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

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1 **Review**

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

4

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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,  
6 formation of pathogenic biofilm in TIVAPs and subsequent infection are associated with  
7 morbidity, mortality and increased healthcare costs. In case of TIVAP-related infection, local  
8 and systemic complications, or infection related to specific pathogens may constitute  
9 indications for device removal. Alternatively, conservative treatment can be proposed with  
10 the combination of systemic antibiotics and antibiotic lock therapy. In light of recent *in vitro*  
11 and *in vivo* fundamental or clinical research addressing epidemiology, diagnosis and  
12 prevention of TIVAP-related infections, with a particular focus on antibiotic lock therapy, this  
13 review presents current challenges and promising strategies to improve the management of  
14 TIVAP-related infections even if some of them are still at an early developmental stage and  
15 need clinical validation.

16

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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 July 2013 including totally implantable venous access  
4 port (TIVAP)-related infections for any indication of TIVAP insertion. We restricted studies  
5 by use of the terms: “Totally implantable venous access”, “Totally Implantable port”, “Port-a-  
6 cath”, "Catheters, Indwelling", “Central venous catheter”, “Port-a-cath infection”, “Port-  
7 pocket infection”, "Catheter-Related Infections", "Bloodstream infections", "Bacteremia" and  
8 “Infection”. We focused on studies assessing TIVAP-related infections epidemiology, risk  
9 factors, microbiology, diagnosis, prevention, treatment and prognosis. Regarding treatment,  
10 we also included the following key-words: “Sepsis/prevention & control”, “Catheter-Related  
11 Infections/drug therapy”, “Bacteremia/drug therapy”, “antibiotic lock therapy”, “ethanol  
12 lock”, “antibiotic lock technique”, “antifungal lock therapy”. For epidemiologic or therapeutic  
13 studies including different types of long-term intravascular catheters (LTIVC), we retained  
14 them if specific data about TIVAP were described. Articles resulting from these searches and  
15 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 into 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 inserted for the administration of antineoplastic chemotherapy, parenteral  
14 nutrition, blood products and for prolonged antimicrobial treatment in CF.<sup>2,6,7</sup> The number of  
15 implanted TIVAPs is increasing and more than 400,000 of them are sold each year in the  
16 USA.<sup>8</sup> 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.<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>6,9,10,13-17</sup> In cancer patients, the risk of TIVAP-related  
6 infection appears to remain unchanged with incidence densities of 0·21 and 0·20/1,000  
7 catheter-days reported in 1993 and 2011, respectively.<sup>9,13</sup>

8 If TIVAP is used for total parenteral nutrition (TPN), incidence density of infection is higher  
9 and is comprised between 0·33 and 3·2/1000 catheter-days with heterogeneous data  
10 depending on the indication for TPN.<sup>7,18,19</sup> In HIV-infected patients, incidence density ranges  
11 from 1·5 to 3·81/1,000 catheter-days, probably because when a LTIVC is required, these  
12 patients combine most of the risk factors of infection identified so far.<sup>20,21</sup> The reported time  
13 to infection from TIVAP insertion ranges from 80 to 192 days with extreme values of 2 and  
14 1406 days.<sup>10,13,20,21</sup>

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

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

31 Regarding antibiotic resistance, a French cohort of cancer patients reported that 58% of CoNS  
32 and 25% of *S. aureus* were methicillin-resistant (MR).<sup>24</sup> MR is more frequent in the USA as  
33 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.<sup>25,26</sup>

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.<sup>27-29</sup> 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.<sup>30</sup>

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.<sup>27,31</sup> 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.<sup>32</sup>

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.<sup>11,30</sup> Biofilm bacteria exhibit tolerance  
20 defined as the ability to survive high concentrations of antibiotics.<sup>33</sup> 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.

25  
26

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

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

9

### 10 *Preventive measures during TIVAP insertion*

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

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

29

### 30 *Preventive measures after TIVAP insertion*

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

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

9

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

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

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

32 Taurolidine, a derivative from of the amino acid taurine, was proposed as a lock therapy in  
33 1993 because of its antimicrobial effect against a broad range of microorganisms *in vitro*.<sup>58-60</sup>  
34 Although studies conducted in hemodialysis patients are encouraging, data supporting its use

1 as a lock in TIVAP are limited.<sup>61,62</sup> 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.<sup>63</sup> 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 tunneled catheters.<sup>59</sup> 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).<sup>64</sup> 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.<sup>65,66</sup> 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.<sup>27</sup> 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.<sup>67</sup> 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).

20  
21

## 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>68</sup>

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).<sup>68</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>68</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>68</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>68</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>24,69,70</sup> 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.<sup>24,71</sup> Peripheral blood cultures should also be performed to rule out an associated  
27 BSI (Figure 2).

28

### 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.<sup>68</sup> 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.<sup>68,72,73</sup> Another  
34 critical point is to precisely label the origin of each blood culture bottle.<sup>68</sup> The two most

1 commonly used methods for diagnosing CRBSI are simultaneous quantitative blood cultures  
2 and the differential time to positivity (DTP) of qualitative blood cultures.<sup>72,74-76</sup> If TIVAP is  
3 the source of BSI, the inoculum will be higher in the blood drawn from TIVAP, as compared  
4 with peripheral vein, therefore leading to a shorter time to positivity (difference  $\geq$  two hours)  
5 or a higher bacterial quantification ( $\geq$ four-fold).<sup>68,72,73,75,76</sup> When used for the diagnosis of  
6 LTIVC-related BSI, these two methods have sensitivity above 90% and specificity close to  
7 100% and between 75% and 91% for quantitative paired blood cultures and DTP,  
8 respectively.<sup>72,75,76</sup> They are nevertheless considered equivalent in recent guidelines and the  
9 choice of a technique will mostly rely on local equipment and training.<sup>68</sup>  
10 To reduce the risk of contamination when blood is drawn from TIVAP, a rigorous skin  
11 disinfection is mandatory before sampling (see “Prevention” section).<sup>68</sup>

12

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

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

30

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

32 Without TIVAP removal, such a diagnosis is challenging as studies assessing paired blood  
33 cultures infrequently included study of fungal infections<sup>72,74,75,80</sup> Some authors have proposed  
34 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±2h) than  
2 candidemia from another source (38±3h).<sup>81</sup> 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).<sup>82</sup>

#### 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).<sup>24</sup> Recent guidelines recommend systematic transesophageal echocardiography in case of  
12 *S. aureus* TIVAP-related BSI.<sup>68</sup> 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.<sup>83-87</sup> 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).<sup>68,88</sup>

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.<sup>68</sup>

21

## 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>68</sup>

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

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

24

### 25 *How to perform ALT?*

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

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

10

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

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

18 Conservative treatment of GNR TIVAP-related BSI is associated with a cure rate between  
19 87% and 95%, when local or distant complications are excluded.<sup>89,93</sup> Although recent  
20 guidelines suggest TIVAP removal in the case of *P. aeruginosa* infection, *Pseudomonas* spp.  
21 have also been included in clinical ALT studies, with the same success rates as  
22 *Enterobacteriaceae*. Fluoroquinolones and aminoglycosides are the antimicrobials most  
23 commonly used for these infections.<sup>89,93</sup>

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

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

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

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

#### 7 8 *Recently developed locks*

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

21

22

## 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>69,73,80,108,109</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>110,111</sup> Whereas these methods are more sensitive than  
13 cultures in case of previous antibiotic administration, their reduced specificity of ~80% due to  
14 false-positive results (external DNA contamination during procedure) leads to other  
15 diagnostic challenges. Other groups have tried to identify biomarkers of biofilm formation  
16 inside the port that would allow an earlier diagnosis of colonization before the onset of BSI.  
17 For instance, certain LPS modifications are only occurring within Gram-negative bacterial  
18 biofilms.<sup>112</sup>

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

22

### 23 *Prevention*

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

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

4

#### 5 *Biofilm eradication inside TIVAP*

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

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

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

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

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

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*.<sup>125,126</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>31,127-130</sup>

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.

16

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

3  
4 *Modifiable risk factors*

5 -Frequency of TIVAP handling with an OR of 1.15 [1.03-1.3] for each 10% increase of the  
6 frequency of LTIVC handling, especially among HIV-infected patients.<sup>21</sup>

7 -Use of total parenteral nutrition, because of a more frequent access to TIVAP, and because of  
8 fluids such as lipid products that can increase microbial growth.<sup>7</sup> OR=28.5 [4.2-200].<sup>131</sup>

9 -Difficulties during insertion (*i.e.* when several punctures are required) through formation of  
10 local thrombus or hematoma that increase the risk of bacterial colonization. OR=25.6 [4.2-  
11 106].<sup>131</sup>

12  
13 *Non-modifiable risk factors*

14 -Age with a threshold depending on each study. <7 year-old,<sup>13</sup> < 10 year-old (OR=18.4 [1.9-  
15 106.7]);<sup>131</sup> < 40 year-old.<sup>10</sup>

16 -Chemotherapy for hematologic malignancies rather than solid tumors.<sup>13,132</sup> OR=5.1 [1.5-  
17 17.5].<sup>133</sup>

18 -Hematopoietic stem cell transplantation, OR=1.74 [1.1-2.4].<sup>23</sup>

19 -Reduced autonomy, as expressed by a Karnofsky performance status  $\leq$  80%, in cancer  
20 patients, OR=5.3 [1.5-19.3].<sup>21</sup>

21 -Presence of metastases in cancer patients, OR=4.1 [0.9-19.5].<sup>21</sup>

22 -Bacterial infection within the prior month, OR=2.1 [1.1-3.8] in HIV-infected patients and  
23 OR=5.4 [1.2-25.3] in cancer patients.<sup>21</sup>

24 -Neutropenia among HIV-infected patients, OR=1.8 [1.1-3.1]<sup>21</sup> and patients with  
25 hematological malignancies, OR=15.1 [2.6-86.5].<sup>36</sup>

26 -Diabetes in CF-patients.<sup>6</sup>

27  
28 To note, no study identified a specific class of antineoplastic chemotherapy or radiation  
29 therapy as being risk factors of TIVAP-related infection.

1 **Panel 2. Future challenges regarding TIVAP and candidemia.**

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

14 In case of CR candidemia, even if catheter removal is recommended, many patients cannot  
15 afford a CVC replacement because of their general condition. Therefore, antifungal lock  
16 therapy has been proposed to increase the likelihood of biofilm eradication, based on the same  
17 principles as ALT.<sup>100</sup> *In vitro* and *in vivo* studies reveal that against *Candida* biofilms: i)  
18 azoles have poor activity; ii) lipid formulations of amphotericin B are more effective than  
19 amphotericin B deoxycholate; and iii) echinocandins have excellent *in vitro* activity.<sup>100</sup> Non-  
20 antifungal lock therapy against *Candida* biofilms have also been proposed such as EDTA in  
21 combination with antifungals or minocycline, ethanol, heparin and even highly concentrated  
22 antibiotics like doxycycline.<sup>100,137-140</sup> Even if no comparative study is available, more than 20  
23 patients were treated with various types of antifungal locks with an overall success rate of  
24 77% with a publication bias that should be taken into account.<sup>100</sup> Hence, ethanol lock therapy  
25 could be a promising candidate with eight successes among ten reported patients.<sup>139,140</sup> Of  
26 note, most of these published cases are of pediatric patients with the limitation of diagnostic  
27 criteria, frequently based on blood cultures drawn from the CVC without any peripheral blood  
28 culture. Studies of antifungal lock therapy specifically for TIVAP-associated fungal infections  
29 are clearly needed.

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

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25

26

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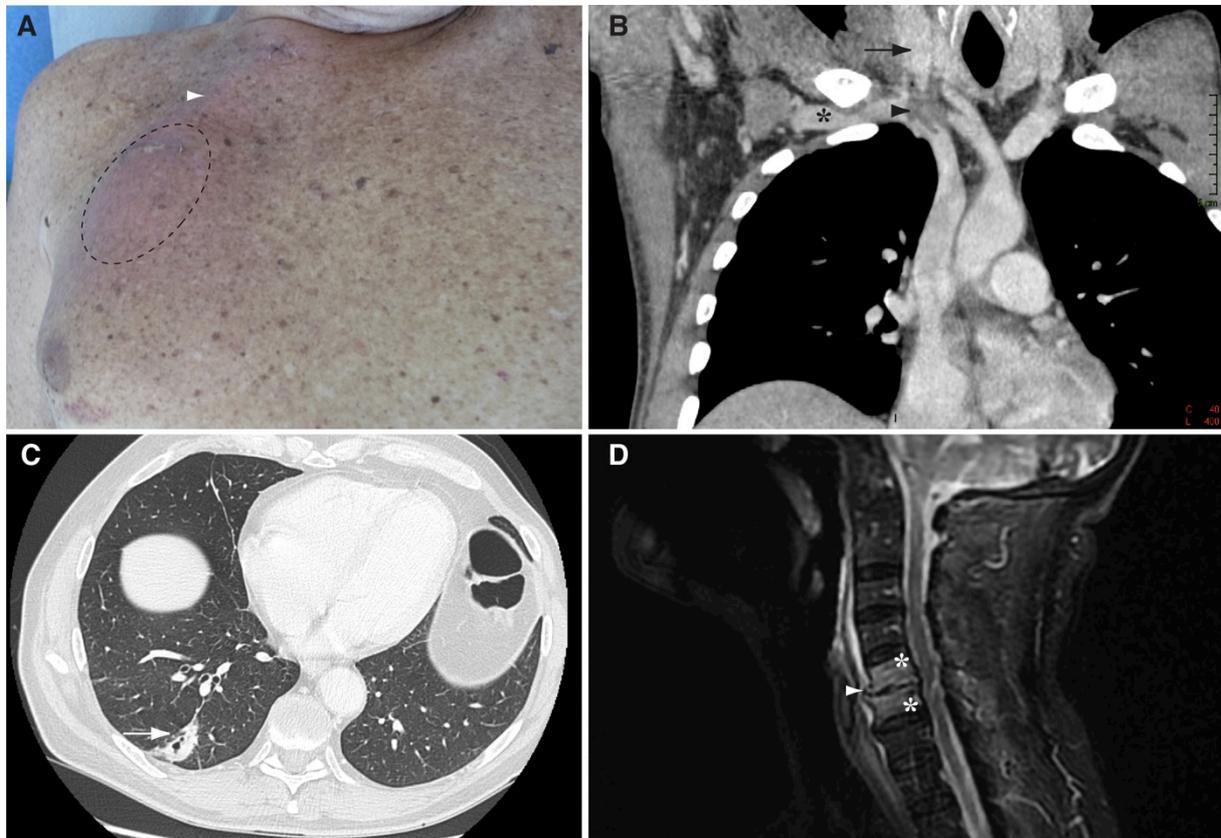
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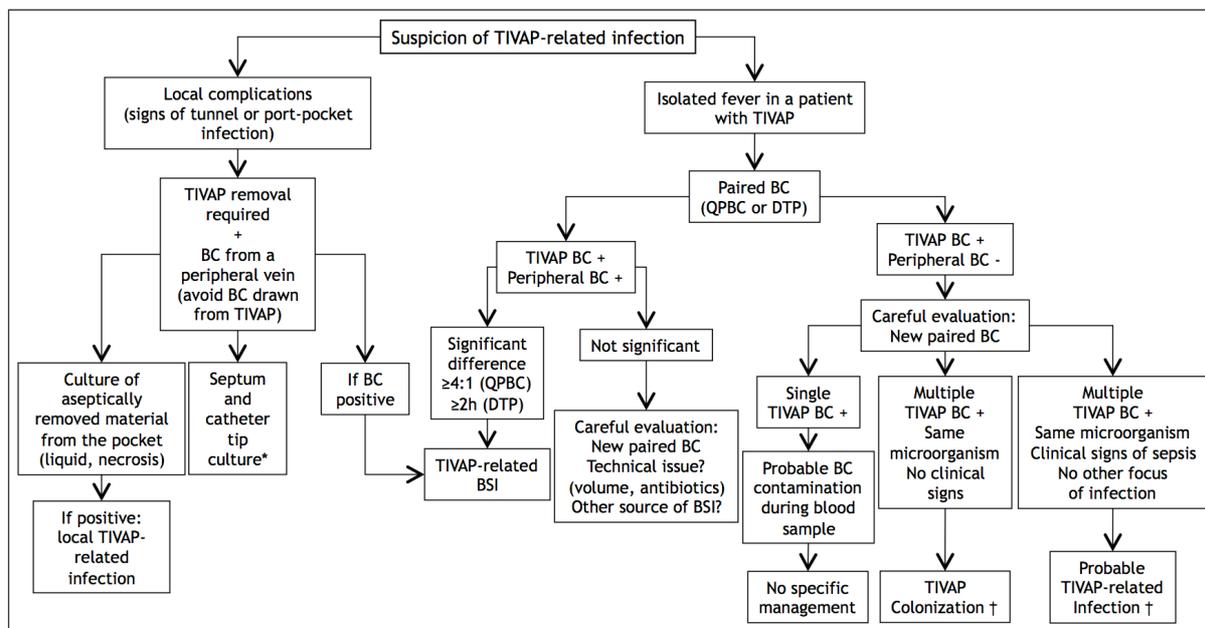
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**Figure 1. Totally implantable venous access port (TIVAP)-related infections may lead to local and hematogenous complications. A.** Port-pocket infection (surrounded by black dashed line) and tunnel infection (white arrowhead) caused by *S. aureus*. **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.<sup>24</sup>

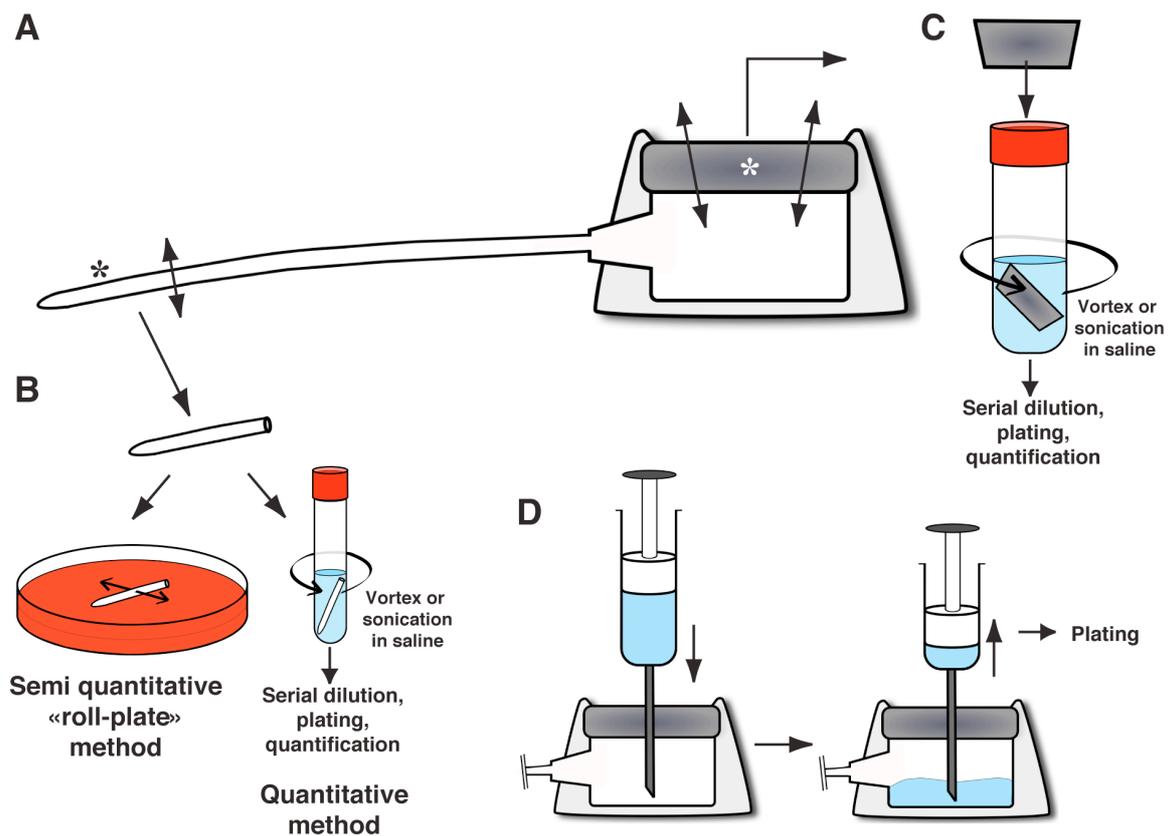


**Figure 2. Diagnostic algorithm in case of suspicion of totally implantable venous access port (TIVAP)-related infection.** ALT=antibiotic lock therapy. BC=blood cultures. BSI=bloodstream infection. DTP=differential time to positivity. QPBC=quantitative paired blood cultures. \*Using quantitative or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

† 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.<sup>68,69,141</sup> 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.<sup>77,78</sup> **C.** After removal, the septum is immersed in saline, vortexed or sonicated for CFU counting.<sup>69,141</sup> **D.** In CML not permitted to use cutting blades, sterile saline (0.2mL) can be injected inside the reservoir then aspirated and plated.<sup>24</sup> Swabbing of the internal surface of the port after septum removal is also proposed.<sup>111,142</sup> 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.<sup>143</sup>

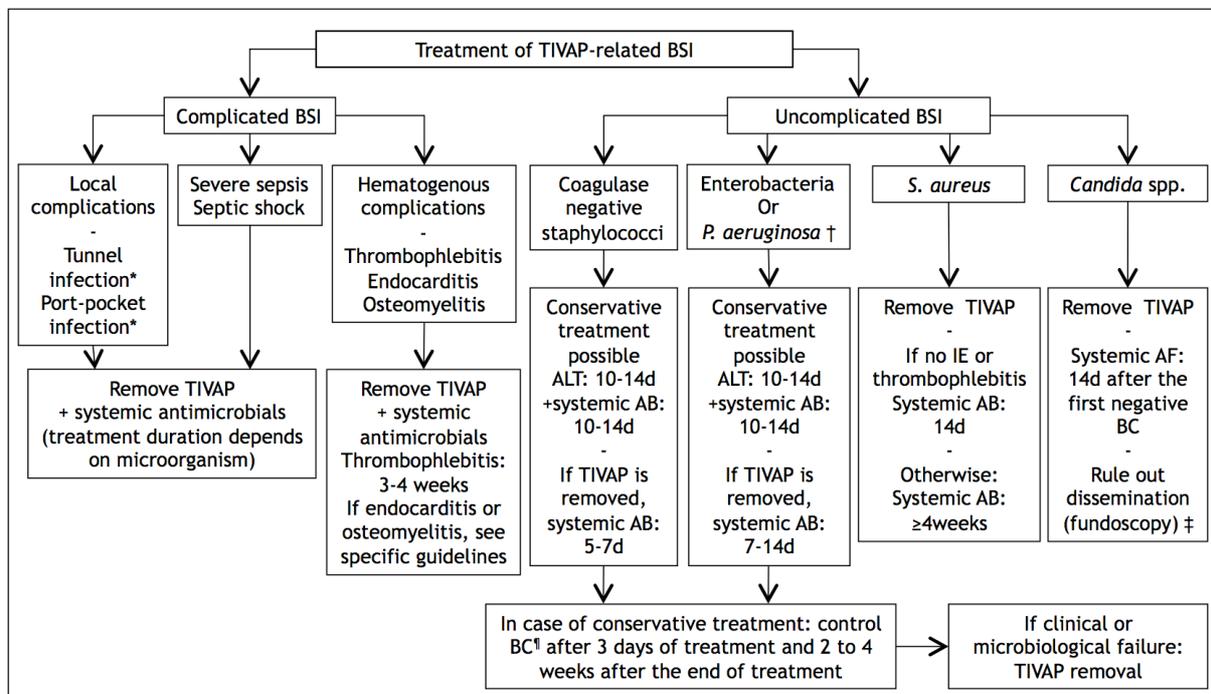


**Figure 4. Treatment of totally implantable venous access port (TIVAP)-related bloodstream infection (BSI), according to IDSA guidelines.<sup>68</sup> AB=antibiotic.**

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>4,68,134</sup>

† In case of *P. aeruginosa* TIVAP-related BSI, IDSA guidelines suggest that TIVAP removal is the first-line option.<sup>68</sup> ‡ In 2009 IDSA guidelines, only ophthalmological examination is recommended for all patients although some clinicians also propose echocardiography and CT-scan.<sup>134</sup> ¶ The source of the blood to be drawn is debated and some authors perform BC only from a peripheral vein or from TIVAP.<sup>102</sup> 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.<sup>68</sup>



**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> <sup>144</sup>	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> <sup>145</sup>	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> <sup>141</sup>	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> <sup>7</sup>	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> <sup>146</sup>	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> <sup>147</sup>	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> <sup>148</sup>	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> <sup>70</sup>	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> <sup>149</sup>	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> <sup>105</sup>	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> <sup>150</sup>	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> <sup>103</sup>	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> <sup>91</sup>	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> <sup>151</sup>	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> <sup>152</sup>	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> <sup>104</sup>	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> <sup>93</sup>	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> <sup>153</sup>	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> <sup>94</sup>	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.