



**HAL**  
open science

## 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-01381818v2

**HAL Id: pasteur-01381818**

**<https://pasteur.hal.science/pasteur-01381818v2>**

Submitted on 5 May 2021

**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 - NoDerivatives 4.0 International License

1 **Review**

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

4

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

7

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

10

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

13

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

16

17 **Correspondance to:**

18 Christophe Beloin. Institut Pasteur, Unité de Génétique des Biofilms. 25 rue du Dr. Roux,  
19 75724 Paris cedex 15 France. E-mail address: cbeloin@pasteur.fr

20 Tel: 33 01 44 38 95 97; Fax: 33 01 45 68 80 07

21

22 Benito Almirante. Servei de Malalties Infeccioses, Hospital Universitari Vall d'Hebron,  
23 Universitat Autònoma de Barcelona. Barcelona, Spain. E-mail address:  
24 benitoalmirante@gmail.com

25 Tel: 34 93 2746090; Fax: 34 93 4894091

26

27

1 **Summary**

2 Use of totally implantable venous access ports (TIVAP) is a standard clinical practice, in  
3 particular for patients with solid cancers, hematologic malignancies and chronic digestive  
4 diseases. Use of TIVAPs allows long-term administration of veinotoxic compounds, improves  
5 patient quality of life and reduces risk of infection. However, microbial contamination and  
6 formation of pathogenic biofilm in TIVAPs is associated with morbidity, mortality and  
7 increased healthcare costs. In case of TIVAP-related infection, local and systemic  
8 complications, or infection related to specific pathogens may constitute indications for device  
9 removal. Alternatively, conservative treatment can be proposed with the combination of  
10 systemic antibiotics and antibiotic lock therapy. In light of recent *in vitro* and *in vivo*  
11 fundamental or clinical research addressing epidemiology, diagnosis and prevention of  
12 TIVAP-related infections, with a particular focus on antibiotic lock therapy, this review  
13 presents current challenges and promising strategies to improve the management of TIVAP-  
14 related infections.

15

16

1 **Search strategy and selection criteria**

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

16

17

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).<sup>1,2</sup> 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.<sup>3,4</sup> 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).<sup>5</sup> TIVAP is composed of a subcutaneously implanted port (or reservoir)  
10 connected to a central venous catheter, most frequently inserted in the internal jugular,  
11 subclavian or cephalic vein.<sup>2</sup> 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.<sup>2</sup>  
13 TIVAPs are used for the administration of antineoplastic chemotherapy, parenteral nutrition,  
14 blood products and for prolonged antimicrobial treatment in CF.<sup>2,6,7</sup> Of note, the number of  
15 implanted TIVAPs is increasing and currently more than 100,000 TIVAPs are inserted each  
16 year in the USA alone.<sup>8</sup> Despite a reduction of the risk of microbial contamination due to total  
17 implantation under the skin, 3 to 10% of TIVAP carriers experience a related infection which  
18 is the most common indication for TIVAP removal, illustrating the impact of this  
19 complication on patient care and the necessity for focused research in this area.<sup>9-14</sup>  
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.

23

24

## 1 **Epidemiology reflects risk factors and routes of colonization**

2 Depending on the indication for TIVAP insertion, patients are exposed to different risk  
3 factors and therefore exhibit different infection rates. For instance, if TIVAP is inserted for  
4 antineoplastic chemotherapy or in CF patients, the incidence density of infection ranges from  
5 0.11 to 0.37/1,000 catheter-days.<sup>6,9,12,13,15-19</sup> If TIVAP is used for total parenteral nutrition  
6 (TPN), incidence density is higher and is comprised between 0.33 and 3.2/1000 catheter-days  
7 with heterogeneous data depending on the indication for TPN.<sup>7,20,21</sup> In HIV-infected patients,  
8 incidence density is also high and ranges from 1.5 to 3.81/1,000 catheter-days, probably  
9 because when they require a LTIVC, these patients combine most of the risk factors of  
10 infection identified so far.<sup>8,22</sup> The reported time to infection from TIVAP insertion is variable,  
11 but major studies report median occurrence ranging from 80 to 192 days with extreme values  
12 of 2 and 1406 days.<sup>8,9,12,22</sup>

13 These discrepancies between patient groups probably reflect exposure towards different risk  
14 factors and TIVAP handling frequency. Indeed, a prospective study demonstrated that the  
15 frequency of LTIVC handling (including about 50% of TIVAP) was associated with infection  
16 incidence.<sup>22</sup> Additional risk factors have also been described such as:

- 17 - Use of TPN, possibly because these patients require more frequent access to their TIVAP,  
18 which are used to administer fluids such as lipid products that increase microbial growth.<sup>7,23,24</sup>
- 19 - Difficulties during insertion (*i.e.* when several punctures are required), through formation of  
20 local thrombus or haematoma that increase the risk of bacterial colonization.<sup>23,25</sup>
- 21 - Young age, chemotherapy for hematologic malignancies rather than solid tumors, reduced  
22 autonomy, presence of metastases in cancer patients, bacterial infection within the prior  
23 month, neutropenia among HIV-infected patients and diabetes in CF-patients.<sup>6,9,12,15,22,23,26</sup>

24 Since frequency of TIVAP handling is one of the major risk factor identified, it is not  
25 surprising to observe that coagulase-negative staphylococci (CoNS), which are frequent  
26 colonizers of the human skin and mucosal flora, are one of the leading pathogens responsible  
27 for TIVAP-related infections.<sup>27</sup> For instance, among 29 cases of TIVAP-related infections, a  
28 majority of infections (57%) were caused by CoNS, other microorganisms being Gram-  
29 negative rods (GNR) (20%), *S. aureus* (7%) and *C. albicans* (3%).<sup>12</sup> More recent studies  
30 described a higher rate of GNR (up to 40%) and yeasts (up to 23%).<sup>8,9,28</sup> This shift has been  
31 suggested to result from antineoplastic chemotherapy intensification with more sustained  
32 neutropenia allowing translocation of microorganisms from the gut to the bloodstream, but  
33 also because of a more frequent use of supportive care such as TPN and use of broad-  
34 spectrum antibiotics. Few data regarding antibiotic resistance in this population are available.

1 In France, a prospective study among 72 oncology patients experiencing TIVAP-related  
2 infections reported that 58% of CoNS (14/24 strains) and 25% of *S. aureus* (4/16 strains)  
3 were methicillin-resistant (MR).<sup>29</sup> It is very likely that MR is more frequent in the US as  
4 suggested in a retrospective study of *S. aureus* catheter-related bloodstream infection  
5 (CRBSI) in cancer patients and in a prospective study including *Staphylococcus* spp.  
6 infections with 37-57% of *S. aureus* and 80% of CoNS being MR.<sup>30,31</sup>

7 As TIVAPs are totally implanted, risk of extraluminal colonization is low and mostly occurs  
8 during TIVAP insertion, resulting in surgical site infection. Once the device is inserted,  
9 contamination may occur during repeated punctures with Huber needles, if the skin has not  
10 been properly cleaned, therefore leading to an intraluminal colonization that can spread from  
11 the port to the catheter tip.<sup>32-34</sup> In case of BSI coming from another focus of infection, bacteria  
12 may adhere on the catheter tip, therefore defining a hematogenous route of colonization. After  
13 device contamination, bacteria adhere to the surface of TIVAP using bacterial appendages  
14 called adhesins.<sup>35</sup> Bacterial adhesion is influenced by the type of catheter material, presence  
15 of layer of blood products such as fibrin or platelets and bacterial characteristics.<sup>32,36</sup> After  
16 adhesion, bacteria multiply and constitute a surface-associated microbial community called a  
17 biofilm, which is embedded in an extracellular matrix (ECM).<sup>10,35</sup> While systemic antibiotics  
18 can cure TIVAP-related BSI, biofilm bacteria are able to survive high concentrations of  
19 antibiotics.<sup>37</sup> This high tolerance towards antibiotics causes infection recurrence unless the  
20 device is removed or intraluminal treatment used. Preventive approaches are therefore pivotal  
21 in order to avoid any microbial contamination and subsequent biofilm formation.

22

23

1 **Preventive strategies to reduce risks of colonization**

2 Because of a reduced risk of infection, TIVAPs are favored over other LTIVC for treatment  
3 of solid tumor and in pediatric hematology patients.<sup>12,28,38</sup> In case of prolonged TPN, due to  
4 higher risk of infection associated with TIVAPs, a tunnelled catheter is preferred for daily  
5 vascular access.<sup>1,7</sup> If TIVAP is chosen in oncology or hematology patients, it should be  
6 inserted as early as possible, due to increased risk of infection in case of neutropenia.<sup>39,40</sup>  
7 Then, preventive strategies must be applied during and after TIVAP insertion.

8

9 *Preventive measures during TIVAP insertion*

10 Trained personnel with maximum sterile barrier precautions, including sterile gloves, cap,  
11 mask, sterile gown and a sterile full body drape, must perform TIVAP insertion.<sup>2,41,42</sup> For skin  
12 preparation, alcohol-based antiseptics such as alcohol-based chlorhexidine or alcohol-based  
13 povidone-iodine ought to be used, but no direct comparative study has been done using these  
14 solutions.<sup>42</sup> A >0.5% chlorhexidine preparation with alcohol may be favored based on the  
15 result of a prospective study comparing chlorhexidine-based antiseptic solution with alcohol-  
16 based povidone-iodine.<sup>43</sup>

17 The choice of venipuncture site is not associated with different infection rates as  
18 demonstrated by a prospective study of 403 patients randomly allocated to an internal jugular  
19 vein or subclavian vein insertion, or a surgical cut-down through the cephalic vein.<sup>44</sup> If the  
20 superior vena cava is not accessible - for instance due to thrombosis - TIVAP can be inserted  
21 in the femoral vein with an infection incidence of 0.69/1,000 catheter-days.<sup>45</sup> Use of  
22 ultrasound guidance for catheter insertion has not been shown to reduce the rate of TIVAP-  
23 related infections but significantly reduces the number of attempts and increases patient  
24 comfort.<sup>44,46</sup> Systemic antibiotic prophylaxis is useless during TIVAP insertion and is not  
25 indicated.<sup>47-49</sup>

26

27 *Preventive measures after TIVAP insertion*

28 Training of patients, nursing teams and physicians is mandatory to minimize the risk of  
29 bacterial contamination.<sup>7</sup> The Huber needle used to access the TIVAP must be inserted by  
30 trained nurses and requires that operators wear a facial mask, a cap and use sterile gloves.  
31 Skin disinfection must be performed with an alcoholic antiseptic, prior to each needle  
32 insertion.<sup>42</sup> The Huber needle can be changed every seven days if vascular access is  
33 maintained continuously.<sup>9</sup> During needle withdrawal, an experimental study suggested that  
34 positive pressure using saline injection reduces the risk of blood reflux, therefore preventing



1 catheter tip occlusion.<sup>50</sup> It is now recommended that heparin locks or flush after TIVAP use  
2 should not be performed, as sterile saline locks are equally efficient to prevent functional or  
3 infectious complications.<sup>42,51</sup>

4

#### 5 *Lock solutions and coatings to prevent TIVAP-related infections*

6 The principle of preventive antibiotic lock therapy (ALT) is to inject highly concentrated  
7 antibiotic solution inside the TIVAP lumen. This solution dwells for extended time periods in  
8 order to eradicate any incoming bacteria. The chosen volume must allow coverage of the  
9 whole internal surface and therefore depends on the type of device. A meta-analysis  
10 demonstrated that ALT or antibiotic flush made of vancomycin reduced the risk of CRBSI.<sup>52</sup>  
11 Other groups have assessed the combination of antibiotic (minocycline) and a chelator such as  
12 ethylene diamine tetra-acetic acid (EDTA). Two studies in the pediatric oncology setting have  
13 shown that minocycline-EDTA ALT was more effective than heparin for the prevention of  
14 CRBSI.<sup>53,54</sup> Nevertheless, systematic use of ALT could lead to increased antibiotic resistance  
15 and should therefore be considered only in high-risk patients, who already experienced  
16 TIVAP-related infections.<sup>36,42,55</sup>

17 Limited data are available for non-antibiotic lock solutions, such as ethanol- or taurolidine-  
18 lock. One preliminary pediatric study using ethanol locks including 12 patients with TIVAP  
19 was interrupted as 3 patients experienced TIVAP occlusion.<sup>56</sup> A meta-analysis showed that  
20 ethanol lock therapy reduces the incidence of CRBSI in pediatric TPN with tunnelled  
21 catheters but increases the risk of thrombosis.<sup>57</sup> Therefore, ethanol lock could be proposed in  
22 case of high-risk TPN patients with tunnelled catheters.<sup>58</sup> Mild and self-limited adverse  
23 effects have been reported, especially after flushing the lock, such as dizziness, nausea,  
24 headaches, facial flushing and, eventually, an alcohol taste in the mouth.<sup>59,60</sup>

25 Taurolidine, a derivative from the aminoacid taurine, was proposed as a lock therapy in 1993  
26 because of its antimicrobial effect against a broad range of microorganisms *in vitro*.<sup>61-63</sup>  
27 Although studies conducted in hemodialysis patients are encouraging, data supporting its use  
28 as a lock in TIVAP are limited.<sup>64,65</sup> In pediatric cancer patients, an initial study showed no  
29 significant reduction of CRBSI with taurolidine/citrate as compared to heparin, with ~75% of  
30 TIVAP patients amongst LTIVC.<sup>66</sup> A more recent study in pediatric hematology patients  
31 showed a significant reduction of CRBSI with taurolidine/citrate as compared to heparin but  
32 included only tunnelled catheters.<sup>62</sup> A randomized study in TPN patients demonstrated that  
33 taurolidine/citrate reduced the rate of CRBSI when initiated after the first episode of  
34 infection, as compared with heparin (TIVAP represented ~ 40% of LTIVC).<sup>67</sup> Based on these

1 results, larger comparative studies with TIVAP are needed to define the precise role and  
2 indications of ethanol or taurolidine as preventive locks.  
3 The use of CVC coatings has been extensively studied in case of short-term CVC, leading to a  
4 significant reduction of the risk of CRBSI.<sup>68,69</sup> As LTIVCs dwell for a longer time in the  
5 blood flow, their surfaces become covered by a film composed of various blood components,  
6 therefore reducing the antimicrobial action of the coating.<sup>32</sup> Furthermore, in case of antibiotic-  
7 releasing surfaces, the effect will stop once the device is exhausted. A single study assessed  
8 LTIVC coated with minocycline/rifampin but with a relatively short catheterization time  
9 period (mean duration of  $66\pm 31$  days) and reported a significant reduction of CRBSI.<sup>70</sup> Thus,  
10 developing an efficient surface modification or antibiotic coating that would help preventing  
11 colonization is still a major challenge.  
12

## 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:<sup>71</sup>

6 -Local infections, defined as a tunnel or port-pocket infection with extended erythema or  
7 induration (more than two cm), purulent collection, skin necrosis and spontaneous rupture and  
8 drainage (Figure 1A).<sup>71</sup>

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.<sup>71</sup>

13 -Catheter-related infection, defined by the association of local or general signs of infection  
14 and a positive culture of the catheter tip.<sup>71</sup>

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

17

### 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.<sup>71</sup> 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.<sup>29,72,73</sup> To confirm local infection, a positive culture of aseptically removed  
24 material surrounding the port such as purulent fluid, skin necrosis or swabbing of the port  
25 surface is mandatory.<sup>29,74</sup> Peripheral blood cultures should also be performed to rule out an  
26 associated BSI (Figure 2).

27

### 28 *Diagnosis of TIVAP-related BSI without device removal*

29 This diagnosis relies on the identification of the same microorganism in paired blood  
30 cultures.<sup>71</sup> Correct interpretation of the test requires blood samples to be performed at the  
31 same moment, with the same volume of blood drawn from a peripheral vein and from the  
32 TIVAP through a Huber needle, ideally before the initiation of antimicrobials.<sup>71,75,76</sup> Another  
33 critical point is to precisely label the origin of each blood culture bottle.<sup>71</sup> The two most  
34 commonly used methods for diagnosing CRBSI are simultaneous quantitative blood cultures

1 and the differential time to positivity (DTP) of qualitative blood cultures.<sup>75,77-79</sup> If TIVAP is  
2 the source of BSI, the inoculum will be higher in the blood drawn from TIVAP, as compared  
3 with peripheral vein, therefore leading to a shorter time to positivity (difference  $\geq$  two hours)  
4 or a higher bacterial quantification ( $\geq$ four-fold).<sup>71,75,76,78,79</sup> When used for the diagnosis of  
5 LTIVC-related BSI, these two methods have sensitivity above 90% and specificity close to  
6 100% and between 75% and 91% for quantitative paired blood cultures and DTP,  
7 respectively.<sup>75,78,79</sup> They are nevertheless considered equivalent in recent guidelines and the  
8 choice of a technique will mostly rely on local equipment and training.<sup>71</sup>

9

#### 10 *Diagnosis of TIVAP-related BSI after device removal*

11 The demonstration that a BSI originates from a TIVAP relies on the identification of the same  
12 microorganism in a TIVAP component and peripheral blood cultures. The catheter tip (four-  
13 cm distal part) can be cultured using the semiquantitative or quantitative methods with  
14 thresholds defining a significant colonization of  $>15$  CFU and  $\geq 10^3$  CFU/mL, respectively  
15 (Figures 3A and B).<sup>80,81</sup> Both methods can be equally used but are associated with sensitivity  
16 below 50% for the diagnosis of TIVAP colonization, stressing the importance of using other  
17 techniques.<sup>71,72,74,82</sup> For instance, it has been proposed to perform quantitative culture of the  
18 TIVAP septum using an adapted Brun-Buisson method (Figures 3A and C).<sup>72</sup> With a  
19 threshold of  $10^3$  CFU/mL, this method was associated with 93% sensitivity and 100%  
20 specificity for the diagnosis of TIVAP-related BSI.<sup>72</sup> Furthermore, after septum removal, if  
21 macroscopic debris or clots are present, they can be sampled and cultured with a sensitivity  
22 and specificity of 100% in case of TIVAP-related BSI.<sup>74</sup> The main limitations of port septum  
23 and port deposit cultures are lack of technical standardization and absence of a consensus  
24 threshold.<sup>71</sup> Therefore, performing both catheter tip culture and a culture of a component of  
25 the port reservoir is advisable.<sup>71</sup>

26

#### 27 *Diagnosis of fungal TIVAP-related BSI*

28 Without TIVAP removal, such a diagnosis is challenging as studies assessing paired blood  
29 cultures infrequently included fungal infections<sup>75,77,78,83</sup> Authors proposed to use the time  
30 taken to detect *Candida* spp. growth in peripheral blood as a diagnostic tool, since time to  
31 positivity is shorter in case of catheter-related (CR) candidemia ( $17\pm 2$ h) than candidemia  
32 from another source ( $38\pm 3$ h).<sup>84</sup> The objective of this approach would be to rule out the  
33 catheter as the source of candidemia if time to positivity is above 30 hours. In case of TIVAP  
34 removal, microbiological methods and thresholds are same and culture on blood agar is

1 sensitive enough for the growth of fungi involved in TIVAP-related infections, even if they  
2 may require a longer incubation time than bacteria (24-72h).<sup>85</sup>

3

#### 4 *Workup to rule out complications*

5 Once TIVAP-related BSI has been diagnosed, clinicians should look for infectious  
6 complications such as severe sepsis, endocarditis, or other hematogenous complications  
7 (Figures 1B, C and D).<sup>29</sup> Recent guidelines recommend systematic transesophageal  
8 echocardiography in case of *S. aureus* TIVAP-related BSI.<sup>71</sup> Nevertheless, it is very likely  
9 that, in selected patients without intracardiac devices and with rapid clearance of BSI, a  
10 transthoracic echocardiography performed at least 5 days after BSI onset can safely rule out  
11 infective endocarditis.<sup>86-90</sup> In case of clinical signs of thrombophlebitis or persistent BSI  
12 despite appropriate systemic antimicrobial therapy, venous ultrasonographic examination  
13 should be performed, especially in case of *S. aureus* TIVAP-related BSI (Figure 1B).<sup>71,91</sup>

14

15

## 1 **Treatment: should TIVAP be removed or retained?**

2 In the case of CRBSI, the treatment of choice is systemic antimicrobial therapy in conjunction  
3 with removal of the colonized device.<sup>4</sup> However, in case of TIVAPs, reduced venous access,  
4 potential presence of coagulation disorders, the need for a new procedure and its cost, all  
5 argue in favor of attempting a catheter salvage, if the clinical situation allows it.<sup>71</sup> TIVAP  
6 removal is mandatory in case of local or distant complications, or in case of infection caused  
7 by *S. aureus* or *Candida* spp., based on the high failure rates of treatment when the colonized  
8 catheter is retained (Figure 1 and 4).<sup>71,92</sup> If a conservative strategy is decided upon, the  
9 TIVAP should be removed in case of persistent positive blood cultures 72 hours after the  
10 initiation of antibiotics.<sup>71</sup>

11 In other cases, conservative treatment using a combination of systemic antimicrobials and  
12 ALT can be considered.<sup>71</sup> Indeed, as most of LTIVC-related infections are associated with  
13 intraluminal colonization, instillation of high concentrations of antimicrobial solution filling  
14 the entire volume of the lumen and dwelling for an extended period of time may allow  
15 sterilization of the device.<sup>93-95</sup> Despite several limitations, there is a growing body of evidence  
16 favoring the use of ALT. For instance, a randomized, placebo-controlled study showed that  
17 ALT plus systemic antimicrobial therapy is more effective than systemic antimicrobial  
18 therapy alone for treating LTIVC-related BSI, although not reaching statistical significance  
19 due to the small sample size.<sup>73</sup> In addition, large uncontrolled studies demonstrated high cure  
20 rates in patients with uncomplicated LTIVC-related BSI due to CoNS (89%) or GNR (95%)  
21 (Table 1).<sup>92,94,96</sup>

### 22 23 *How to perform ALT?*

24 No clinical trials have compared one drug to another and some *in vitro* studies have given  
25 conflicting results with mitigated clinical relevance.<sup>97,98</sup> As described in Table 1, more  
26 frequently used antibiotics are glycopeptides, aminoglycosides or fluoroquinolones and their  
27 use has been associated with high rates of therapeutic success. Ideally, antimicrobials should  
28 be administered at a concentration at least 1000-fold above the minimal inhibitory  
29 concentration (MIC) (frequently between 1 and 5 mg/mL) with a volume that fills the entire  
30 TIVAP lumen. In most studies, ALT is prescribed for 10 to 14 days (Table 1) and the lock  
31 solution is usually replaced every 12 to 24 hours, depending on the necessity for vascular  
32 access.<sup>71</sup> Replacing the solution every 48 or 72 hours has also been performed safely.<sup>96</sup> In  
33 case of TIVAP-related BSI, systemic antimicrobials should always be administered for 10 to  
34 14 days.<sup>71</sup> Addition of heparin in ALT has been proposed to avoid thrombosis of the catheter

1 but no comparative data support its use and adverse effects have been reported such as  
2 bleeding or the enhancement of *S. aureus* biofilm formation *in vitro*.<sup>99,100</sup> Therefore, ALT can  
3 be performed in saline or heparin, at 10 to 100 IU/mL (Table 1).<sup>71</sup>

4

#### 5 *Adapting treatment to the identified microorganism (Figure 4)*

6 In case of CoNS infection, the cure rate of ALT is high (>80%), and failures are mainly due  
7 to relapses during the first month of follow-up.<sup>92,94</sup> In case of treatment failure or recurrence  
8 of infection, TIVAP removal should be considered. Glycopeptides for 10 to 14 days have  
9 been extensively used in this setting and a prospective uncontrolled study identified a trend  
10 toward a higher success rate with teicoplanin as compared to vancomycin.<sup>92,94</sup> Additionally,  
11 daptomycin can be considered as a possible alternative (see below).<sup>97,98</sup>

12 Conservative treatment of GNR TIVAP-related BSI is associated with a cure rate between  
13 87% and 95%, when local or distant complications are excluded.<sup>92,96</sup> Although recent  
14 guidelines suggest TIVAP removal in the case of *P. aeruginosa* infection, *Pseudomonas* spp.  
15 have also been included in clinical ALT studies, with the same success rates as  
16 *Enterobacteriaceae*. Fluoroquinolones and aminoglycosides are the antimicrobials most  
17 commonly used for these infections.<sup>92,96</sup>

18 *S. aureus* TIVAP-related BSI should lead to catheter removal due to the high failure rates of  
19 ALT (45% to 60%), with some cases of related mortality.<sup>92,101</sup> ALT can nevertheless be  
20 considered in exceptional circumstances after having excluded local or distant complications,  
21 such as infective endocarditis with transesophageal echocardiography.<sup>71</sup> Cefazolin and  
22 vancomycin are the antimicrobials most frequently used in this setting and the efficacy of  
23 other antimicrobials such as aminoglycosides or daptomycin should be evaluated in clinical  
24 studies.<sup>92,98,101,102</sup>

25 Infections due to *Candida* spp. should lead to catheter removal, and conservative treatment  
26 should only be considered in limited situations after ruling out local or distant complications  
27 (see below). Although optimal antifungal-lock therapy has not been established in this  
28 unusual situation, amphotericin B (liposomal or deoxycholate) and ethanol are the most  
29 commonly used compounds.<sup>103</sup> In case of catheter retention, a systemic antifungal with  
30 activity against *Candida* biofilms should be favored such as lipid-based amphotericin B or  
31 echinocandins.<sup>104</sup>

#### 32 *Recently developed locks*

1 Aside from commonly used antimicrobials in ALT, ethanol and daptomycin have been more  
2 recently used as ALT for conservative treatment. Regarding ethanol, no comparative studies  
3 have been published and most uncontrolled studies have been conducted in pediatric patients,  
4 with a less accurate diagnosis due to lack of peripheral blood cultures.<sup>105-107</sup> For instance, a  
5 retrospective study of 51 patients treated with 70% ethanol dwelling for five days reported a  
6 cure rate of 100% but recurrences in 10% of cases.<sup>107</sup> More recently, daptomycin has been  
7 proposed as lock therapy because of its potent *in vitro* effect against biofilms.<sup>108,109</sup> A phase II  
8 clinical study was conducted using daptomycin ALT in 13 patients with LTIVC-related  
9 infections caused by CoNS or *E. faecalis*, half of them occurring on TIVAP.<sup>97</sup> After a mean  
10 of 14 days of treatment, cure rate was 85% (11/13 patients).<sup>97</sup> Comparative clinical studies are  
11 now expected to determine if ethanol or daptomycin are more efficient or more quickly  
12 effective than already used antibiotics.

13

14



## 1 **Future treatments and needs**

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

### 4 5 *Improving diagnosis*

6 Despite their help in diagnosing TIVAP-related BSI without device removal, paired blood  
7 cultures are not foolproof as both methods give false-positive and false-negative  
8 results.<sup>72,76,83,110,111</sup> Therefore, different investigators have tried to develop molecular biology  
9 tools for the diagnosis of TIVAP-related infections. For example, amplification and  
10 sequencing of bacterial DNA (16S ribosomal RNA gene) has been performed on blood drawn  
11 from CVCs in cases of CRBSI or after TIVAP removal, on port sonication fluid and biofilms  
12 from the internal surface of the port.<sup>112,113</sup> These methods are more sensitive than cultures in  
13 case of previous antibiotic administration. Beside, other groups have tried to identify  
14 biomarkers of biofilm formation inside the port that would allow an earlier diagnosis of  
15 colonization before the onset of BSI. For instance, certain LPS modifications are only  
16 occurring within Gram-negative bacterial biofilms.<sup>114</sup>

17 Regarding fungal infections, the use of selective blood culture bottles, polymerase chain  
18 reaction or antigen detection on blood samples could allow faster and/or more sensitive  
19 diagnosis but still need to be assessed in the setting of TIVAP.<sup>115,116</sup>

### 20 21 *Prevention*

22 Improvement of hygiene measures should always be attempted through definition and  
23 implementation of local clinical bundles for TIVAP insertion and handling.<sup>4,42,71</sup> Dedicated  
24 infusion therapy teams could be involved in the education of healthcare workers and patients.<sup>4</sup>  
25 Other preventive strategies are limited by the long-term implantation of TIVAP leading to  
26 coverage by host blood components of any modified surface, and reduction of the effect of  
27 antibiotic-coated catheters over time. One possible solution would be to use anti-adhesive  
28 compounds inhibiting the deposition of blood components or inhibiting local thrombosis that  
29 would delay or reduce the risk of formation of the protein film. For instance, a surface  
30 modification using nonleaching polymeric sulfobetaine (polySB) is associated with a  
31 significant reduction of adherence and activation of platelets and white blood cells.<sup>117</sup> Using  
32 an *in vivo* canine model, this surface modification has been demonstrated to reduce thrombus  
33 accumulation and bacterial adhesion.<sup>117</sup> Although this and other approaches provided  
34 encouraging results, they need to be assessed in long-term settings.

1

## 2 *Biofilm eradication inside TIVAP*

3 Currently used antibiotics as lock therapy have drawbacks, such as possible treatment failure  
4 or a long treatment duration.<sup>71</sup> Several investigators have attempted to develop more efficient  
5 and faster ALT to face these challenges. Use of *in vitro* and *in vivo* models led to the  
6 identification of several potential lock candidates for clinical studies; for instance, ethanol or  
7 daptomycin are now being clinically assessed.<sup>97,105</sup> Another approach is to use an adjuvant to  
8 increase antibiotic efficiency against biofilms. For example, the association of an antibiotic  
9 and a chelator such as EDTA or citrate has been proposed, since divalent cations play a key-  
10 role in maintaining biofilm ECM stability.<sup>118</sup> Addition of chelators destabilize ECM and  
11 therefore increase antimicrobial activity.<sup>119</sup> Many *in vitro* studies have reported an antibiofilm  
12 effect of EDTA alone and a synergistic effect when combined with gentamicin or  
13 minocycline/25% ethanol.<sup>120,121</sup> *In vivo*, the combination of gentamicin and EDTA led to  
14 complete eradication of biofilms of Gram-positive as well as Gram-negative bacteria formed  
15 inside TIVAP implanted in rats, therefore paving the way to clinical studies.<sup>122</sup>

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

19 -It has been demonstrated that the association of an aminoglycoside and a sugar such as  
20 mannitol or fructose could increase antibiotic uptake in the most tolerant bacteria inside  
21 biofilms called persister cells. Killing of persister cells may lead to a more efficient treatment  
22 of *in vivo* biofilm.<sup>123</sup> Such an approach could easily be converted to an ALT composed of an  
23 aminoglycoside plus sugar.

24 -As quorum sensing (QS) is a key component of biofilm communication, many authors  
25 speculated that interfering with QS signals might alter biofilm maturation thereby leading to  
26 easier eradication. For instance, RNAlII inhibiting peptide (RIP), a compound interfering  
27 with *S. aureus* QS is efficiently preventing CVC-related infection *in vivo*.<sup>124</sup> Other  
28 compounds interfering with *S. epidermidis* QS such as farnesol have also demonstrated  
29 synergy with antibiotics *in vitro* and *in vivo* and should be considered as potential locks.<sup>125</sup>

30 -Another approach would be to favor bacterial biofilm dispersion as biofilm bacteria lose  
31 most of their antibiotic tolerance when they return to a planktonic state.<sup>37</sup> However, the  
32 dispersal approach needs to be associated with antibiotics as released bacteria from the  
33 biofilm into the bloodstream may express virulence genes and lead to severe sepsis.<sup>126</sup> Many  
34 compounds such as dispersin B, DNase I or autoinducing peptides have been described to

1 favor biofilm dispersion *in vitro*, and to a lesser extent *in vivo* but none of them have been  
2 proposed as ALT yet.<sup>127,128</sup>

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.<sup>36,129-132</sup>

### 7 8 *Treatment of fungal infections*

9 All published international guidelines so far strongly recommend the early removal of CVC in  
10 case of candidemia whether or not it is CR.<sup>71,104,133</sup> Two situations should be distinguished.  
11 On one hand, if the candidemia is not CR, it is plausible that catheter retention does not  
12 influence outcome, especially if an antifungal efficient against *Candida* biofilm is used.<sup>134</sup> A  
13 comparative study is needed to definitively answer this question. On the other hand, if the  
14 candidemia is CR, it is very likely that catheter removal is required. For instance, a  
15 retrospective study including 404 patients with cancer, CVC and candidemia identified after  
16 multivariate analysis that early catheter removal improved response to antifungal therapy only  
17 among patients with CR candidemia.<sup>135</sup> In this context, one major issue is that the diagnosis  
18 of fungal CRBSI without catheter removal is still challenging due to poor clinical evaluation  
19 of paired blood cultures in this setting.<sup>75,77,78</sup>

20 In case of CR candidemia, even if catheter removal is recommended, many patients cannot  
21 afford a CVC replacement because of their general condition. Therefore, antifungal lock  
22 therapy has been proposed to increase the likelihood of biofilm eradication, based on the same  
23 principles as ALT.<sup>103</sup> *In vitro* and *in vivo* studies reveal that against *Candida* biofilms: i)  
24 azoles have poor activity; ii) lipid formulations of amphotericin B are more effective than  
25 amphotericin B deoxycholate; and iii) echinocandins have excellent *in vitro* activity.<sup>103</sup> Non-  
26 antifungal lock therapy against *Candida* biofilms have also been proposed such as EDTA in  
27 combination with antifungals or minocycline, ethanol, heparin and even highly concentrated  
28 antibiotics like doxycycline.<sup>103,136-139</sup> Although from a clinical point of view no comparative  
29 study is available, more than 20 patients were treated with various types of antifungal locks  
30 with an overall success rate of 77% with a publication bias that should be taken into  
31 account.<sup>103</sup> Hence, ethanol lock therapy could be a promising candidate with eight successes  
32 among ten reported patients.<sup>138,139</sup> Of note, most of these published cases are of pediatric  
33 patients with the limitation of diagnostic criteria, frequently based only on blood cultures

1 drawn from the CVC without any peripheral blood culture. Studies of antifungal lock therapy  
2 specifically for TIVAP-associated fungal infections are clearly needed.

3

4

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.

16

1 **Contributors**

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

5

6 **Conflicts of interest**

7 All authors: no conflicts of interest.

8

9 **Acknowledgments**

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

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

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

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

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

23

1 **References**

2

3 1 Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M. ESPEN Guidelines on  
4 Parenteral Nutrition: central venous catheters (access, care, diagnosis and therapy of  
5 complications). *Clin Nutr* 2009; **28**: 365-77.

6 2 Vescia S, Baumgartner AK, Jacobs VR, et al. Management of venous port systems in  
7 oncology: a review of current evidence. *Ann Oncol* 2008; **19**: 9-15.

8 3 Reed WP, Newman KA, de Jongh C, et al. Prolonged venous access for chemotherapy  
9 by means of the Hickman catheter. *Cancer* 1983; **52**: 185-92.

10 4 Raad I, Hanna H, Maki D. Intravascular catheter-related infections: advances in  
11 diagnosis, prevention, and management. *Lancet Infect Dis* 2007; **7**: 645-57.

12 5 Niederhuber JE, Ensminger W, Gyves JW, Liepman M, Doan K, Cozzi E. Totally  
13 implanted venous and arterial access system to replace external catheters in cancer treatment.  
14 *Surgery* 1982; **92**: 706-12.

15 6 Dal Molin A, Di Massimo DS, Braggion C, et al. Totally implantable central venous  
16 access ports in patients with cystic fibrosis: a multicenter prospective cohort study. *J Vasc*  
17 *Access* 2012; **13**: 290-5.

18 7 Santarpia L, Pasanisi F, Alfonsi L, et al. Prevention and treatment of implanted central  
19 venous catheter (CVC) - related sepsis: a report after six years of home parenteral nutrition  
20 (HPN). *Clin Nutr* 2002; **21**: 207-11.

21 8 Sotir MJ, Lewis C, Bisher EW, Ray SM, Soucie JM, Blumberg HM. Epidemiology of  
22 device-associated infections related to a long-term implantable vascular access device. *Infect*  
23 *Control Hosp Epidemiol* 1999; **20**: 187-91.

24 9 Chang L, Tsai JS, Huang SJ, Shih CC. Evaluation of infectious complications of the  
25 implantable venous access system in a general oncologic population. *Am J Infect Control*  
26 2003; **31**: 34-9.

27 10 Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of  
28 persistent infections. *Science* 1999; **284**: 1318-22.

29 11 Fischer L, Knebel P, Schroder S, et al. Reasons for explantation of totally implantable  
30 access ports: a multivariate analysis of 385 consecutive patients. *Ann Surg Oncol* 2008; **15**:  
31 1124-9.

32 12 Groeger JS, Lucas AB, Thaler HT, et al. Infectious morbidity associated with long-  
33 term use of venous access devices in patients with cancer. *Ann Intern Med* 1993; **119**: 1168-  
34 74.

35 13 Hsieh CC, Weng HH, Huang WS, et al. Analysis of risk factors for central venous port  
36 failure in cancer patients. *World J Gastroenterol* 2009; **15**: 4709-14.

37 14 Minassian VA, Sood AK, Lowe P, Sorosky JI, Al-Jurf AS, Buller RE. Longterm  
38 central venous access in gynecologic cancer patients. *J Am Coll Surg* 2000; **191**: 403-9.

- 1 15 Kock HJ, Pietsch M, Krause U, Wilke H, Eigler FW. Implantable vascular access  
2 systems: experience in 1500 patients with totally implanted central venous port systems.  
3 *World J Surg* 1998; **22**: 12-6.
- 4 16 Biffi R, de Braud F, Orsi F, et al. Totally implantable central venous access ports for  
5 long-term chemotherapy. A prospective study analyzing complications and costs of 333  
6 devices with a minimum follow-up of 180 days. *Ann Oncol* 1998; **9**: 767-73.
- 7 17 Wolosker N, Yazbek G, Nishinari K, et al. Totally implantable venous catheters for  
8 chemotherapy: experience in 500 patients. *Sao Paulo Med J* 2004; **122**: 147-51.
- 9 18 Royle TJ, Davies RE, Gannon MX. Totally implantable venous access devices - 20  
10 years' experience of implantation in cystic fibrosis patients. *Ann R Coll Surg Engl* 2008; **90**:  
11 679-84.
- 12 19 Burdon J, Conway SP, Murchan P, Lansdown M, Kester RC. Five years' experience of  
13 PAS Port intravenous access system in adult cystic fibrosis. *Eur Respir J* 1998; **12**: 212-6.
- 14 20 Shirotani N, Iino T, Numata K, Kameoka S. Complications of central venous catheters  
15 in patients on home parenteral nutrition: an analysis of 68 patients over 16 years. *Surg Today*  
16 2006; **36**: 420-4.
- 17 21 Cotogni P, Pittiruti M, Barbero C, Monge T, Palmo A, Boggio Bertinet D. Catheter-  
18 Related Complications in Cancer Patients on Home Parenteral Nutrition: A Prospective Study  
19 of Over 51,000 Catheter Days. *JPEN J Parenter Enteral Nutr* 2013;
- 20 22 Astagneau P, Maugat S, Tran-Minh T, et al. Long-term central venous catheter  
21 infection in HIV-infected and cancer patients: a multicenter cohort study. *Infect Control Hosp*  
22 *Epidemiol* 1999; **20**: 494-8.
- 23 23 Penel N, Neu JC, Clisant S, Hoppe H, Devos P, Yazdanpanah Y. Risk factors for early  
24 catheter-related infections in cancer patients. *Cancer* 2007; **110**: 1586-92.
- 25 24 Zingg W, Cartier-Fassler V, Walder B. Central venous catheter-associated infections.  
26 *Best Pract Res Clin Anaesthesiol* 2008; **22**: 407-21.
- 27 25 Baskin JL, Pui CH, Reiss U, et al. Management of occlusion and thrombosis  
28 associated with long-term indwelling central venous catheters. *Lancet* 2009; **374**: 159-69.
- 29 26 Samaras P, Dold S, Braun J, et al. Infectious port complications are more frequent in  
30 younger patients with hematologic malignancies than in solid tumor patients. *Oncology* 2008;  
31 **74**: 237-44.
- 32 27 Kloos WE, Musselwhite MS. Distribution and persistence of *Staphylococcus* and  
33 *Micrococcus* species and other aerobic bacteria on human skin. *Appl Microbiol* 1975; **30**:  
34 381-5.
- 35 28 Adler A, Yaniv I, Steinberg R, et al. Infectious complications of implantable ports and  
36 Hickman catheters in paediatric haematology-oncology patients. *J Hosp Infect* 2006; **62**: 358-  
37 65.



- 1 29 Lebeaux D, Larroque B, Gellen-Dautremer J, et al. Clinical outcome after a totally  
2 implantable venous access port-related infection in cancer patients: a prospective study and  
3 review of the literature. *Medicine (Baltimore)* 2012; **91**: 309-18.
- 4 30 Ghanem GA, Boktour M, Warneke C, et al. Catheter-related *Staphylococcus aureus*  
5 bacteremia in cancer patients: high rate of complications with therapeutic implications.  
6 *Medicine (Baltimore)* 2007; **86**: 54-60.
- 7 31 Wilcox MH, Tack KJ, Bouza E, et al. Complicated skin and skin-structure infections  
8 and catheter-related bloodstream infections: noninferiority of linezolid in a phase 3 study.  
9 *Clin Infect Dis* 2009; **48**: 203-12.
- 10 32 Raad I, Costerton W, Sabharwal U, Sacilowski M, Anaissie E, Bodey GP.  
11 Ultrastructural analysis of indwelling vascular catheters: a quantitative relationship between  
12 luminal colonization and duration of placement. *J Infect Dis* 1993; **168**: 400-7.
- 13 33 Safdar N, Maki DG. The pathogenesis of catheter-related bloodstream infection with  
14 noncuffed short-term central venous catheters. *Intensive Care Med* 2004; **30**: 62-7.
- 15 34 Mermel LA. What is the predominant source of intravascular catheter infections? *Clin*  
16 *Infect Dis* 2011; **52**: 211-2.
- 17 35 Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant  
18 microorganisms. *Clin Microbiol Rev* 2002; **15**: 167-93.
- 19 36 Donlan RM. Biofilm elimination on intravascular catheters: important considerations  
20 for the infectious disease practitioner. *Clin Infect Dis* 2011; **52**: 1038-45.
- 21 37 Lewis K. Riddle of biofilm resistance. *Antimicrob Agents Chemother* 2001; **45**: 999-  
22 1007.
- 23 38 Ng F, Mastoroudes H, Paul E, et al. A comparison of Hickman line- and Port-a-Cath-  
24 associated complications in patients with solid tumours undergoing chemotherapy. *Clin Oncol*  
25 *(R Coll Radiol)* 2007; **19**: 551-6.
- 26 39 Ohno H, Mizumoto C, Otsuki Y, Oguma S, Yoshida Y. The duration of functioning of  
27 a subcutaneous implantable port for the treatment of hematological tumors: a single  
28 institution-based study. *Int J Clin Oncol* 2010; **15**: 172-8.
- 29 40 Howell PB, Walters PE, Donowitz GR, Farr BM. Risk factors for infection of adult  
30 patients with cancer who have tunnelled central venous catheters. *Cancer* 1995; **75**: 1367-75.
- 31 41 Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-  
32 related bloodstream infections in the ICU. *N Engl J Med* 2006; **355**: 2725-32.
- 33 42 O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of  
34 intravascular catheter-related infections. *Clin Infect Dis* 2011; **52**: e162-93.
- 35 43 Mimos O, Villeminey S, Ragot S, et al. Chlorhexidine-based antiseptic solution vs  
36 alcohol-based povidone-iodine for central venous catheter care. *Arch Intern Med* 2007; **167**:  
37 2066-72.

- 1 44 Biffi R, Orsi F, Pozzi S, et al. Best choice of central venous insertion site for the  
2 prevention of catheter-related complications in adult patients who need cancer therapy: a  
3 randomized trial. *Ann Oncol* 2009; **20**: 935-40.
- 4 45 Wolosker N, Yazbek G, Munia MA, Zerati AE, Langer M, Nishinari K. Totally  
5 implantable femoral vein catheters in cancer patients. *Eur J Surg Oncol* 2004; **30**: 771-5.
- 6 46 Peris A, Zagli G, Bonizzoli M, et al. Implantation of 3951 long-term central venous  
7 catheters: performances, risk analysis, and patient comfort after ultrasound-guidance  
8 introduction. *Anesth Analg* 2010; **111**: 1194-201.
- 9 47 Karanlik H, Kurul S, Saip P, et al. The role of antibiotic prophylaxis in totally  
10 implantable venous access device placement: results of a single-center prospective  
11 randomized trial. *Am J Surg* 2011; **202**: 10-5.
- 12 48 Di Carlo I, Toro A, Pulvirenti E, Palermo F, Scibilia G, Cordio S. Could antibiotic  
13 prophylaxis be not necessary to implant totally implantable venous access devices?  
14 Randomized prospective study. *Surg Oncol* 2011; **20**: 20-5.
- 15 49 van de Wetering MD, van Woensel JB. Prophylactic antibiotics for preventing early  
16 central venous catheter Gram positive infections in oncology patients. *Cochrane Database*  
17 *Syst Rev* 2007; CD003295.
- 18 50 Lapalu J, Losser MR, Albert O, et al. Totally implantable port management: impact of  
19 positive pressure during needle withdrawal on catheter tip occlusion (an experimental study).  
20 *J Vasc Access* 2010; **11**: 46-51.
- 21 51 Goossens GA, Jerome M, Janssens C, et al. Comparing normal saline versus diluted  
22 heparin to lock non-valved totally implantable venous access devices in cancer patients: a  
23 randomised, non-inferiority, open trial. *Ann Oncol* 2013;
- 24 52 Safdar N, Maki DG. Use of vancomycin-containing lock or flush solutions for  
25 prevention of bloodstream infection associated with central venous access devices: a meta-  
26 analysis of prospective, randomized trials. *Clin Infect Dis* 2006; **43**: 474-84.
- 27 53 Ferreira Chacon JM, Hato de Almeida E, de Lourdes Simoes R, et al. Randomized  
28 study of minocycline and edetic acid as a locking solution for central line (port-a-cath) in  
29 children with cancer. *Chemotherapy* 2011; **57**: 285-91.
- 30 54 Chatzinikolaou I, Zipf TF, Hanna H, et al. Minocycline-ethylenediaminetetraacetate  
31 lock solution for the prevention of implantable port infections in children with cancer. *Clin*  
32 *Infect Dis* 2003; **36**: 116-9.
- 33 55 Landry DL, Braden GL, Gobeille SL, Haessler SD, Vaidya CK, Sweet SJ. Emergence  
34 of gentamicin-resistant bacteremia in hemodialysis patients receiving gentamicin lock  
35 catheter prophylaxis. *Clin J Am Soc Nephrol* 2010; **5**: 1799-804.
- 36 56 Kayton ML, Garmey EG, Ishill NM, et al. Preliminary results of a phase I trial of  
37 prophylactic ethanol-lock administration to prevent mediport catheter-related bloodstream  
38 infections. *J Pediatr Surg* 2010; **45**: 1961-6.

- 1 57 Oliveira C, Nasr A, Brindle M, Wales PW. Ethanol locks to prevent catheter-related  
2 bloodstream infections in parenteral nutrition: a meta-analysis. *Pediatrics* 2012; **129**: 318-29.
- 3 58 Wales PW, Kosar C, Carricato M, de Silva N, Lang K, Avitzur Y. Ethanol lock  
4 therapy to reduce the incidence of catheter-related bloodstream infections in home parenteral  
5 nutrition patients with intestinal failure: preliminary experience. *J Pediatr Surg* 2011; **46**:  
6 951-6.
- 7 59 Slobbe L, Doorduijn JK, Lugtenburg PJ, et al. Prevention of catheter-related  
8 bacteremia with a daily ethanol lock in patients with tunneled catheters: a randomized,  
9 placebo-controlled trial. *PLoS One* 2010; **5**: e10840.
- 10 60 Wolf J, Shenep JL, Clifford V, Curtis N, Flynn PM. Ethanol lock therapy in pediatric  
11 hematology and oncology. *Pediatr Blood Cancer* 2013; **60**: 18-25.
- 12 61 Bradshaw JH, Puntis JW. Taurolidine and catheter-related bloodstream infection: a  
13 systematic review of the literature. *J Pediatr Gastroenterol Nutr* 2008; **47**: 179-86.
- 14 62 Dumichen MJ, Seeger K, Lode HN, et al. Randomized controlled trial of taurolidine  
15 citrate versus heparin as catheter lock solution in paediatric patients with haematological  
16 malignancies. *J Hosp Infect* 2012; **80**: 304-9.
- 17 63 Johnston DA, Phillips G, Perry M, McAlpine H, Richards J, Pennington CR. Taurolin  
18 for the prevention of parenteral nutrition related infection: antimicrobial activity and long-  
19 term use. *Clin Nutr* 1993; **12**: 365-8.
- 20 64 Solomon LR, Cheesbrough JS, Bhargava R, et al. Observational study of need for  
21 thrombolytic therapy and incidence of bacteremia using taurolidine-citrate-heparin,  
22 taurolidine-citrate and heparin catheter locks in patients treated with hemodialysis. *Semin*  
23 *Dial* 2012; **25**: 233-8.
- 24 65 Betjes MG, van Agteren M. Prevention of dialysis catheter-related sepsis with a  
25 citrate-taurolidine-containing lock solution. *Nephrol Dial Transplant* 2004; **19**: 1546-51.
- 26 66 Simon A, Ammann RA, Wiszniewsky G, Bode U, Fleischhack G, Besuden MM.  
27 Taurolidine-citrate lock solution (TauroLock) significantly reduces CVAD-associated  
28 grampositive infections in pediatric cancer patients. *BMC Infect Dis* 2008; **8**: 102.
- 29 67 Bisseling TM, Willems MC, Versleijen MW, Hendriks JC, Vissers RK, Wanten GJ.  
30 Taurolidine lock is highly effective in preventing catheter-related bloodstream infections in  
31 patients on home parenteral nutrition: a heparin-controlled prospective trial. *Clin Nutr* 2010;  
32 **29**: 464-8.
- 33 68 Sousa C, Henriques M, Oliveira R. Mini-review: Antimicrobial central venous  
34 catheters--recent advances and strategies. *Biofouling* 2011; **27**: 609-20.
- 35 69 Darouiche RO, Raad, II, Heard SO, et al. A comparison of two antimicrobial-  
36 impregnated central venous catheters. Catheter Study Group. *N Engl J Med* 1999; **340**: 1-8.
- 37 70 Hanna H, Benjamin R, Chatzinikolaou I, et al. Long-term silicone central venous  
38 catheters impregnated with minocycline and rifampin decrease rates of catheter-related

- 1 bloodstream infection in cancer patients: a prospective randomized clinical trial. *J Clin Oncol*  
2 2004; **22**: 3163-71.
- 3 71 Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis  
4 and management of intravascular catheter-related infection: 2009 Update by the Infectious  
5 Diseases Society of America. *Clin Infect Dis* 2009; **49**: 1-45.
- 6 72 Douard MC, Arlet G, Longuet P, et al. Diagnosis of venous access port-related  
7 infections. *Clin Infect Dis* 1999; **29**: 1197-202.
- 8 73 Rijnders BJ, Van Wijngaerden E, Vandecasteele SJ, Stas M, Peetermans WE.  
9 Treatment of long-term intravascular catheter-related bacteraemia with antibiotic lock:  
10 randomized, placebo-controlled trial. *J Antimicrob Chemother* 2005; **55**: 90-4.
- 11 74 Whitman ED, Boatman AM. Comparison of diagnostic specimens and methods to  
12 evaluate infected venous access ports. *Am J Surg* 1995; **170**: 665-9; discussion 9-70.
- 13 75 Blot F, Nitenberg G, Chachaty E, et al. Diagnosis of catheter-related bacteraemia: a  
14 prospective comparison of the time to positivity of hub-blood versus peripheral-blood  
15 cultures. *Lancet* 1999; **354**: 1071-7.
- 16 76 Capdevila JA, Planes AM, Palomar M, et al. Value of differential quantitative blood  
17 cultures in the diagnosis of catheter-related sepsis. *Eur J Clin Microbiol Infect Dis* 1992; **11**:  
18 403-7.
- 19 77 Chatzinikolaou I, Hanna H, Hachem R, Alakech B, Tarrand J, Raad I. Differential  
20 quantitative blood cultures for the diagnosis of catheter-related bloodstream infections  
21 associated with short- and long-term catheters: a prospective study. *Diagn Microbiol Infect*  
22 *Dis* 2004; **50**: 167-72.
- 23 78 Raad I, Hanna HA, Alakech B, Chatzinikolaou I, Johnson MM, Tarrand J. Differential  
24 time to positivity: a useful method for diagnosing catheter-related bloodstream infections.  
25 *Ann Intern Med* 2004; **140**: 18-25.
- 26 79 Safdar N, Fine JP, Maki DG. Meta-analysis: methods for diagnosing intravascular  
27 device-related bloodstream infection. *Ann Intern Med* 2005; **142**: 451-66.
- 28 80 Brun-Buisson C, Abrouk F, Legrand P, Huet Y, Larabi S, Rapin M. Diagnosis of  
29 central venous catheter-related sepsis. Critical level of quantitative tip cultures. *Arch Intern*  
30 *Med* 1987; **147**: 873-7.
- 31 81 Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying  
32 intravenous-catheter-related infection. *N Engl J Med* 1977; **296**: 1305-9.
- 33 82 Siegman-Igra Y, Anglim AM, Shapiro DE, Adal KA, Strain BA, Farr BM. Diagnosis  
34 of vascular catheter-related bloodstream infection: a meta-analysis. *J Clin Microbiol* 1997;  
35 **35**: 928-36.
- 36 83 Chen WT, Liu TM, Wu SH, Tan TD, Tseng HC, Shih CC. Improving diagnosis of  
37 central venous catheter-related bloodstream infection by using differential time to positivity  
38 as a hospital-wide approach at a cancer hospital. *J Infect* 2009; **59**: 317-23.

- 1 84 Ben-Ami R, Weinberger M, Orni-Wasserlauff R, et al. Time to blood culture  
2 positivity as a marker for catheter-related candidemia. *J Clin Microbiol* 2008; **46**: 2222-6.
- 3 85 Nett JE, Andes D. Review of techniques for diagnosis of catheter-related *Candida*  
4 biofilm infections. *Current Fungal Infection Reports* 2008; **2**: 237-43.
- 5 86 Kaasch AJ, Fowler VG, Jr., Rieg S, et al. Use of a simple criteria set for guiding  
6 echocardiography in nosocomial *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2011; **53**:  
7 1-9.
- 8 87 Van Hal SJ, Mathur G, Kelly J, Aronis C, Cranney GB, Jones PD. The role of  
9 transthoracic echocardiography in excluding left sided infective endocarditis in  
10 *Staphylococcus aureus* bacteraemia. *J Infect* 2005; **51**: 218-21.
- 11 88 Fowler VG, Jr., Li J, Corey GR, et al. Role of echocardiography in evaluation of  
12 patients with *Staphylococcus aureus* bacteremia: experience in 103 patients. *J Am Coll*  
13 *Cardiol* 1997; **30**: 1072-8.
- 14 89 Rosen AB, Fowler VG, Jr., Corey GR, et al. Cost-effectiveness of transesophageal  
15 echocardiography to determine the duration of therapy for intravascular catheter-associated  
16 *Staphylococcus aureus* bacteremia. *Ann Intern Med* 1999; **130**: 810-20.
- 17 90 Pigrau C, Rodriguez D, Planes AM, et al. Management of catheter-related  
18 *Staphylococcus aureus* bacteremia: when may sonographic study be unnecessary? *Eur J Clin*  
19 *Microbiol Infect Dis* 2003; **22**: 713-9.
- 20 91 Crowley AL, Peterson GE, Benjamin DK, Jr., et al. Venous thrombosis in patients  
21 with short- and long-term central venous catheter-associated *Staphylococcus aureus*  
22 bacteremia. *Crit Care Med* 2008; **36**: 385-90.
- 23 92 Fernandez-Hidalgo N, Almirante B, Calleja R, et al. Antibiotic-lock therapy for long-  
24 term intravascular catheter-related bacteraemia: results of an open, non-comparative study. *J*  
25 *Antimicrob Chemother* 2006; **57**: 1172-80.
- 26 93 Segarra-Newnham M, Martin-Cooper EM. Antibiotic lock technique: a review of the  
27 literature. *Ann Pharmacother* 2005; **39**: 311-8.
- 28 94 Del Pozo JL, Garcia Cenoz M, Hernaez S, et al. Effectiveness of teicoplanin versus  
29 vancomycin lock therapy in the treatment of port-related coagulase-negative staphylococci  
30 bacteraemia: a prospective case-series analysis. *Int J Antimicrob Agents* 2009; **34**: 482-5.
- 31 95 Messing B, Peitra-Cohen S, Debure A, Beliah M, Bernier JJ. Antibiotic-lock  
32 technique: a new approach to optimal therapy for catheter-related sepsis in home-parenteral  
33 nutrition patients. *JPEN J Parenter Enteral Nutr* 1988; **12**: 185-9.
- 34 96 Funalleras G, Fernandez-Hidalgo N, Borrego A, et al. Effectiveness of antibiotic-lock  
35 therapy for long-term catheter-related bacteremia due to Gram-negative bacilli: a prospective  
36 observational study. *Clin Infect Dis* 2011; **53**: e129-32.
- 37 97 Del Pozo JL, Rodil R, Aguinaga A, et al. Daptomycin lock therapy for grampositive  
38 long-term catheter-related bloodstream infections. *Int J Clin Pract* 2012; **66**: 305-8.

- 1 98 Van Praagh AD, Li T, Zhang S, et al. Daptomycin antibiotic lock therapy in a rat  
2 model of staphylococcal central venous catheter biofilm infections. *Antimicrob Agents*  
3 *Chemother* 2011; **55**: 4081-9.
- 4 99 Shanks RM, Donegan NP, Graber ML, et al. Heparin stimulates *Staphylococcus*  
5 *aureus* biofilm formation. *Infect Immun* 2005; **73**: 4596-606.
- 6 100 Novak M, Cvitkovic M, Galic S, Luetic T, Cavar S, Puretic Z. The life-threatening  
7 hemodialysis catheter heparin lock caused bleeding in a child after peritoneal catheter  
8 removal. *J Pediatr Surg* 2008; **43**: E41-4.
- 9 101 Maya ID, Carlton D, Estrada E, Allon M. Treatment of dialysis catheter-related  
10 *Staphylococcus aureus* bacteremia with an antibiotic lock: a quality improvement report. *Am*  
11 *J Kidney Dis* 2007; **50**: 289-95.
- 12 102 Fernandez-Hidalgo N, Gavalda J, Almirante B, et al. Evaluation of linezolid,  
13 vancomycin, gentamicin and ciprofloxacin in a rabbit model of antibiotic-lock technique for  
14 *Staphylococcus aureus* catheter-related infection. *J Antimicrob Chemother* 2010; **65**: 525-30.
- 15 103 Walraven CJ, Lee SA. Antifungal lock therapy. *Antimicrob Agents Chemother* 2013;  
16 **57**: 1-8.
- 17 104 Cornely OA, Bassetti M, Calandra T, et al. ESCMID\* guideline for the diagnosis and  
18 management of *Candida* diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect*  
19 2012; **18 Suppl 7**: 19-37.
- 20 105 Broom J, Woods M, Allworth A, et al. Ethanol lock therapy to treat tunnelled central  
21 venous catheter-associated blood stream infections: results from a prospective trial. *Scand J*  
22 *Infect Dis* 2008; **40**: 399-406.
- 23 106 McGrath EJ, Salloum R, Chen X, et al. Short-dwell ethanol lock therapy in children is  
24 associated with increased clearance of central line-associated bloodstream infections. *Clin*  
25 *Pediatr (Phila)* 2011; **50**: 943-51.
- 26 107 Onland W, Shin CE, Fustar S, Rushing T, Wong WY. Ethanol-lock technique for  
27 persistent bacteremia of long-term intravascular devices in pediatric patients. *Arch Pediatr*  
28 *Adolesc Med* 2006; **160**: 1049-53.
- 29 108 Mascio CT, Alder JD, Silverman JA. Bactericidal action of daptomycin against  
30 stationary-phase and nondividing *Staphylococcus aureus* cells. *Antimicrob Agents Chemother*  
31 2007; **51**: 4255-60.
- 32 109 Raad I, Hanna H, Jiang Y, et al. Comparative activities of daptomycin, linezolid, and  
33 tigecycline against catheter-related methicillin-resistant *Staphylococcus* bacteremic isolates  
34 embedded in biofilm. *Antimicrob Agents Chemother* 2007; **51**: 1656-60.
- 35 110 Douard MC, Clementi E, Arlet G, et al. Negative catheter-tip culture and diagnosis of  
36 catheter-related bacteremia. *Nutrition* 1994; **10**: 397-404.
- 37 111 Chen WT, Tseng HC, Shih CC. Approximately 17% of catheterised cancer patients  
38 with non-catheter-related bacteraemia have positive differential time. *J Hosp Infect* 2011; **78**:  
39 76-7.

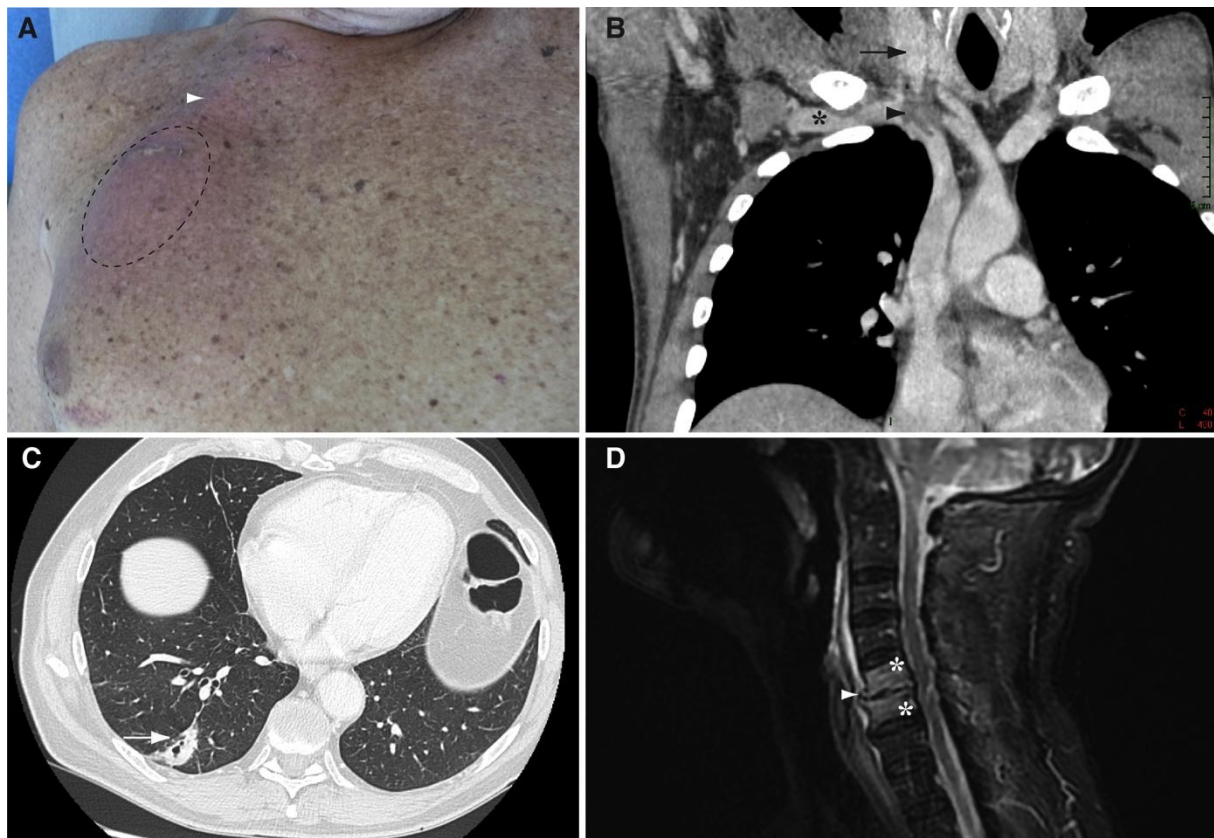
- 1 112 Warwick S, Wilks M, Hennessy E, et al. Use of quantitative 16S ribosomal DNA  
2 detection for diagnosis of central vascular catheter-associated bacterial infection. *J Clin*  
3 *Microbiol* 2004; **42**: 1402-8.
- 4 113 Guembe M, Marin M, Martin-Rabadan P, et al. Use of Universal 16S rRNA Gene  
5 PCR as a Diagnostic Tool for Venous Access Port-Related Bloodstream Infections. *J Clin*  
6 *Microbiol* 2013; **51**: 799-804.
- 7 114 Chalabaev S, Chauhan A, Novikov A, et al. Biofilm monitoring using biofilm specific  
8 biomarkers. *Biofilms 5 International Conference, 10-12th December 2012, Paris 2012*;
- 9 115 Meyer MH, Letscher-Bru V, Jaulhac B, Waller J, Candolfi E. Comparison of Mycosis  
10 IC/F and plus Aerobic/F media for diagnosis of fungemia by the bactec 9240 system. *J Clin*  
11 *Microbiol* 2004; **42**: 773-7.
- 12 116 Nguyen MH, Wissel MC, Shields RK, et al. Performance of *Candida* real-time  
13 polymerase chain reaction, beta-D-glucan assay, and blood cultures in the diagnosis of  
14 invasive candidiasis. *Clin Infect Dis* 2012; **54**: 1240-8.
- 15 117 Smith RS, Zhang Z, Bouchard M, et al. Vascular catheters with a nonleaching poly-  
16 sulfobetaine surface modification reduce thrombus formation and microbial attachment. *Sci*  
17 *Transl Med* 2012; **4**: 153ra32.
- 18 118 Turakhia MH, Cooksey KE, Characklis WG. Influence of a calcium-specific chelant  
19 on biofilm removal. *Appl Environ Microbiol* 1983; **46**: 1236-8.
- 20 119 Raad, II, Fang X, Keutgen XM, Jiang Y, Sherertz R, Hachem R. The role of chelators  
21 in preventing biofilm formation and catheter-related bloodstream infections. *Curr Opin Infect*  
22 *Dis* 2008; **21**: 385-92.
- 23 120 Bookstaver PB, Williamson JC, Tucker BK, Raad, II, Sherertz RJ. Activity of novel  
24 antibiotic lock solutions in a model against isolates of catheter-related bloodstream infections.  
25 *Ann Pharmacother* 2009; **43**: 210-9.
- 26 121 Raad I, Rosenblatt J, Reitzel R, Jiang Y, Dvorak T, Hachem R. Chelator-based  
27 catheter lock solutions in eradicating organisms in biofilm. *Antimicrob Agents Chemother*  
28 2013; **57**: 586-8.
- 29 122 Chauhan A, Lebeaux D, Ghigo JM, Beloin C. Full and broad-spectrum *in vivo*  
30 eradication of catheter-associated biofilms using gentamicin-EDTA antibiotic lock therapy.  
31 *Antimicrob Agents Chemother* 2012;
- 32 123 Allison KR, Brynildsen MP, Collins JJ. Metabolite-enabled eradication of bacterial  
33 persisters by aminoglycosides. *Nature* 2011; **473**: 216-20.
- 34 124 Cirioni O, Giacometti A, Ghiselli R, et al. RNAIII-inhibiting peptide significantly  
35 reduces bacterial load and enhances the effect of antibiotics in the treatment of central venous  
36 catheter-associated *Staphylococcus aureus* infections. *J Infect Dis* 2006; **193**: 180-6.
- 37 125 Pammi M, Liang R, Hicks JM, Barrish J, Versalovic J. Farnesol decreases biofilms of  
38 *Staphylococcus epidermidis* and exhibits synergy with nafcillin and vancomycin. *Pediatr Res*  
39 2011; **70**: 578-83.

- 1 126 O'Toole GA. Microbiology: Jekyll or hide? *Nature* 2004; **432**: 680-1.
- 2 127 Boles BR, Horswill AR. Agr-mediated dispersal of *Staphylococcus aureus* biofilms.  
3 *PLoS Pathog* 2008; **4**: e1000052.
- 4 128 Fey PD. Modality of bacterial growth presents unique targets: how do we treat  
5 biofilm-mediated infections? *Curr Opin Microbiol* 2010; **13**: 610-5.
- 6 129 Cobrado L, Silva-Dias A, Azevedo MM, Pina-Vaz C, Rodrigues AG. *In vivo*  
7 antibiofilm effect of cerium, chitosan and hamamelitannin against usual agents of catheter-  
8 related bloodstream infections. *J Antimicrob Chemother* 2012; **68**: 126-30.
- 9 130 Ebert T, Smith S, Pancari G, et al. Development of a rat central venous catheter model  
10 for evaluation of vaccines to prevent *Staphylococcus epidermidis* and *Staphylococcus aureus*  
11 early biofilms. *Hum Vaccin* 2011; **7**: 630-8.
- 12 131 Mansouri MD, Hull RA, Stager CE, Cadle RM, Darouiche RO. *In vitro* activity and  
13 durability of a combination of an antibiofilm and an antibiotic against vascular catheter  
14 colonization. *Antimicrob Agents Chemother* 2013; **57**: 621-5.
- 15 132 Castagnola E, Ginocchio F. Rescue therapy of difficult-to-treat indwelling central  
16 venous catheter-related bacteremias in cancer patients: a review for practical purposes. *Expert*  
17 *Rev Anti Infect Ther* 2013; **11**: 179-86.
- 18 133 Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the  
19 management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin*  
20 *Infect Dis* 2009; **48**: 503-35.
- 21 134 Nucci M, Anaissie E, Betts RF, et al. Early removal of central venous catheter in  
22 patients with candidemia does not improve outcome: analysis of 842 patients from 2  
23 randomized clinical trials. *Clin Infect Dis* 2010; **51**: 295-303.
- 24 135 Raad I, Hanna H, Boktour M, et al. Management of central venous catheters in  
25 patients with cancer and candidemia. *Clin Infect Dis* 2004; **38**: 1119-27.
- 26 136 Raad I, Hanna H, Dvorak T, Chaiban G, Hachem R. Optimal antimicrobial catheter  
27 lock solution, using different combinations of minocycline, EDTA, and 25-percent ethanol,  
28 rapidly eradicates organisms embedded in biofilm. *Antimicrob Agents Chemother* 2007; **51**:  
29 78-83.
- 30 137 Rane HS, Bernardo SM, Walraven CJ, Lee SA. *In vitro* analyses of ethanol activity  
31 against *Candida albicans* biofilms. *Antimicrob Agents Chemother* 2012; **56**: 4487-9.
- 32 138 Blackwood RA, Klein KC, Micel LN, et al. Ethanol locks therapy for resolution of  
33 fungal catheter infections. *Pediatr Infect Dis J* 2011; **30**: 1105-7.
- 34 139 Pieroni KP, Nespor C, Poole RL, Kerner JA, Jr., Berquist WE. Echinocandin and  
35 Ethanol Lock Therapy Treatment of Fungal Catheter Infections. *Pediatr Infect Dis J* 2013;
- 36 140 Longuet P, Douard MC, Arlet G, Molina JM, Benoit C, Lepout C. Venous access port-  
37 -related bacteremia in patients with acquired immunodeficiency syndrome or cancer: the  
38 reservoir as a diagnostic and therapeutic tool. *Clin Infect Dis* 2001; **32**: 1776-83.

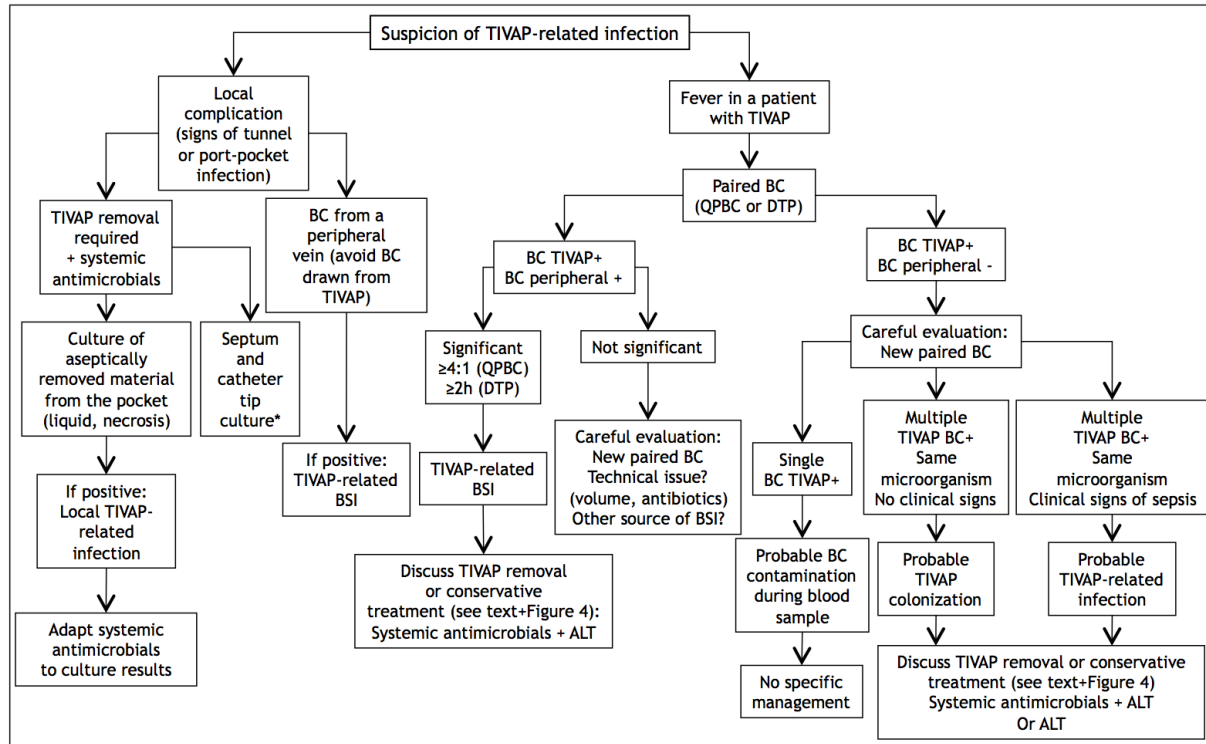


- 1 141 Domingo P, Fontanet A, Sanchez F, Allende L, Vazquez G. Morbidity associated with  
2 long-term use of totally implantable ports in patients with AIDS. *Clin Infect Dis* 1999; **29**:  
3 346-51.
- 4 142 Piketty C, Hoi AB, Gilquin J, et al. Failure of antibiotic therapy in *Staphylococcus*  
5 *epidermidis* infection of implantable venous access devices in patients with AIDS, as  
6 documented by molecular typing. *Clin Microbiol Infect* 1999; **5**: 190-4.
- 7 143 Reimund JM, Arondel Y, Finck G, Zimmermann F, Duclos B, Baumann R. Catheter-  
8 related infection in patients on home parenteral nutrition: results of a prospective survey. *Clin*  
9 *Nutr* 2002; **21**: 33-8.
- 10 144 Viale P, Pagani L, Petrosillo N, et al. Antibiotic lock-technique for the treatment of  
11 catheter-related bloodstream infections. *J Chemother* 2003; **15**: 152-6.
- 12 145 Koldehoff M, Zakrzewski JL. Taurolidine is effective in the treatment of central  
13 venous catheter-related bloodstream infections in cancer patients. *Int J Antimicrob Agents*  
14 2004; **24**: 491-5.
- 15 146 Fortun J, Grill F, Martin-Davila P, et al. Treatment of long-term intravascular catheter-  
16 related bacteraemia with antibiotic-lock therapy. *J Antimicrob Chemother* 2006; **58**: 816-21.
- 17 147 Souza Dias MB, Habert AB, Borrasca V, et al. Salvage of long-term central venous  
18 catheters during an outbreak of *Pseudomonas putida* and *Stenotrophomonas maltophilia*  
19 infections associated with contaminated heparin catheter-lock solution. *Infect Control Hosp*  
20 *Epidemiol* 2008; **29**: 125-30.
- 21 148 Del Pozo JL, Alonso M, Serrera A, Hernaez S, Aguinaga A, Leiva J. Effectiveness of  
22 the antibiotic lock therapy for the treatment of port-related enterococci, Gram-negative, or  
23 Gram-positive bacilli bloodstream infections. *Diagn Microbiol Infect Dis* 2009; **63**: 208-12.
- 24 149 Rajpurkar M, Boldt-Macdonald K, McLenon R, et al. Ethanol lock therapy for the  
25 treatment of catheter-related infections in haemophilia patients. *Haemophilia* 2009; **15**: 1267-  
26 71.
- 27 150 Valentine KM. Ethanol lock therapy for catheter-associated blood stream infections in  
28 a pediatric intensive care unit. *Pediatr Crit Care Med* 2011; **12**: e292-6.  
29  
30

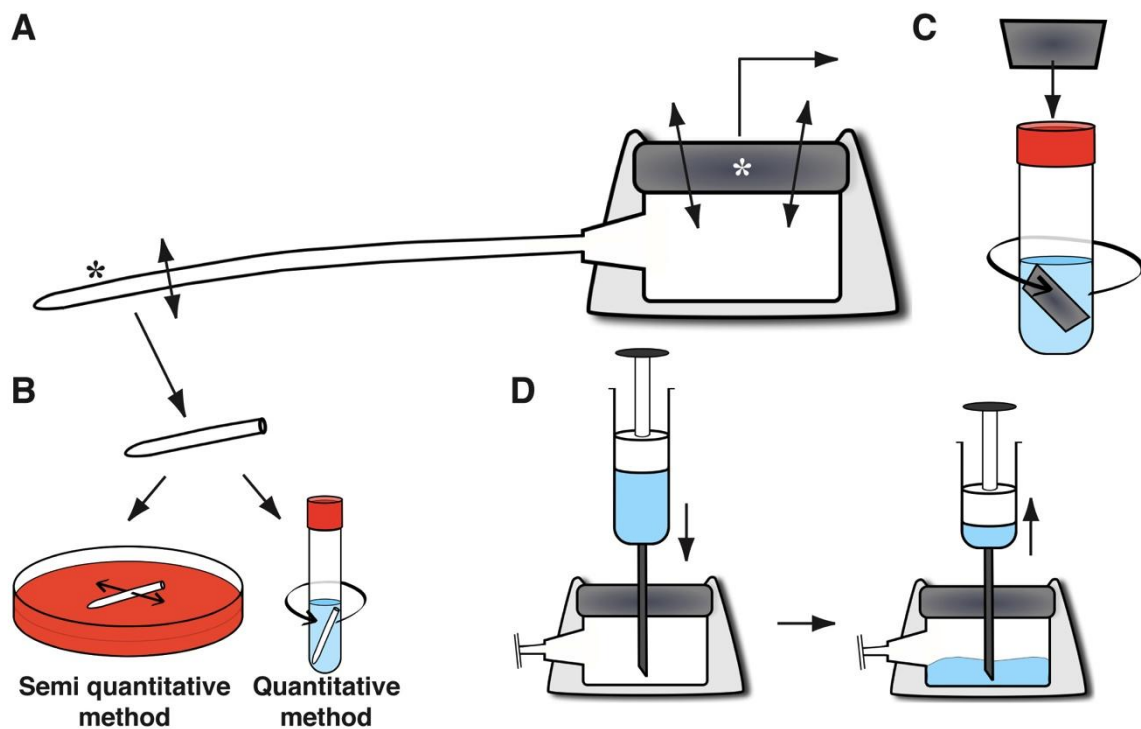
**Figure 1. Totally implantable venous access port (TIVAP)-related infections may lead to local and hematogenous complications. A.** Complicated local infection caused by *S. aureus* occurring six days after TIVAP surgical insertion with port-pocket infection (surrounded by black dashed line) and tunnel infection (white arrowhead). **B.** Thrombophlebitis diagnosed 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). TIVAP was inserted in the right subclavian vein. Coronal view of computed tomography (CT) scan of the chest after iodine-based contrast agent injection. **C.** Right pulmonary abscess (white arrow) with cavitation secondary to a *S. aureus* TIVAP-related BSI. Axial view of computed tomography (CT) scan of the chest. **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.<sup>29</sup>



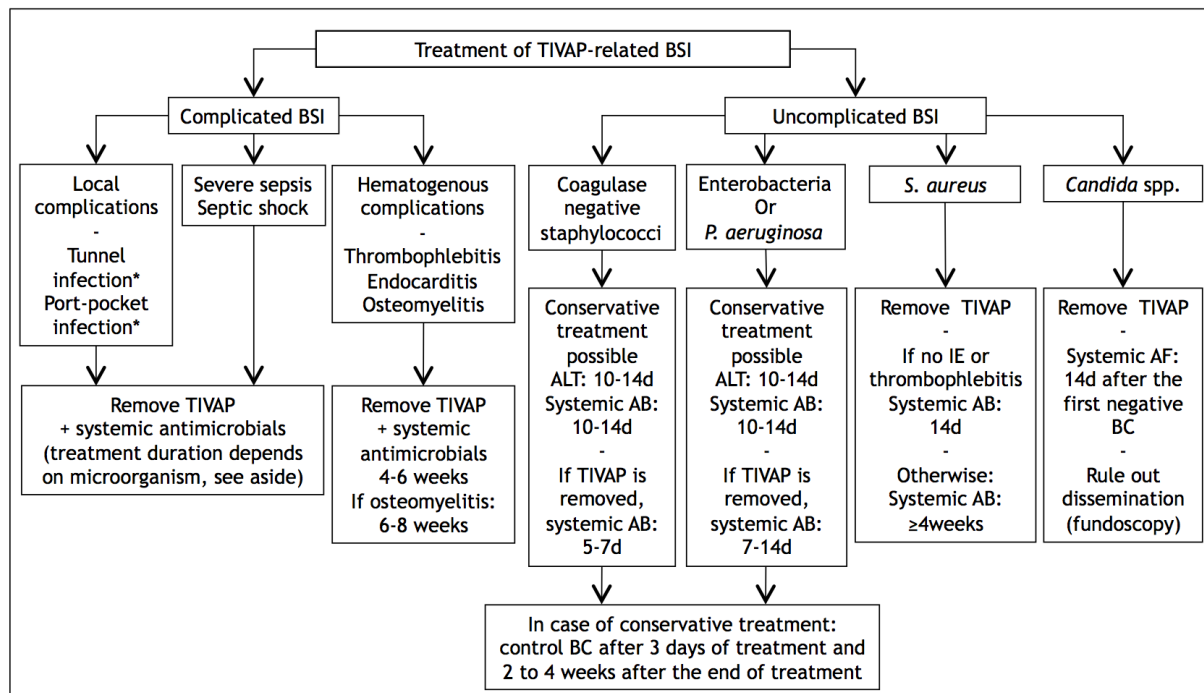
**Figure 2. Diagnostic algorithm in case of suspicion of totally implantable venous access port (TIVAP)-related infection.** ALT=antibiotic lock therapy. BC=blood cultures. BSI=bloodstream infection. DTP=differential time to positivity. QPBC=quantitative paired blood cultures. \*Using quantitative or semi-quantitative method, see text and Figure 3.<sup>4,71</sup>



**Figure 3. Microbiological methods for the diagnosis of totally implantable venous access port (TIVAP) colonization.** **A.** Schematic view of a removed TIVAP. Catheter tip (black star) is cut and the septum (white star) removed using sterile blade.<sup>71,72,140</sup> **B.** Culture of the catheter tip can be performed according to two methods. The semiquantitative method, also called roll-plate method or Maki-method during which catheter tip is rolled on blood agar plate.<sup>81</sup> Otherwise, catheter tip can be immersed in 1mL saline, vortexed or sonicated for CFU counting (quantitative or Brun-Buisson method).<sup>80</sup> **C.** After removal, the septum is immersed in saline, vortexed or sonicated for CFU counting.<sup>72,140</sup> **D.** In clinical microbiology laboratories not permitted to use cutting blades, an alternative method for port culture is to use a needle in order to inject a small volume of sterile saline (0.2mL) inside the reservoir then aspirated and plated on blood agar plate.<sup>29</sup> This approach is as sensitive and specific as catheter tip culture.<sup>29</sup>



**Figure 4. Treatment of totally implantable venous access port (TIVAP)-related bloodstream infection (BSI).** 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.<sup>4,71,133</sup>



**Table 1.** Published studies on antibiotic or ethanol lock therapy for the conservative treatment of bacterial totally implantable venous access port-related bloodstream infections.

Clinical studies, year-reference	No of episodes treated with ALT	Type of catheter†	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> <sup>141</sup>	27	100-0-0	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> <sup>142</sup>	31	100-0-0	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> <sup>140</sup>	16	100-0-0	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> <sup>7</sup>	60	86-14-0	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> <sup>143</sup>	25	64-36-0	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> <sup>144</sup>	30	37-40-23	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> <sup>145</sup>	11	100-0-0	Antineoplastic CT	11 (100)	Taurolidine (5)	No	1 [1-3]	11 (100) ‡	Undefined
2005-Rijnders B.J. <i>et al.</i> <sup>73</sup>	22	91-9-0	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> <sup>146</sup>	19	74-26-0	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-Fernández-Hidalgo N. <i>et al.</i> <sup>92</sup>	115	16-73-11	Antineoplastic CT, TPN, hemodialysis	115 (100)	VAN (2), AMK (2) or CIP (2)	Yes, 20	12 [8-14]	94 (82)	Clinical + negative BC 1 month after the end of ALT
2006-Onland W. <i>et al.</i> <sup>107</sup>	51	21-79-0	Mostly antineoplastic CT	51 (100)	Ethanol 70%	No	5	45 (88)	Clinical. No systematic BC
2008-Souza Dias M.B. <i>et al.</i> <sup>147</sup>	17	78-22-0	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> <sup>105</sup>	17	11-89-0	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> <sup>94</sup>	44	100-0-0	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> <sup>148</sup>	18	100-0-0	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> <sup>149</sup>	3	66-33-0	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> <sup>106</sup>	80	24-72-4	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> <sup>96</sup>	46	28-72-0	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> <sup>150</sup>	26	15-54-31	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> <sup>97</sup>	13	46-54-0	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.

‡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.