.^{100,137-140} Even if no comparative study is available, more than 20 patients were treated with various types of antifungal locks with an overall success rate of 77% with a publication bias that should be taken into account.¹⁰⁰ Hence, ethanol lock therapy could be a promising candidate with eight successes among ten reported patients.^{139,140} Of note, most of these published cases are of pediatric patients with the limitation of diagnostic criteria, frequently based on blood cultures drawn from the CVC without any peripheral blood culture. Studies of antifungal lock therapy specifically for TIVAP-associated fungal infections are clearly needed.

Contributors

DL, NFH and BA undertook the initial literature searches and wrote the first draft of the manuscript. DL prepared the figures. All authors participated equally in the intellectual content, revision and final approval of this manuscript.

Conflicts of interest

All authors: no conflicts of interest.

Acknowledgments

D.L. was supported by a grant from the AXA Research Fund and from the French Government's Investissement d'Avenir program, Laboratoire d'Excellence "Integrative Biology of Emerging Infectious Diseases" (grant n°ANR-10-LABX-62-IBEID). D.L received a travel grant in 2009 from Schering-Plough for an international conference.

N.F.H. and B.A. were supported by Ministerio de Economía y Competitividad, Instituto de Salud Carlos III - cofinanced by European Development Regional Fund "A way to achieve Europe" ERDF, Spanish Network for the Research in Infectious Diseases (REIPI RD12/0015).

S.A.L. was supported by a grant from the Department of Veterans Affairs and the Biomedical Research Institute of New Mexico.

These sources of funding had no involvement in the preparation of this manuscript.

The authors would like to thank Chantal Dreyer from Hôpital Beaujon, Clichy who kindly provided a clinical photograph.

D.L. would also like to thank patients and physicians of the Hôpital Beaujon, and especially the Service de Médecine Interne.

References

- 1 Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M. ESPEN Guidelines on Parenteral Nutrition: central venous catheters (access, care, diagnosis and therapy of complications). *Clin Nutr* 2009; **28**: 365-77.
- 2 Vescia S, Baumgartner AK, Jacobs VR, et al. Management of venous port systems in oncology: a review of current evidence. *Ann Oncol* 2008; **19**: 9-15.
- 3 Reed WP, Newman KA, de Jongh C, et al. Prolonged venous access for chemotherapy by means of the Hickman catheter. *Cancer* 1983; **52**: 185-92.
- 4 Raad I, Hanna H, Maki D. Intravascular catheter-related infections: advances in diagnosis, prevention, and management. *Lancet Infect Dis* 2007; **7**: 645-57.
- 5 Niederhuber JE, Ensminger W, Gyves JW, Liepman M, Doan K, Cozzi E. Totally implanted venous and arterial access system to replace external catheters in cancer treatment. *Surgery* 1982; **92**: 706-12.
- 6 Dal Molin A, Di Massimo DS, Braggion C, et al. Totally implantable central venous access ports in patients with cystic fibrosis: a multicenter prospective cohort study. *J Vasc Access* 2012; **13**: 290-5.
- 7 Santarpia L, Pasanisi F, Alfonsi L, et al. Prevention and treatment of implanted central venous catheter (CVC) - related sepsis: a report after six years of home parenteral nutrition (HPN). *Clin Nutr* 2002; **21**: 207-11.
- 8 U.S. Markets for Vascular Access Devices and Accessories from iData Research Inc. Published in November 2012. 2012;
- 9 Barbetakis N, Asteriou C, Kleontas A, Tsilikas C. Totally implantable central venous access ports. Analysis of 700 cases. *J Surg Oncol* 2011; **104**: 654-6.
- 10 Chang L, Tsai JS, Huang SJ, Shih CC. Evaluation of infectious complications of the implantable venous access system in a general oncologic population. *Am J Infect Control* 2003; **31**: 34-9.
- 11 Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. *Science* 1999; **284**: 1318-22.
- 12 Fischer L, Knebel P, Schroder S, et al. Reasons for explantation of totally implantable access ports: a multivariate analysis of 385 consecutive patients. *Ann Surg Oncol* 2008; **15**: 1124-9.
- 13 Groeger JS, Lucas AB, Thaler HT, et al. Infectious morbidity associated with long-term use of venous access devices in patients with cancer. *Ann Intern Med* 1993; **119**: 1168-74.
- 14 Hsieh CC, Weng HH, Huang WS, et al. Analysis of risk factors for central venous port failure in cancer patients. *World J Gastroenterol* 2009; **15**: 4709-14.

- 1 15 Burdon J, Conway SP, Murchan P, Lansdown M, Kester RC. Five years' experience of
2 PAS Port intravenous access system in adult cystic fibrosis. *Eur Respir J* 1998; **12**: 212-6.
- 3 16 Royle TJ, Davies RE, Gannon MX. Totally implantable venous access devices - 20
4 years' experience of implantation in cystic fibrosis patients. *Ann R Coll Surg Engl* 2008; **90**:
5 679-84.
- 6 17 Wolosker N, Yazbek G, Nishinari K, et al. Totally implantable venous catheters for
7 chemotherapy: experience in 500 patients. *Sao Paulo Med J* 2004; **122**: 147-51.
- 8 18 Shirotani N, Iino T, Numata K, Kameoka S. Complications of central venous catheters
9 in patients on home parenteral nutrition: an analysis of 68 patients over 16 years. *Surg Today*
10 2006; **36**: 420-4.
- 11 19 Cotogni P, Pittiruti M, Barbero C, Monge T, Palmo A, Boggio Bertinet D. Catheter-
12 Related Complications in Cancer Patients on Home Parenteral Nutrition: A Prospective Study
13 of Over 51,000 Catheter Days. *JPEN J Parenter Enteral Nutr* 2013;
- 14 20 Sotir MJ, Lewis C, Bisher EW, Ray SM, Soucie JM, Blumberg HM. Epidemiology of
15 device-associated infections related to a long-term implantable vascular access device. *Infect*
16 *Control Hosp Epidemiol* 1999; **20**: 187-91.
- 17 21 Astagneau P, Maugat S, Tran-Minh T, et al. Long-term central venous catheter
18 infection in HIV-infected and cancer patients: a multicenter cohort study. *Infect Control Hosp*
19 *Epidemiol* 1999; **20**: 494-8.
- 20 22 Kloos WE, Musselwhite MS. Distribution and persistence of *Staphylococcus* and
21 *Micrococcus* species and other aerobic bacteria on human skin. *Appl Microbiol* 1975; **30**:
22 381-5.
- 23 23 Adler A, Yaniv I, Steinberg R, et al. Infectious complications of implantable ports and
24 Hickman catheters in paediatric haematology-oncology patients. *J Hosp Infect* 2006; **62**: 358-
25 65.
- 26 24 Lebeaux D, Larroque B, Gellen-Dautremer J, et al. Clinical outcome after a totally
27 implantable venous access port-related infection in cancer patients: a prospective study and
28 review of the literature. *Medicine (Baltimore)* 2012; **91**: 309-18.
- 29 25 Ghanem GA, Boktour M, Warneke C, et al. Catheter-related *Staphylococcus aureus*
30 bacteremia in cancer patients: high rate of complications with therapeutic implications.
31 *Medicine (Baltimore)* 2007; **86**: 54-60.
- 32 26 Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-Resistant Pathogens
33 Associated with Healthcare-Associated Infections: Summary of Data Reported to the National
34 Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-2010.
35 *Infection Control and Hospital Epidemiology* 2013; **34**: 1-14.
- 36 27 Raad I, Costerton W, Sabharwal U, Sacilowski M, Anaissie E, Bodey GP.
37 Ultrastructural analysis of indwelling vascular catheters: a quantitative relationship between
38 luminal colonization and duration of placement. *J Infect Dis* 1993; **168**: 400-7.

1 28 Safdar N, Maki DG. The pathogenesis of catheter-related bloodstream infection with
2 noncuffed short-term central venous catheters. *Intensive Care Med* 2004; **30**: 62-7.

3 29 Mermel LA. What is the predominant source of intravascular catheter infections? *Clin*
4 *Infect Dis* 2011; **52**: 211-2.

5 30 Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant
6 microorganisms. *Clin Microbiol Rev* 2002; **15**: 167-93.

7 31 Donlan RM. Biofilm elimination on intravascular catheters: important considerations
8 for the infectious disease practitioner. *Clin Infect Dis* 2011; **52**: 1038-45.

9 32 Raad, II, Luna M, Khalil SA, Costerton JW, Lam C, Bodey GP. The relationship
10 between the thrombotic and infectious complications of central venous catheters. *JAMA* 1994;
11 **271**: 1014-6.

12 33 Lewis K. Riddle of biofilm resistance. *Antimicrob Agents Chemother* 2001; **45**: 999-
13 1007.

14 34 Ng F, Mastoroudes H, Paul E, et al. A comparison of Hickman line- and Port-a-Cath-
15 associated complications in patients with solid tumours undergoing chemotherapy. *Clin Oncol*
16 *(R Coll Radiol)* 2007; **19**: 551-6.

17 35 Ohno H, Mizumoto C, Otsuki Y, Oguma S, Yoshida Y. The duration of functioning of
18 a subcutaneous implantable port for the treatment of hematological tumors: a single
19 institution-based study. *Int J Clin Oncol* 2010; **15**: 172-8.

20 36 Howell PB, Walters PE, Donowitz GR, Farr BM. Risk factors for infection of adult
21 patients with cancer who have tunneled central venous catheters. *Cancer* 1995; **75**: 1367-75.

22 37 Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-
23 related bloodstream infections in the ICU. *N Engl J Med* 2006; **355**: 2725-32.

24 38 O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of
25 intravascular catheter-related infections. *Clin Infect Dis* 2011; **52**: e162-93.

26 39 Goudet V, Timsit JF, Lucet JC, et al. Comparison of four skin preparation strategies to
27 prevent catheter-related infection in intensive care unit (CLEAN trial): a study protocol for a
28 randomized controlled trial. *Trials* 2013; **14**:

29 40 Biffi R, Orsi F, Pozzi S, et al. Best choice of central venous insertion site for the
30 prevention of catheter-related complications in adult patients who need cancer therapy: a
31 randomized trial. *Ann Oncol* 2009; **20**: 935-40.

32 41 Wolosker N, Yazbek G, Munia MA, Zerati AE, Langer M, Nishinari K. Totally
33 implantable femoral vein catheters in cancer patients. *Eur J Surg Oncol* 2004; **30**: 771-5.

34 42 Peris A, Zagli G, Bonizzoli M, et al. Implantation of 3951 long-term central venous
35 catheters: performances, risk analysis, and patient comfort after ultrasound-guidance
36 introduction. *Anesth Analg* 2010; **111**: 1194-201.

- 1 43 Karanlik H, Kurul S, Saip P, et al. The role of antibiotic prophylaxis in totally
2 implantable venous access device placement: results of a single-center prospective
3 randomized trial. *Am J Surg* 2011; **202**: 10-5.
- 4 44 Di Carlo I, Toro A, Pulvirenti E, Palermo F, Scibilia G, Cordio S. Could antibiotic
5 prophylaxis be not necessary to implant totally implantable venous access devices?
6 Randomized prospective study. *Surg Oncol* 2011; **20**: 20-5.
- 7 45 van de Wetering MD, van Woensel JB. Prophylactic antibiotics for preventing early
8 central venous catheter Gram positive infections in oncology patients. *Cochrane Database*
9 *Syst Rev* 2007; CD003295.
- 10 46 Lapalu J, Losser MR, Albert O, et al. Totally implantable port management: impact of
11 positive pressure during needle withdrawal on catheter tip occlusion (an experimental study).
12 *J Vasc Access* 2010; **11**: 46-51.
- 13 47 Goossens GA, Jerome M, Janssens C, et al. Comparing normal saline versus diluted
14 heparin to lock non-valved totally implantable venous access devices in cancer patients: a
15 randomised, non-inferiority, open trial. *Ann Oncol* 2013;
- 16 48 Safdar N, Maki DG. Use of vancomycin-containing lock or flush solutions for
17 prevention of bloodstream infection associated with central venous access devices: a meta-
18 analysis of prospective, randomized trials. *Clin Infect Dis* 2006; **43**: 474-84.
- 19 49 Raad II, Fang X, Keutgen XM, Jiang Y, Sherertz R, Hachem R. The role of chelators
20 in preventing biofilm formation and catheter-related bloodstream infections. *Curr Opin Infect*
21 *Dis* 2008; **21**: 385-92.
- 22 50 Ferreira Chacon JM, Hato de Almeida E, de Lourdes Simoes R, et al. Randomized
23 study of minocycline and edetic acid as a locking solution for central line (port-a-cath) in
24 children with cancer. *Chemotherapy* 2011; **57**: 285-91.
- 25 51 Chatzinikolaou I, Zipf TF, Hanna H, et al. Minocycline-ethylenediaminetetraacetate
26 lock solution for the prevention of implantable port infections in children with cancer. *Clin*
27 *Infect Dis* 2003; **36**: 116-9.
- 28 52 Landry DL, Braden GL, Gobeille SL, Haessler SD, Vaidya CK, Sweet SJ. Emergence
29 of gentamicin-resistant bacteremia in hemodialysis patients receiving gentamicin lock
30 catheter prophylaxis. *Clin J Am Soc Nephrol* 2010; **5**: 1799-804.
- 31 53 Kayton ML, Garmey EG, Ishill NM, et al. Preliminary results of a phase I trial of
32 prophylactic ethanol-lock administration to prevent mediport catheter-related bloodstream
33 infections. *J Pediatr Surg* 2010; **45**: 1961-6.
- 34 54 Oliveira C, Nasr A, Brindle M, Wales PW. Ethanol locks to prevent catheter-related
35 bloodstream infections in parenteral nutrition: a meta-analysis. *Pediatrics* 2012; **129**: 318-29.
- 36 55 Wales PW, Kosar C, Carricato M, de Silva N, Lang K, Avitzur Y. Ethanol lock
37 therapy to reduce the incidence of catheter-related bloodstream infections in home parenteral
38 nutrition patients with intestinal failure: preliminary experience. *J Pediatr Surg* 2011; **46**:
39 951-6.

1 56 Slobbe L, Doorduijn JK, Lugtenburg PJ, et al. Prevention of catheter-related
2 bacteremia with a daily ethanol lock in patients with tunnelled catheters: a randomized,
3 placebo-controlled trial. *PLoS One* 2010; **5**: e10840.

4 57 Wolf J, Shenep JL, Clifford V, Curtis N, Flynn PM. Ethanol lock therapy in pediatric
5 hematology and oncology. *Pediatr Blood Cancer* 2013; **60**: 18-25.

6 58 Bradshaw JH, Puntis JW. Taurolidine and catheter-related bloodstream infection: a
7 systematic review of the literature. *J Pediatr Gastroenterol Nutr* 2008; **47**: 179-86.

8 59 Dumichen MJ, Seeger K, Lode HN, et al. Randomized controlled trial of taurolidine
9 citrate *versus* heparin as catheter lock solution in paediatric patients with haematological
10 malignancies. *J Hosp Infect* 2012; **80**: 304-9.

11 60 Johnston DA, Phillips G, Perry M, McAlpine H, Richards J, Pennington CR. Taurolin
12 for the prevention of parenteral nutrition related infection: antimicrobial activity and long-
13 term use. *Clin Nutr* 1993; **12**: 365-8.

14 61 Solomon LR, Cheesbrough JS, Bhargava R, et al. Observational study of need for
15 thrombolytic therapy and incidence of bacteremia using taurolidine-citrate-heparin,
16 taurolidine-citrate and heparin catheter locks in patients treated with hemodialysis. *Semin*
17 *Dial* 2012; **25**: 233-8.

18 62 Betjes MG, van Agteren M. Prevention of dialysis catheter-related sepsis with a
19 citrate-taurolidine-containing lock solution. *Nephrol Dial Transplant* 2004; **19**: 1546-51.

20 63 Simon A, Ammann RA, Wiszniewsky G, Bode U, Fleischhack G, Besuden MM.
21 Taurolidine-citrate lock solution (TauroLock) significantly reduces CVAD-associated
22 grampositive infections in pediatric cancer patients. *BMC Infect Dis* 2008; **8**: 102.

23 64 Bisseling TM, Willems MC, Versleijen MW, Hendriks JC, Vissers RK, Wanten GJ.
24 Taurolidine lock is highly effective in preventing catheter-related bloodstream infections in
25 patients on home parenteral nutrition: a heparin-controlled prospective trial. *Clin Nutr* 2010;
26 **29**: 464-8.

27 65 Sousa C, Henriques M, Oliveira R. Mini-review: Antimicrobial central venous
28 catheters--recent advances and strategies. *Biofouling* 2011; **27**: 609-20.

29 66 Darouiche RO, Raad, II, Heard SO, et al. A comparison of two antimicrobial-
30 impregnated central venous catheters. Catheter Study Group. *N Engl J Med* 1999; **340**: 1-8.

31 67 Hanna H, Benjamin R, Chatzinikolaou I, et al. Long-term silicone central venous
32 catheters impregnated with minocycline and rifampin decrease rates of catheter-related
33 bloodstream infection in cancer patients: a prospective randomized clinical trial. *J Clin Oncol*
34 2004; **22**: 3163-71.

35 68 Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis
36 and management of intravascular catheter-related infection: 2009 Update by the Infectious
37 Diseases Society of America. *Clin Infect Dis* 2009; **49**: 1-45.

38 69 Douard MC, Arlet G, Longuet P, et al. Diagnosis of venous access port-related
39 infections. *Clin Infect Dis* 1999; **29**: 1197-202.

1 70 Rijnders BJ, Van Wijngaerden E, Vandecasteele SJ, Stas M, Peetermans WE.
2 Treatment of long-term intravascular catheter-related bacteraemia with antibiotic lock:
3 randomized, placebo-controlled trial. *J Antimicrob Chemother* 2005; **55**: 90-4.

4 71 Whitman ED, Boatman AM. Comparison of diagnostic specimens and methods to
5 evaluate infected venous access ports. *Am J Surg* 1995; **170**: 665-9; discussion 9-70.

6 72 Blot F, Nitenberg G, Chachaty E, et al. Diagnosis of catheter-related bacteraemia: a
7 prospective comparison of the time to positivity of hub-blood versus peripheral-blood
8 cultures. *Lancet* 1999; **354**: 1071-7.

9 73 Capdevila JA, Planes AM, Palomar M, et al. Value of differential quantitative blood
10 cultures in the diagnosis of catheter-related sepsis. *Eur J Clin Microbiol Infect Dis* 1992; **11**:
11 403-7.

12 74 Chatzinikolaou I, Hanna H, Hachem R, Alakech B, Tarrand J, Raad I. Differential
13 quantitative blood cultures for the diagnosis of catheter-related bloodstream infections
14 associated with short- and long-term catheters: a prospective study. *Diagn Microbiol Infect*
15 *Dis* 2004; **50**: 167-72.

16 75 Raad I, Hanna HA, Alakech B, Chatzinikolaou I, Johnson MM, Tarrand J. Differential
17 time to positivity: a useful method for diagnosing catheter-related bloodstream infections.
18 *Ann Intern Med* 2004; **140**: 18-25.

19 76 Safdar N, Fine JP, Maki DG. Meta-analysis: methods for diagnosing intravascular
20 device-related bloodstream infection. *Ann Intern Med* 2005; **142**: 451-66.

21 77 Brun-Buisson C, Abrouk F, Legrand P, Huet Y, Larabi S, Rapin M. Diagnosis of
22 central venous catheter-related sepsis. Critical level of quantitative tip cultures. *Arch Intern*
23 *Med* 1987; **147**: 873-7.

24 78 Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying
25 intravenous-catheter-related infection. *N Engl J Med* 1977; **296**: 1305-9.

26 79 Siegman-Igra Y, Anglim AM, Shapiro DE, Adal KA, Strain BA, Farr BM. Diagnosis
27 of vascular catheter-related bloodstream infection: a meta-analysis. *J Clin Microbiol* 1997;
28 **35**: 928-36.

29 80 Chen WT, Liu TM, Wu SH, Tan TD, Tseng HC, Shih CC. Improving diagnosis of
30 central venous catheter-related bloodstream infection by using differential time to positivity
31 as a hospital-wide approach at a cancer hospital. *J Infect* 2009; **59**: 317-23.

32 81 Ben-Ami R, Weinberger M, Orni-Wasserlauff R, et al. Time to blood culture
33 positivity as a marker for catheter-related candidemia. *J Clin Microbiol* 2008; **46**: 2222-6.

34 82 Nett JE, Andes D. Review of techniques for diagnosis of catheter-related *Candida*
35 biofilm infections. *Current Fungal Infection Reports* 2008; **2**: 237-43.

36 83 Kaasch AJ, Fowler VG, Jr., Rieg S, et al. Use of a simple criteria set for guiding
37 echocardiography in nosocomial *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2011; **53**:
38 1-9.

1 84 Van Hal SJ, Mathur G, Kelly J, Aronis C, Cranney GB, Jones PD. The role of
2 transthoracic echocardiography in excluding left sided infective endocarditis in
3 *Staphylococcus aureus* bacteraemia. *J Infect* 2005; **51**: 218-21.

4 85 Fowler VG, Jr., Li J, Corey GR, et al. Role of echocardiography in evaluation of
5 patients with *Staphylococcus aureus* bacteremia: experience in 103 patients. *J Am Coll*
6 *Cardiol* 1997; **30**: 1072-8.

7 86 Rosen AB, Fowler VG, Jr., Corey GR, et al. Cost-effectiveness of transesophageal
8 echocardiography to determine the duration of therapy for intravascular catheter-associated
9 *Staphylococcus aureus* bacteremia. *Ann Intern Med* 1999; **130**: 810-20.

10 87 Pigrau C, Rodriguez D, Planes AM, et al. Management of catheter-related
11 *Staphylococcus aureus* bacteremia: when may sonographic study be unnecessary? *Eur J Clin*
12 *Microbiol Infect Dis* 2003; **22**: 713-9.

13 88 Crowley AL, Peterson GE, Benjamin DK, Jr., et al. Venous thrombosis in patients
14 with short- and long-term central venous catheter-associated *Staphylococcus aureus*
15 bacteremia. *Crit Care Med* 2008; **36**: 385-90.

16 89 Fernandez-Hidalgo N, Almirante B, Calleja R, et al. Antibiotic-lock therapy for long-
17 term intravascular catheter-related bacteraemia: results of an open, non-comparative study. *J*
18 *Antimicrob Chemother* 2006; **57**: 1172-80.

19 90 Segarra-Newnham M, Martin-Cooper EM. Antibiotic lock technique: a review of the
20 literature. *Ann Pharmacother* 2005; **39**: 311-8.

21 91 Del Pozo JL, Garcia Cenoz M, Hernaez S, et al. Effectiveness of teicoplanin versus
22 vancomycin lock therapy in the treatment of port-related coagulase-negative staphylococci
23 bacteraemia: a prospective case-series analysis. *Int J Antimicrob Agents* 2009; **34**: 482-5.

24 92 Messing B, Peitra-Cohen S, Debure A, Beliah M, Bernier JJ. Antibiotic-lock
25 technique: a new approach to optimal therapy for catheter-related sepsis in home-parenteral
26 nutrition patients. *JPEN J Parenter Enteral Nutr* 1988; **12**: 185-9.

27 93 Funalleras G, Fernandez-Hidalgo N, Borrego A, et al. Effectiveness of antibiotic-lock
28 therapy for long-term catheter-related bacteremia due to Gram-negative bacilli: a prospective
29 observational study. *Clin Infect Dis* 2011; **53**: e129-32.

30 94 Del Pozo JL, Rodil R, Aguinaga A, et al. Daptomycin lock therapy for grampositive
31 long-term catheter-related bloodstream infections. *Int J Clin Pract* 2012; **66**: 305-8.

32 95 Van Praagh AD, Li T, Zhang S, et al. Daptomycin antibiotic lock therapy in a rat
33 model of staphylococcal central venous catheter biofilm infections. *Antimicrob Agents*
34 *Chemother* 2011; **55**: 4081-9.

35 96 Shanks RM, Donegan NP, Graber ML, et al. Heparin stimulates *Staphylococcus*
36 *aureus* biofilm formation. *Infect Immun* 2005; **73**: 4596-606.

37 97 Novak M, Cvitkovic M, Galic S, Luetic T, Cavar S, Puretic Z. The life-threatening
38 hemodialysis catheter heparin lock caused bleeding in a child after peritoneal catheter
39 removal. *J Pediatr Surg* 2008; **43**: E41-4.

1 98 Maya ID, Carlton D, Estrada E, Allon M. Treatment of dialysis catheter-related
2 *Staphylococcus aureus* bacteremia with an antibiotic lock: a quality improvement report. *Am*
3 *J Kidney Dis* 2007; **50**: 289-95.

4 99 Fernandez-Hidalgo N, Gavalda J, Almirante B, et al. Evaluation of linezolid,
5 vancomycin, gentamicin and ciprofloxacin in a rabbit model of antibiotic-lock technique for
6 *Staphylococcus aureus* catheter-related infection. *J Antimicrob Chemother* 2010; **65**: 525-30.

7 100 Walraven CJ, Lee SA. Antifungal lock therapy. *Antimicrob Agents Chemother* 2013;
8 **57**: 1-8.

9 101 Cornely OA, Bassetti M, Calandra T, et al. ESCMID* guideline for the diagnosis and
10 management of *Candida* diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect*
11 2012; **18 Suppl 7**: 19-37.

12 102 Fernandez-Hidalgo N, Almirante B, Calleja R, et al. Antibiotic-lock therapy for long-
13 term intravascular catheter-related bacteraemia: results of an open, non-comparative study. *J*
14 *Antimicrob Chemother*; 2006. p. 1172-80.

15 103 Broom J, Woods M, Allworth A, et al. Ethanol lock therapy to treat tunnelled central
16 venous catheter-associated blood stream infections: results from a prospective trial. *Scand J*
17 *Infect Dis* 2008; **40**: 399-406.

18 104 McGrath EJ, Salloum R, Chen X, et al. Short-dwell ethanol lock therapy in children is
19 associated with increased clearance of central line-associated bloodstream infections. *Clin*
20 *Pediatr (Phila)* 2011; **50**: 943-51.

21 105 Onland W, Shin CE, Fustar S, Rushing T, Wong WY. Ethanol-lock technique for
22 persistent bacteremia of long-term intravascular devices in pediatric patients. *Arch Pediatr*
23 *Adolesc Med* 2006; **160**: 1049-53.

24 106 Mascio CT, Alder JD, Silverman JA. Bactericidal action of daptomycin against
25 stationary-phase and nondividing *Staphylococcus aureus* cells. *Antimicrob Agents Chemother*
26 2007; **51**: 4255-60.

27 107 Raad I, Hanna H, Jiang Y, et al. Comparative activities of daptomycin, linezolid, and
28 tigecycline against catheter-related methicillin-resistant *Staphylococcus* bacteremic isolates
29 embedded in biofilm. *Antimicrob Agents Chemother* 2007; **51**: 1656-60.

30 108 Douard MC, Clementi E, Arlet G, et al. Negative catheter-tip culture and diagnosis of
31 catheter-related bacteremia. *Nutrition* 1994; **10**: 397-404.

32 109 Chen WT, Tseng HC, Shih CC. Approximately 17% of catheterised cancer patients
33 with non-catheter-related bacteraemia have positive differential time. *J Hosp Infect* 2011; **78**:
34 76-7.

35 110 Warwick S, Wilks M, Hennessy E, et al. Use of quantitative 16S ribosomal DNA
36 detection for diagnosis of central vascular catheter-associated bacterial infection. *J Clin*
37 *Microbiol* 2004; **42**: 1402-8.

1 111 Guembe M, Marin M, Martin-Rabadan P, et al. Use of Universal 16S rRNA Gene
2 PCR as a Diagnostic Tool for Venous Access Port-Related Bloodstream Infections. *J Clin*
3 *Microbiol* 2013; **51**: 799-804.

4 112 Chalabaev S, Chauhan A, Novikov A, et al. Biofilm monitoring using biofilm specific
5 biomarkers. *Biofilms 5 International Conference, 10-12th December 2012, Paris* 2012;

6 113 Meyer MH, Letscher-Bru V, Jaulhac B, Waller J, Candolfi E. Comparison of Mycosis
7 IC/F and plus Aerobic/F media for diagnosis of fungemia by the bactec 9240 system. *J Clin*
8 *Microbiol* 2004; **42**: 773-7.

9 114 Nguyen MH, Wissel MC, Shields RK, et al. Performance of *Candida* real-time
10 polymerase chain reaction, beta-D-glucan assay, and blood cultures in the diagnosis of
11 invasive candidiasis. *Clin Infect Dis* 2012; **54**: 1240-8.

12 115 Smith RS, Zhang Z, Bouchard M, et al. Vascular catheters with a nonleaching poly-
13 sulfobetaine surface modification reduce thrombus formation and microbial attachment. *Sci*
14 *Transl Med* 2012; **4**: 153ra32.

15 116 Busscher HJ, van der Mei HC, Subbiahdoss G, et al. Biomaterial-associated infection:
16 locating the finish line in the race for the surface. *Sci Transl Med* 2012; **4**: 153rv10.

17 117 Turakhia MH, Cooksey KE, Characklis WG. Influence of a calcium-specific chelant
18 on biofilm removal. *Appl Environ Microbiol* 1983; **46**: 1236-8.

19 118 Raad II, Fang X, Keutgen XM, Jiang Y, Sherertz R, Hachem R. The role of chelators
20 in preventing biofilm formation and catheter-related bloodstream infections. *Curr Opin Infect*
21 *Dis* 2008; **21**: 385-92.

22 119 Bookstaver PB, Williamson JC, Tucker BK, Raad II, Sherertz RJ. Activity of novel
23 antibiotic lock solutions in a model against isolates of catheter-related bloodstream infections.
24 *Ann Pharmacother* 2009; **43**: 210-9.

25 120 Raad I, Rosenblatt J, Reitzel R, Jiang Y, Dvorak T, Hachem R. Chelator-based
26 catheter lock solutions in eradicating organisms in biofilm. *Antimicrob Agents Chemother*
27 2013; **57**: 586-8.

28 121 Chauhan A, Lebeaux D, Ghigo JM, Beloin C. Full and broad-spectrum *in vivo*
29 eradication of catheter-associated biofilms using gentamicin-EDTA antibiotic lock therapy.
30 *Antimicrob Agents Chemother* 2012;

31 122 Allison KR, Brynildsen MP, Collins JJ. Metabolite-enabled eradication of bacterial
32 persisters by aminoglycosides. *Nature* 2011; **473**: 216-20.

33 123 Cirioni O, Giacometti A, Ghiselli R, et al. RNAIII-inhibiting peptide significantly
34 reduces bacterial load and enhances the effect of antibiotics in the treatment of central venous
35 catheter-associated *Staphylococcus aureus* infections. *J Infect Dis* 2006; **193**: 180-6.

36 124 O'Toole GA. Microbiology: Jekyll or hide? *Nature* 2004; **432**: 680-1.

37 125 Boles BR, Horswill AR. Agr-mediated dispersal of *Staphylococcus aureus* biofilms.
38 *PLoS Pathog* 2008; **4**: e1000052.

1 126 Fey PD. Modality of bacterial growth presents unique targets: how do we treat
2 biofilm-mediated infections? *Curr Opin Microbiol* 2010; **13**: 610-5.

3 127 Cobrado L, Silva-Dias A, Azevedo MM, Pina-Vaz C, Rodrigues AG. *In vivo*
4 antibiofilm effect of cerium, chitosan and hamamelitannin against usual agents of catheter-
5 related bloodstream infections. *J Antimicrob Chemother* 2012; **68**: 126-30.

6 128 Ebert T, Smith S, Pancari G, et al. Development of a rat central venous catheter model
7 for evaluation of vaccines to prevent *Staphylococcus epidermidis* and *Staphylococcus aureus*
8 early biofilms. *Hum Vaccin* 2011; **7**: 630-8.

9 129 Mansouri MD, Hull RA, Stager CE, Cadle RM, Darouiche RO. *In vitro* activity and
10 durability of a combination of an antibiofilm and an antibiotic against vascular catheter
11 colonization. *Antimicrob Agents Chemother* 2013; **57**: 621-5.

12 130 Castagnola E, Ginocchio F. Rescue therapy of difficult-to-treat indwelling central
13 venous catheter-related bacteremias in cancer patients: a review for practical purposes. *Expert*
14 *Rev Anti Infect Ther* 2013; **11**: 179-86.

15 131 Penel N, Neu JC, Clisant S, Hoppe H, Devos P, Yazdanpanah Y. Risk factors for early
16 catheter-related infections in cancer patients. *Cancer* 2007; **110**: 1586-92.

17 132 Samaras P, Dold S, Braun J, et al. Infectious port complications are more frequent in
18 younger patients with hematologic malignancies than in solid tumor patients. *Oncology* 2008;
19 **74**: 237-44.

20 133 Caers J, Fontaine C, Vinh-Hung V, et al. Catheter tip position as a risk factor for
21 thrombosis associated with the use of subcutaneous infusion ports. *Support Care Cancer*
22 2005; **13**: 325-31.

23 134 Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the
24 management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin*
25 *Infect Dis* 2009; **48**: 503-35.

26 135 Nucci M, Anaissie E, Betts RF, et al. Early removal of central venous catheter in
27 patients with candidemia does not improve outcome: analysis of 842 patients from 2
28 randomized clinical trials. *Clin Infect Dis* 2010; **51**: 295-303.

29 136 Raad I, Hanna H, Boktour M, et al. Management of central venous catheters in
30 patients with cancer and candidemia. *Clin Infect Dis* 2004; **38**: 1119-27.

31 137 Raad I, Hanna H, Dvorak T, Chaiban G, Hachem R. Optimal antimicrobial catheter
32 lock solution, using different combinations of minocycline, EDTA, and 25-percent ethanol,
33 rapidly eradicates organisms embedded in biofilm. *Antimicrob Agents Chemother* 2007; **51**:
34 78-83.

35 138 Rane HS, Bernardo SM, Walraven CJ, Lee SA. *In vitro* analyses of ethanol activity
36 against *Candida albicans* biofilms. *Antimicrob Agents Chemother* 2012; **56**: 4487-9.

37 139 Blackwood RA, Klein KC, Micel LN, et al. Ethanol locks therapy for resolution of
38 fungal catheter infections. *Pediatr Infect Dis J* 2011; **30**: 1105-7.

- 1 140 Pieroni KP, Nespor C, Poole RL, Kerner JA, Jr., Berquist WE. Echinocandin and
2 Ethanol Lock Therapy Treatment of Fungal Catheter Infections. *Pediatr Infect Dis J* 2013;
- 3 141 Longuet P, Douard MC, Arlet G, Molina JM, Benoit C, Leport C. Venous access port-
4 -related bacteremia in patients with acquired immunodeficiency syndrome or cancer: the
5 reservoir as a diagnostic and therapeutic tool. *Clin Infect Dis* 2001; **32**: 1776-83.
- 6 142 Kim MJ, Bancroft E, Lehnkering E, Donlan RM, Mascola L. *Alcaligenes xylosoxidans*
7 bloodstream infections in outpatient oncology office. *Emerg Infect Dis* 2008; **14**: 1046-52.
- 8 143 Viola GM, Mansouri MD, Nasir N, Jr., Darouiche RO. Incubation alone is adequate as
9 a culturing technique for cardiac rhythm management devices. *J Clin Microbiol* 2009; **47**:
10 4168-70.
- 11 144 Domingo P, Fontanet A, Sanchez F, Allende L, Vazquez G. Morbidity associated with
12 long-term use of totally implantable ports in patients with AIDS. *Clin Infect Dis* 1999; **29**:
13 346-51.
- 14 145 Piketty C, Hoi AB, Gilquin J, et al. Failure of antibiotic therapy in *Staphylococcus*
15 *epidermidis* infection of implantable venous access devices in patients with AIDS, as
16 documented by molecular typing. *Clin Microbiol Infect* 1999; **5**: 190-4.
- 17 146 Reimund JM, Arondel Y, Finck G, Zimmermann F, Duclos B, Baumann R. Catheter-
18 related infection in patients on home parenteral nutrition: results of a prospective survey. *Clin*
19 *Nutr* 2002; **21**: 33-8.
- 20 147 Viale P, Pagani L, Petrosillo N, et al. Antibiotic lock-technique for the treatment of
21 catheter-related bloodstream infections. *J Chemother* 2003; **15**: 152-6.
- 22 148 Koldehoff M, Zakrzewski JL. Taurolidine is effective in the treatment of central
23 venous catheter-related bloodstream infections in cancer patients. *Int J Antimicrob Agents*
24 2004; **24**: 491-5.
- 25 149 Fortun J, Grill F, Martin-Davila P, et al. Treatment of long-term intravascular catheter-
26 related bacteraemia with antibiotic-lock therapy. *J Antimicrob Chemother* 2006; **58**: 816-21.
- 27 150 Souza Dias MB, Habert AB, Borrasca V, et al. Salvage of long-term central venous
28 catheters during an outbreak of *Pseudomonas putida* and *Stenotrophomonas maltophilia*
29 infections associated with contaminated heparin catheter-lock solution. *Infect Control Hosp*
30 *Epidemiol* 2008; **29**: 125-30.
- 31 151 Del Pozo JL, Alonso M, Serrera A, Hernaez S, Aguinaga A, Leiva J. Effectiveness of
32 the antibiotic lock therapy for the treatment of port-related enterococci, Gram-negative, or
33 Gram-positive bacilli bloodstream infections. *Diagn Microbiol Infect Dis* 2009; **63**: 208-12.
- 34 152 Rajpurkar M, Boldt-Macdonald K, McLenon R, et al. Ethanol lock therapy for the
35 treatment of catheter-related infections in haemophilia patients. *Haemophilia* 2009; **15**: 1267-
36 71.
- 37 153 Valentine KM. Ethanol lock therapy for catheter-associated blood stream infections in
38 a pediatric intensive care unit. *Pediatr Crit Care Med* 2011; **12**: e292-6.
- 39
40

Figure 1. Totally implantable venous access port (TIVAP)-related infections may lead to local and hematogenous complications. A. Port-pocket infection (surrounded by black dashed line) and tunnel infection (white arrowhead) caused by *S. aureus*. **B.** Thrombophlebitis after TIVAP-related bloodstream infection (BSI) caused by *S. aureus*. Thrombus (black arrowhead) developed at the junction of internal jugular vein (black arrow) and subclavian vein (black star). **C.** Right pulmonary abscess (white arrow) with cavitation secondary to a *S. aureus* TIVAP-related BSI. **D.** C5-C6 spondylitis caused by *S. lugdunensis* after an episode of TIVAP-related BSI. Sagittal view of cervical spine T2-weighted magnetic resonance imaging showing disc space narrowing (white arrowhead) and vertebral edema (white stars). Picture A kindly provided by Chantal Dreyer, Hôpital Beaujon, Clichy, France. All clinical photographs are from patients included in a previously published study.²⁴

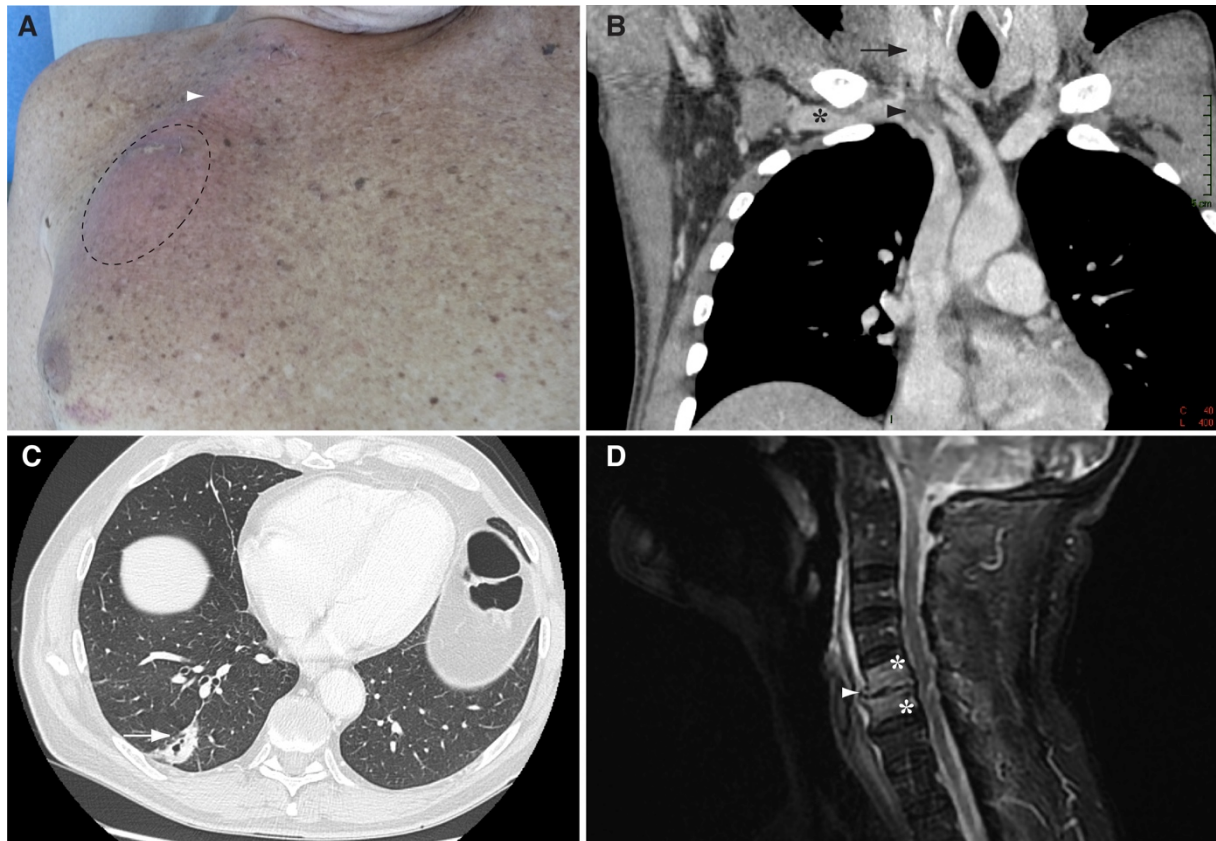


Figure 2. Diagnostic algorithm in case of suspicion of totally implantable venous access port (TIVAP)-related infection. ALT=antibiotic lock therapy. BC=blood cultures. BSI=bloodstream infection. DTP=differential time to positivity. QPBC=quantitative paired blood cultures. *Using quantitative or semi-quantitative method, see text and Figure 3.^{4,68}

† Difference between TIVAP colonization and probable TIVAP-related infection is made by the presence of clinical signs of sepsis and requires ruling out another focus of infection.

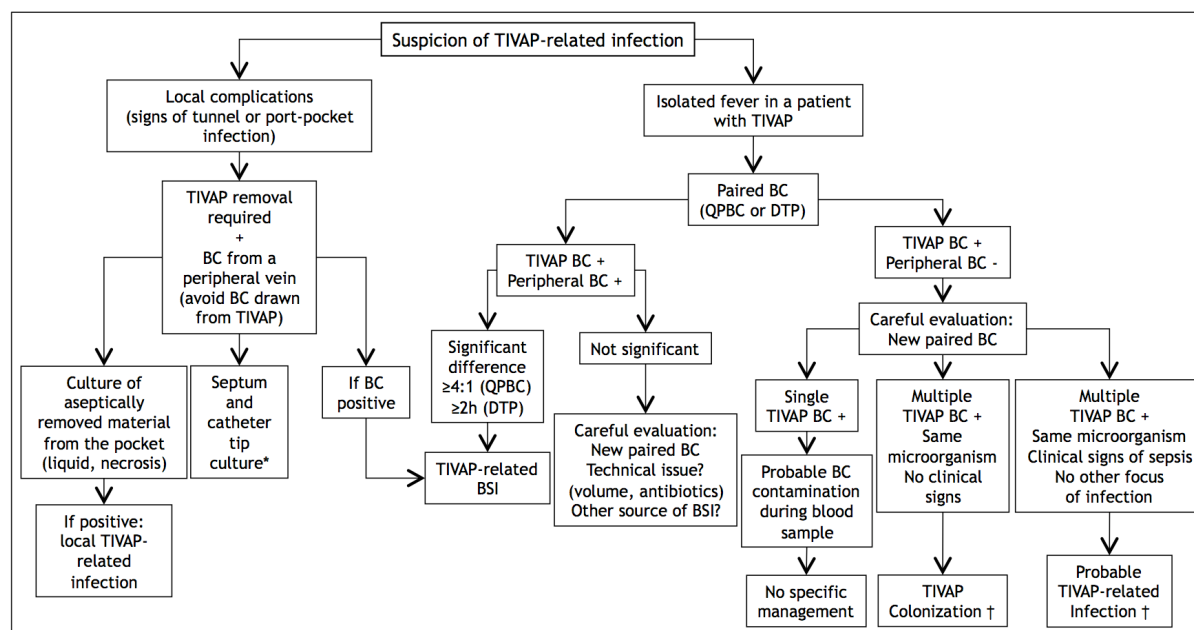


Figure 3. Microbiological methods for the diagnosis of totally implantable venous access port (TIVAP) colonization. **A.** Schematic view of a removed TIVAP. Samples should be transferred in sterile tubes and sent to the clinical microbiology laboratory (CML) right away or stored overnight at +4°C. Catheter tip (black star) is cut and the septum (white star) removed using sterile blade.^{68,69,141} Biological safety cabinets can be used. **B.** Culture of the catheter tip can be performed using the semiquantitative (Maki) or the quantitative (Brun-Buisson) method.^{77,78} **C.** After removal, the septum is immersed in saline, vortexed or sonicated for CFU counting.^{69,141} **D.** In CML not permitted to use cutting blades, sterile saline (0.2mL) can be injected inside the reservoir then aspirated and plated.²⁴ Swabbing of the internal surface of the port after septum removal is also proposed.^{111,142} As demonstrated for cardiac devices, incubating the explanted parts of TIVAP in broth for 48h without sonication or vortexing could be an option but needs to be validated.¹⁴³

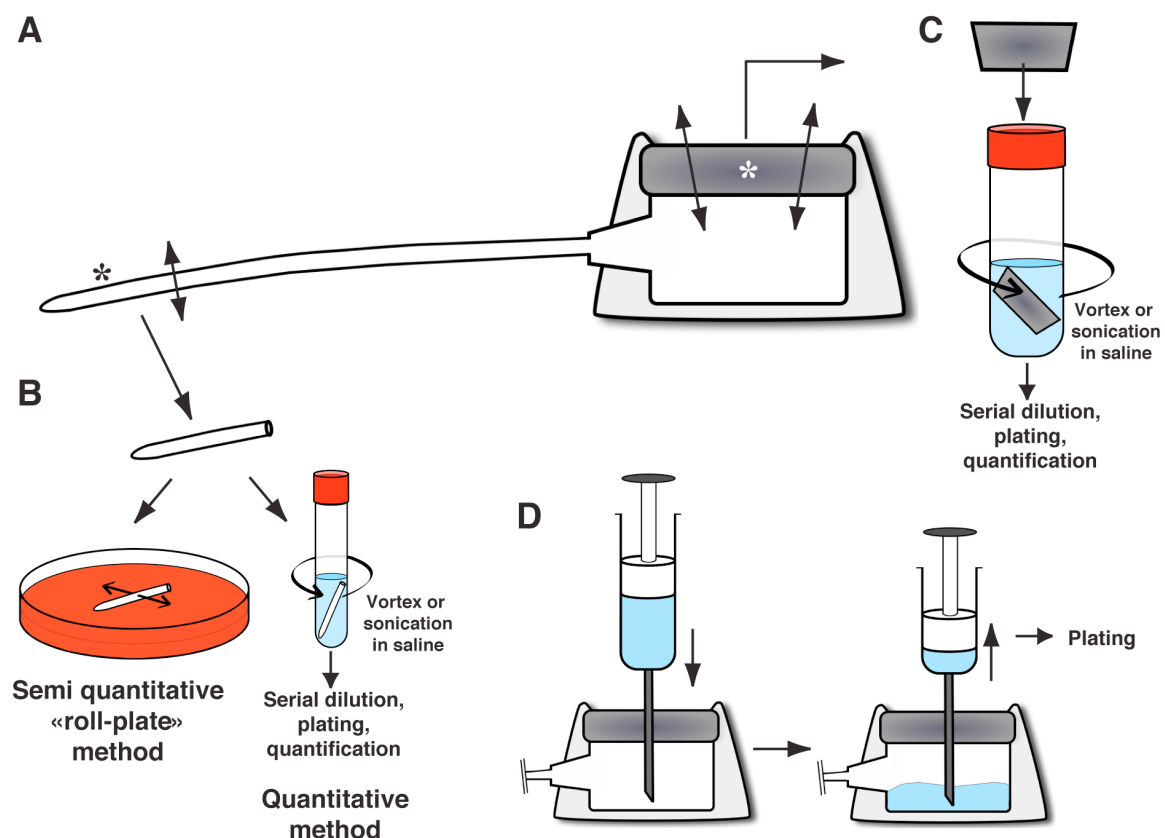


Figure 4. Treatment of totally implantable venous access port (TIVAP)-related bloodstream infection (BSI), according to IDSA guidelines.⁶⁸ AB=antibiotic. AF=antifungal. ALT=antibiotic lock therapy. BC=blood cultures. IE=infective endocarditis.

*In case of tunnel or port-pocket infection without BSI, TIVAP removal is also required with five to seven days of systemic antimicrobials.^{4,68,134}

† In case of *P. aeruginosa* TIVAP-related BSI, IDSA guidelines suggest that TIVAP removal is the first-line option.⁶⁸ ‡ In 2009 IDSA guidelines, only ophthalmological examination is recommended for all patients although some clinicians also propose echocardiography and CT-scan.¹³⁴ ¶ The source of the blood to be drawn is debated and some authors perform BC only from a peripheral vein or from TIVAP.¹⁰² To note, some authors consider that the presence of intracardiac or intravascular devices should preclude the use of ALT, even if this situation is not mentioned in IDSA guidelines.⁶⁸

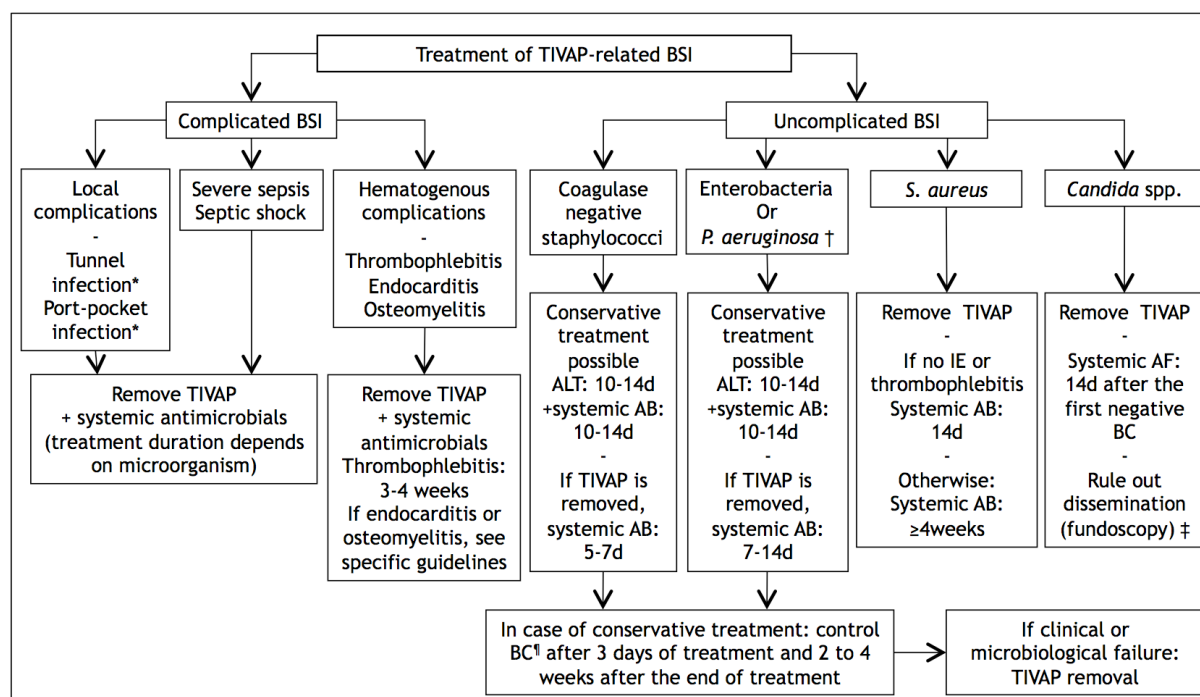


Table 1. Published studies on antibiotic or ethanol lock therapy for the conservative treatment of bacterial totally implantable venous access port (TIVAP)-related bloodstream infections (BSI) identified with the criteria described in the “search strategy” panel. Of note, most published studies excluded patients with complicated TIVAP-related BSI or infections caused by *S. aureus* or *Candida* spp.

Clinical studies, year-reference	No of episodes treated with ALT	Type of catheter†	Micro organisms‡	Catheter use	Systemic antimicrobial treatment, n (%)	ALT or ELT (drug and concentration in mg/mL)	Association with heparin*, IU/mL	No of days of locks	Cure rate, n (%)	Success criteria
1999-Domingo P. <i>et al.</i> ¹⁴⁴	27	100-0-0	57-3-3-6-30	Antiinfectious CT in AIDS patients	9 (33)	VAN (1), AMK (1)	No	5	22 (81)	Clinical + negative paired BC at the end of ALT
1999-Piketty C. <i>et al.</i> ¹⁴⁵	31	100-0-0	100-0-0-0-0	Antiinfectious CT in AIDS patients	31 (100)	VAN (40), AMK (60)	Yes, ND	3 [1-5]	13 (42)	Clinical. No systematic BC
2001-Longuet P. <i>et al.</i> ¹⁴¹	16	100-0-0	41-24-0-12-23	Antiinfectious or antineoplastic CT	16 (100)	VAN (5) or TEC (5) +/- AMK (ND)	No	8 [3-15]	7 (44)	Clinical + negative paired BC 2-7 days after the end of ALT
2002-Santarpia L. <i>et al.</i> ⁷	60	86-14-0	67-15-0-6-12	TPN	60 (100)	TEC (33-100), PIP (166-500), NET (50-150) or CLI (100-300)	Yes, ND	7	50 (83)	Undefined
2002-Reimund J.M. <i>et al.</i> ¹⁴⁶	25	64-36-0	61-24-0-12-3	TPN	39 (100)	VAN (1), AMK (1.5) or MIN (0.2)	No	ND	25% if TIVAP-50% if tunnelled	Undefined
2003-Viale P. <i>et al.</i> ¹⁴⁷	30	37-40-23	35-9-9-28-22	Antiinfectious or antineoplastic CT, TPN	15 (50)	VAN (20), TEC (20), AMK (10), IMP (ND)	No	14	28 (93)	Clinical + negative paired BC 14 and 28 days after the beginning of ALT
2004-Koldehoff M. <i>et al.</i> ¹⁴⁸	11	100-0-0	46-8-8-8-30	Antineoplastic CT	11 (100)	Taurolidine (5)	No	1 [1-3]	11 (100) §	Undefined
2005-Rijnders B.J. <i>et al.</i> ⁷⁰	22	91-9-0	63-14-0-0-23	Mostly antineoplastic CT	22 (100)	VAN (0.5) or CAZ (0.5)	Yes, 100	11 [7-14]	14 (67)	Clinical. No systematic BC
2006-Fortún J. <i>et al.</i> ¹⁴⁹	19	74-26-0	74-0-10-16-0	Antineoplastic CT and TPN	19 (100)	VAN (2), GEN (2) or CIP (2)	Yes, 20	12 [5-14]	16 (84)	Clinical + negative catheter BC 2-5 days after the end of ALT

2006-Onland W. <i>et al.</i> ¹⁰⁵	51	21-79-0	52-11-0-14-23	Mostly antineoplastic CT	51 (100)	Ethanol 70%	No	5	45 (88)	Clinical. No systematic BC
2008-Souza Dias M.B. <i>et al.</i> ¹⁵⁰	17	78-22-0	0-0-100-0-0	Mostly antineoplastic CT	17 (100)	CEF (ND), AMK (2) or LVX (ND)	Yes, 100	ND	14 (82)	Undefined
2008-Broom J. <i>et al.</i> ¹⁰³	17	11-89-0	25-21-21-0-33	Antineoplastic CT	17 (100)	Ethanol 70%	No	5	15 (88)	Clinical + catheter BC negative 1 day after the end of ALT
2009-Del Pozo J.L. <i>et al.</i> ⁹¹	44	100-0-0	100-0-0-0-0	Antineoplastic CT and TPN	44 (100)	VAN (2), TEC (10)	Yes, 100	10 [10-14]	39 (89)	Clinical + catheter BC negative 7 days after the end of ALT
2009-Del Pozo J.L. <i>et al.</i> ¹⁵¹	18	100-0-0	5-35-0-0-60	Antineoplastic CT	18 (100)	VAN (2) +/- GEN (2) (if <i>E. faecium</i>), TEC (10), TZP (10), LVX (5), TMP/SXT (16/3.2)	Yes, 100	12 [5-14]	16 (89)	Clinical + catheter BC negative 30 days after the end of ALT
2009-Rajpurkar M. <i>et al.</i> ¹⁵²	3	66-33-0	40-0-0-0-60	Hemophilia	3 (100)	Ethanol 70%	No	3 [1-3]	3 (100)	Clinical + catheter BC negative after the end of ALT
2011-McGrath E.J. <i>et al.</i> ¹⁰⁴	80	24-72-4	33-20-9-8-0-30	Antiinfectious or antineoplastic CT, TPN	80 (100)	Ethanol 70%	No	1	59 (75)	Clinical + catheter BC negative 30 days after the beginning of ALT
2011-Funalleras G. <i>et al.</i> ⁹³	46	28-72-0	0-59-26-0-15	Antineoplastic CT, hemodialysis	46 (100)	AMK (2) or CIP (2)	Yes, 20	13 [10-16]	44 (96)	Clinical + catheter BC negative 30 days after the beginning of ALT
2011-Valentine K.M. <i>et al.</i> ¹⁵³	26	15-54-31	14-36-3-11-36	Antineoplastic CT, ICU	26 (100)	Ethanol 70%	No	1.5 [1-5]	24 (92)	Clinical + negative catheter BC 2 days after the beginning of ALT
2012-Del Pozo J.L. <i>et al.</i> ⁹⁴	13	46-54-0	87-0-0-0-13	Antineoplastic CT, hemodialysis	11 (85)	DAP (5) ¶	Yes, 100 if TIVAP and 5000 if dialysis	14 [10-14]	11 (85)	Clinical + catheter BC negative 30 days after the end of ALT

†Expressed as % TIVAP-tunnelled-other.

‡Expressed as % coagulase-negative staphylococci-*Enterobacteriaceae*-*Pseudomonas* spp.-*S. aureus*-others.

*Of note, the heparin that is used does not contain antimicrobial preservative.

§But 3 retreatments needed.

¶In lactated Ringer's solution providing 45 mg of calcium/L.

AIDS=acquired immunodeficiency syndrome. ALT=antibiotic lock therapy. AMK=amikacin. BC=blood cultures. CIP=ciprofloxacin. CLI=clindamycin. CT=chemotherapy. DAP=daptomycin. ELT=ethanol lock therapy. GEN=gentamicin. ICU=intensive care unit. IMP=imipenem. MIN=minocycline. ND=not determined. NET=netilmicin. PIP=piperacillin. TMP-SMX=trimethoprim-sulfamethoxazole. TPN=total parenteral nutrition. TZP=piperacillin/tazobactam.