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Review

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

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Summary

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

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

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

Depending on the indication for TIVAP insertion, patients are exposed to different risk factors and therefore exhibit different infection rates. For instance, if TIVAP is inserted for antineoplastic chemotherapy or in CF patients, the incidence density of infection ranges from 0·11 to 0·37/1,000 catheter-days. In cancer patients, the risk of TIVAP-related infection appears to remain unchanged with incidence densities of 0·21 and 0·20/1,000 catheter-days reported in 1993 and 2011, respectively. If TIVAP is used for total parenteral nutrition (TPN), incidence density of infection is higher and is comprised between 0·33 and 3·2/1000 catheter-days with heterogeneous data depending on the indication for TPN. In HIV-infected patients, incidence density ranges from 1·5 to 3·81/1,000 catheter-days, probably because when a LTIVC is required, these patients combine most of the risk factors of infection identified so far. The reported time to infection from TIVAP insertion ranges from 80 to 192 days with extreme values of 2 and 1406 days. These discrepancies between patient groups probably reflect exposure towards different risk factors and TIVAP handling frequency. Indeed, a prospective study demonstrated that the frequency of LTIVC handling (including about 50% of TIVAP) was associated with infection incidence. Additional risk factors are described in Panel 1. Since frequency of TIVAP handling is one of the major risk factor identified, it is not surprising to observe that coagulase-negative staphylococci (CoNS), which are frequent colonizers of the human skin and mucosal flora, are one of the leading pathogens responsible for TIVAP-related infections. For instance, among 29 cases of TIVAP-related infections, a majority of infections (57%) were caused by CoNS, other microorganisms being Gram-negative rods (GNR) (20%), S. aureus (7%) and C. albicans (3%). More recent studies described a higher rate of GNR (up to 40%) and yeasts (up to 23%). This shift may be explained by different factors such as antineoplastic chemotherapy intensification with more sustained neutropenia allowing translocation of microorganisms from the gut to bloodstream, besides more frequent use of TPN and broad-spectrum antibiotics. To note, early TIVAP-related infections (≤30 days) are more frequently caused by S. aureus than late infections (50% vs. 12%, respectively). Regarding antibiotic resistance, a French cohort of cancer patients reported that 58% of CoNS and 25% of S. aureus were methicillin-resistant (MR). MR is more frequent in the USA as suggested by data reported by the National Healthcare Safety Network and also in a study of
S. aureus catheter-related bloodstream infection (CRBSI) in cancer patients, with 37 to 55% of S. aureus being MR.\textsuperscript{25,26} As TIVAPs are totally implanted, risk of extraluminal colonization is low and mostly occurs during TIVAP insertion, resulting in surgical site infection. Once the device is inserted, contamination may occur during repeated punctures with Huber needles, if the skin has not been completely cleaned, therefore leading to an intraluminal colonization that can spread from the port to the catheter tip.\textsuperscript{27-29} In case of BSI coming from another focus of infection, bacteria may adhere on the catheter tip, therefore defining a hematogenous route of colonization, which is rare except in case of S. aureus. After device contamination, bacteria adhere to the internal or external surface of TIVAP, depending on the source of contamination, using proteinaceous stalks called adhesins.\textsuperscript{30} Bacterial adhesion is influenced by the type of catheter material, bacterial characteristics or by the presence of a layer of blood components. Indeed, once an indwelling device is inserted, a conditioning film made of host components like fibrin or platelets covers it.\textsuperscript{27,31} These deposits may enhance or inhibit bacterial adhesion besides reducing the efficacy of any antibiotic-releasing surface. After several days, all catheters get covered by a fibrin sheath.\textsuperscript{32} Following adhesion, bacteria multiply and constitute a surface-associated microbial community called a biofilm, which is embedded in a matrix of extracellular polymeric substances produced by both bacteria and the host.\textsuperscript{11,30} Biofilm bacteria exhibit tolerance defined as the ability to survive high concentrations of antibiotics.\textsuperscript{33} Thus, systemic antibiotics can cure TIVAP-related BSI but the source of infection cannot be eradicated unless the device is removed or intraluminal treatment used. This high tolerance is responsible for infection relapse with the same pathogen. Preventive approaches are therefore pivotal in order to avoid any microbial contamination and subsequent biofilm formation.
Preventive strategies to reduce risks of colonization

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

Preventive measures during TIVAP insertion

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

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

Preventive measures after TIVAP insertion

Training of patients, nursing teams and physicians is mandatory to minimize the risk of bacterial contamination. The Huber needle used to access the TIVAP must be inserted by trained nurses and requires that operators wear a facial mask, a cap and use sterile gloves. Skin disinfection must be performed with an alcoholic antiseptic, prior to each needle
insertion (see above). The Huber needle can be changed every seven days if vascular access is maintained continuously. During needle withdrawal, an experimental study suggested that positive pressure using saline injection reduces the risk of blood reflux, therefore preventing catheter tip occlusion. It is now recommended that heparin lock or flush after TIVAP use should not be performed, as sterile saline locks are equally efficient to prevent functional or infectious complications. Even if different studies demonstrated the benefits of chlorhexidine-impregnated sponges or dressings for the prevention of CRBSI in intensive care units, no studies including TIVAP have been published.

Lock solutions and coatings to prevent TIVAP-related infections

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

Limited data are available for non-antibiotic lock solutions, such as ethanol- or taurolidine-locks. One preliminary pediatric study using ethanol locks including 12 patients with TIVAP was interrupted as 3 patients experienced TIVAP occlusion. A meta-analysis showed that ethanol lock therapy reduces the incidence of CRBSI in pediatric TPN with tunnelled catheters but increases the risk of thrombosis. Therefore, ethanol lock could be proposed in cases of high-risk TPN patients with tunnelled catheters. Mild and self-limited adverse effects have been reported, especially after flushing the lock, such as dizziness, nausea, headaches, facial flushing and, eventually, an alcohol taste in the mouth. Taurolidine, a derivative from of the amino acid taurine, was proposed as a lock therapy in 1993 because of its antimicrobial effect against a broad range of microorganisms in vitro. Although studies conducted in hemodialysis patients are encouraging, data supporting its use
as a lock in TIVAP are limited.\textsuperscript{61,62} In pediatric cancer patients, an initial study showed no significant reduction of CRBSI with taurolidine/citrate as compared to heparin, with \textasciitilde75\% of TIVAP patients amongst LTIVC.\textsuperscript{63} A more recent study in pediatric hematology patients showed a significant reduction of CRBSI with taurolidine/citrate as compared to heparin but included only tunneled catheters.\textsuperscript{59} A randomized study in TPN patients demonstrated that taurolidine/citrate reduced the rate of CRBSI when initiated after the first episode of infection, as compared with heparin (TIVAP represented \textasciitilde40\% of LTIVC).\textsuperscript{64} Based on these results, larger comparative studies with TIVAP are needed to define the precise role and indications of ethanol or taurolidine as preventive locks.

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

TIVAP-related infection is easily suspected if the patient exhibits local signs such as pain or erythema at the site of TIVAP implantation. However, diagnosis is more difficult in case of isolated fever, chills or severe sepsis. Recent IDSA guidelines have proposed three classes of TIVAP-related infections:\(^6^8\)

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

- TIVAP-related BSI, defined as a positive blood culture drawn from a peripheral vein associated with evidence that the BSI originates from the TIVAP using paired blood cultures or culture of a component of the removed TIVAP (see below). TIVAP-related BSI can therefore be defined with or without device removal.\(^6^8\)

- Catheter-related infection, defined by the association of local or general signs of infection and a positive culture of the catheter tip.\(^6^8\)

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

Diagnosis of local infection

Clinical signs of local infection such as erythema or purulent exudate at the site of TIVAP implantation has high specificity, but little sensitivity for the diagnosis of TIVAP-related infection.\(^6^8\) Indeed, local signs are reported in only 7 to 12% of TIVAP-related BSI and as local infections are caused by extraluminal contamination, they can occur without any concomitant BSI.\(^2^4,6^9,7^0\) Erythema can also be caused by non-infectious factors such as allergy. To confirm local infection, a positive culture of aseptically removed material surrounding the port such as purulent fluid, skin necrosis or swabbing of the port surface is mandatory.\(^2^4,7^1\) Peripheral blood cultures should also be performed to rule out an associated BSI (Figure 2).

Diagnosis of TIVAP-related BSI without device removal

This diagnosis relies on the identification of the same microorganism in paired blood cultures.\(^6^8\) Correct interpretation of the test requires blood samples to be performed consecutively, with the same volume of blood drawn from a peripheral vein and from the TIVAP through a Huber needle, ideally before the initiation of antimicrobials.\(^6^8,7^2,7^3\) Another critical point is to precisely label the origin of each blood culture bottle.\(^6^8\) The two most
commonly used methods for diagnosing CRBSI are simultaneous quantitative blood cultures and the differential time to positivity (DTP) of qualitative blood cultures.\textsuperscript{72,74-76} If TIVAP is the source of BSI, the inoculum will be higher in the blood drawn from TIVAP, as compared with peripheral vein, therefore leading to a shorter time to positivity (difference ≥ two hours) or a higher bacterial quantification (≥ four-fold).\textsuperscript{68,72,73,75,76} When used for the diagnosis of LTIVC-related BSI, these two methods have sensitivity above 90% and specificity close to 100% and between 75% and 91% for quantitative paired blood cultures and DTP, respectively.\textsuperscript{72,75,76} They are nevertheless considered equivalent in recent guidelines and the choice of a technique will mostly rely on local equipment and training.\textsuperscript{68}

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

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

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

**Diagnosis of fungal TIVAP-related BSI**

Without TIVAP removal, such a diagnosis is challenging as studies assessing paired blood cultures infrequently included study of fungal infections\textsuperscript{72,74,75,80} Some authors have proposed to use the time taken to detect *Candida* spp. growth in peripheral blood as a diagnostic tool,
since time to positivity is shorter in case of catheter-related (CR) candidemia (17±2h) than candidemia from another source (38±3h). The objective of this approach would be to rule out the catheter as the source of candidemia if time to positivity is above 30 hours. In case of TIVAP removal, microbiological methods and thresholds are the same, and culture on blood agar is sensitive enough for the growth of fungi involved in TIVAP-related infections, even if they may require a longer incubation time than bacteria (24-72h).

Workup to rule out complications
When TIVAP-related BSI is suspected, clinicians should look for infectious complications such as severe sepsis, endocarditis, or other hematogenous complications (Figures 1B, C and D). Recent guidelines recommend systematic transesophageal echocardiography in case of S. aureus TIVAP-related BSI. Nevertheless, it is very likely that in selected patients without intracardiac devices and with rapid clearance of BSI, a transthoracic echocardiography performed at least 5 days after BSI onset can safely rule out infective endocarditis. In case of clinical signs of thrombophlebitis or persistent BSI despite appropriate systemic antimicrobial therapy, venous ultrasonographic examination should be performed, especially in case of S. aureus TIVAP-related BSI (Figure 1B). Whatever the microorganism, persistent BSI after 3 days of adequate antimicrobials should prompt a complete workup including echocardiography and, venous ultrasonographic examination with or without a computed tomography (CT)-scan.
Treatment: should TIVAP be removed or retained?

In the case of CRBSI, the treatment of choice is systemic antimicrobial therapy in conjunction with removal of the colonized device. However, in case of TIVAPs, reduced venous access, potential presence of coagulation disorders, the need for a new procedure and its cost, all argue in favor of attempting a catheter salvage, if the clinical situation allows it. TIVAP removal is mandatory, regardless of the microbial etiology, in case of complicated TIVAP-related infection defined by tunnel or port-pocket infections, severe sepsis or septic shock, endocarditis, septic thrombophlebitis, osteomyelitis or other hematogenous seeding, as suggested by IDSA guidelines (Figure 1 and 4). Furthermore, infections caused by *S. aureus* or *Candida* spp. warrant TIVAP removal, except in exceptional circumstances (see below) (Figure 4). If a conservative strategy is decided upon, the TIVAP should be removed in case of persistent positive blood cultures 72 hours after the initiation of antibiotics. In case of uncomplicated TIVAP-related BSI not caused by *S. aureus* or *Candida* spp., a conservative treatment using a combination of systemic antimicrobials and ALT can be considered. Indeed, as most of LTIVC-related infections are associated with intraluminal colonization, instillation of high concentrations of antimicrobial solution filling the entire volume of the lumen and dwelling for an extended period of time may allow sterilization of the device. Despite several limitations, there is a growing body of evidence favoring the use of ALT. For instance, a randomized, placebo-controlled study showed that ALT plus systemic antimicrobial therapy is more effective than systemic antimicrobial therapy alone for treating LTIVC-related BSI, although not reaching statistical significance due to the small sample size. In addition, large uncontrolled studies demonstrated high cure rates in patients with uncomplicated LTIVC-related BSI due to CoNS (89%) or GNR (95%) (Table 1).

How to perform ALT?

No clinical trials have compared one drug to another and some *in vitro* studies have given conflicting results with mitigated clinical relevance. As described in Table 1, more frequently used antibiotics are glycopeptides, aminoglycosides or fluoroquinolones and their use has been associated with high rates of therapeutic success. The chosen antibiotic must be active *in vitro* against the identified microorganism. Ideally, antimicrobials should be administered at a concentration at least 1000-fold above the minimal inhibitory concentration (MIC) (frequently between 1 and 5 mg/mL) with a volume that fills the entire TIVAP lumen. In most studies, ALT is prescribed for 10 to 14 days (Table 1) and the lock solution is usually replaced every 12 to 24 hours, depending on the necessity for vascular access. Replacing the
solution every 48 or 72 hours has also been performed safely.\textsuperscript{93} In case of TIVAP-related BSI, systemic antimicrobials should always be administered for 10 to 14 days.\textsuperscript{68} Addition of heparin in ALT has been proposed to avoid thrombosis of the catheter but no comparative data support its use and adverse effects have been reported such as bleeding or the enhancement of \textit{S. aureus} biofilm formation \textit{in vitro}.\textsuperscript{96,97} Therefore, ALT can be performed in saline or heparin, at 10 to 100 IU/mL (Table 1).\textsuperscript{68} In case of conservative treatment, close follow-up is mandatory to detect treatment failure and includes, at least, blood cultures performed 3 days after the beginning of the treatment and 2-4 weeks after the end of the treatment (Figure 4).

\textit{Adapting treatment to the identified microorganism (Figure 4)}

In case of uncomplicated CoNS infection, the cure rate of ALT is high (>80%), and failures are mainly due to relapses during the first month of follow-up.\textsuperscript{89,91} In case of treatment failure or recurrence of infection, TIVAP removal should be considered. Glycopeptides for 10 to 14 days have been extensively used and a prospective uncontrolled study identified a trend toward a higher success rate with teicoplanin as compared to vancomycin.\textsuperscript{89,91} Additionally, daptomycin can be considered as a possible alternative (see below).\textsuperscript{94,95} Conservative treatment of GNR TIVAP-related BSI is associated with a cure rate between 87% and 95%, when local or distant complications are excluded.\textsuperscript{89,93} Although recent guidelines suggest TIVAP removal in the case of \textit{P. aeruginosa} infection, \textit{Pseudomonas} spp. have also been included in clinical ALT studies, with the same success rates as \textit{Enterobacteriaceae}. Fluoroquinolones and aminoglycosides are the antimicrobials most commonly used for these infections.\textsuperscript{89,93}

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

Infections due to \textit{Candida} spp. should lead to catheter removal, and conservative treatment should only be considered in limited situations after ruling out local or distant complications (see below). Although optimal antifungal-lock therapy has not been established in this unusual situation, amphotericin B (liposomal or deoxycholate) and ethanol are the most
commonly used compounds. In case of catheter retention, a systemic antifungal with activity against Candida biofilms should be favored such as lipid-based amphotericin B or echinocandins (see Panel 2). In case of polymicrobial infections, ALT can be proposed if two criteria are met: i) none of the involved microorganisms is S. aureus or Candida spp. and ii) a single antimicrobial can be used to treat them all or a stable association of antimicrobials can be used.

Recently developed locks

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

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

**Improving diagnosis**

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

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

**Prevention**

Improvement of hygiene measures should always be attempted through definition and implementation of local clinical bundles for TIVAP insertion and handling.\(^\text{4,38,68}\) Dedicated infusion therapy teams could be involved in the education of healthcare workers and patients.\(^\text{4}\)

Other preventive strategies are limited by the long-term implantation of TIVAP leading to coverage by host blood components of any modified surface, and reduction of the effect of antibiotic-coated catheters over time. One possible solution would be to use anti-adhesive compounds inhibiting the deposition of blood components or inhibiting local thrombosis that would delay or reduce the risk of formation of the protein film. For instance, a surface modification using nonleaching polymeric sulfobetaine (polySB) is associated with a significant reduction of adherence and activation of platelets and white blood cells.\(^\text{115}\) This scaffold retains water on the catheter surface and not only reduces proteins, host cells and
microbial adhesion but also thrombus formation *in vitro* and *in vivo*.† Although this and
other approaches provided encouraging results, they need to be assessed in long-term
settings.††

**Biofilm eradication inside TIVAP**

Currently used antibiotics as lock therapy have drawbacks, such as possible treatment failure
or a long treatment duration.‡‡ Several investigators have attempted to develop more efficient
and faster ALT to face these challenges. *In vitro* and *in vivo* studies identified several
potential lock candidates and, for instance, ethanol or daptomycin are now being clinically
assessed.¶¶ Another approach is to use an adjuvant to increase antibiotic efficiency against
biofilms. For example, the association of an antibiotic and a chelator such as EDTA or citrate
has been proposed, since divalent cations play a key-role in maintaining biofilm matrix
stability.¶¶ Addition of chelators destabilize the matrix and therefore increase antimicrobial
activity.¶¶ Many *in vitro* studies have reported an antibiofilm effect of EDTA alone and a
synergistic effect when combined with gentamicin or minocycline/25% ethanol.¶¶¶ *In vivo*,
the combination of gentamicin and EDTA led to complete eradication of biofilms of Gram-
positive as well as Gram-negative bacteria formed inside TIVAP implanted in rats, therefore
paving the way to clinical studies.¶¶¶¶ Fundamental research also led to the identification of compounds exhibiting promising
effects. Even though none of them have been assessed as ALT *per se*, their effect should be
examined in this perspective:

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

As quorum sensing (QS) is a key component of biofilm communication, many investigators
have speculated that interfering with QS signals might alter biofilm maturation thereby
leading to easier eradication. For instance, RNAIII inhibiting peptide (RIP), a compound
interfering with *S. aureus* QS efficiently prevented CVC-related infection *in vivo*.¶¶¶¶ Another approach would be to favor bacterial biofilm dispersion as biofilm bacteria lose most
of their antibiotic tolerance when they return to a planktonic state.¶¶¶¶ However, the dispersal
approach needs to be associated with systemic and local antibiotics as released bacteria from
the biofilm into the bloodstream may express virulence genes and lead to severe sepsis.¶¶¶¶
Many compounds such as dispersin B, DNase I or autoinducing peptides have been described to favor biofilm dispersion in vitro, and to a lesser extent in vivo.\textsuperscript{125,126}

Many other compounds or strategies are currently being investigated and developed such as vaccination, bacteriophages or association of antibiotics with non antibiotic compounds through the screening of chemical libraries, but substantial research is still required before reaching clinical studies.\textsuperscript{31,127-130}
Conclusion

Thirty years of intense study of TIVAP-related infection epidemiology has led to an improved delineation of patients at risk of infection, which is of key importance with regard to the increasing number of inserted TIVAPs. Although ALT has proven to be a pivotal strategy for the conservative treatment of selected uncomplicated TIVAP-related BSI, there is still much work to be done, especially in light of recent experimental progresses made on reduction of antimicrobial tolerance in TIVAP-associated infections using combinations of antibiotics and antibiotic compounds. It is also to be foreseen that preventive approaches will benefit from device development specifically conceived to reduce microbial colonization and infection, for instance using surface modifications with anti-adhesion properties. Finally, while the diagnosis of TIVAP infections remains challenging, there are indications that infection and biofilm biomarkers could be developed in a near future to assist clinicians in taking appropriate preventive or curative decisions at early stages of TIVAP colonization. Such timely therapeutic actions could significantly reduce the rate of device removal and fundamentally change our current view of TIVAP management.
Panel 1. Risk factors of TIVAP-related infections. When available, odd-ratios (OR) are expressed with 95% confidence interval [95% CI].

**Modifiable risk factors**

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

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

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

**Non-modifiable risk factors**

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

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

- Hematopoietic stem cell transplantation, OR=1·74 [1·1-2·4].\(^{23}\)

- Reduced autonomy, as expressed by a Karnofsky performance status ≤ 80%, in cancer patients, OR=5·3 [1·5-19·3].\(^{21}\)

- Presence of metastases in cancer patients, OR=4·1 [0·9-19·5].\(^{21}\)

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

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

- Diabetes in CF-patients.\(^{6}\)

To note, no study identified a specific class of antineoplastic chemotherapy or radiation therapy as being risk factors of TIVAP-related infection.
Panel 2. Future challenges regarding TIVAP and candidemia.

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

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

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

Conflicts of interest

All authors: no conflicts of interest.

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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.24
Figure 2. Diagnostic algorithm in case of suspicion of totally implantable venous access port (TIVAP)-related infection. ALT=antibiotic lock therapy. BC=blood cultures. BSI=bloodstream infection. DTP=differential time to positivity. QPBC=quantitative paired blood cultures. *Using quantitative or semi-quantitative method, see text and Figure 3. † 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. 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. **C.** After removal, the septum is immersed in saline, vortexed or sonicated for CFU counting. **D.** In CML not permitted to use cutting blades, sterile saline (0.2mL) can be injected inside the reservoir then aspirated and plated. Swabbing of the internal surface of the port after septum removal is also proposed. 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.
Figure 4. Treatment of totally implantable venous access port (TIVAP)-related bloodstream infection (BSI), according to IDSA guidelines. AB=antibiotic. AF=antifungal. ALT=antibiotic lock therapy. BC=blood cultures. IE=infective endocarditis.

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

† In case of *P. aeruginosa* TIVAP-related BSI, IDSA guidelines suggest that TIVAP removal is the first-line option.68 ‡ In 2009 IDSA guidelines, only ophthalmological examination is recommended for all patients although some clinicians also propose echocardiography and CT-scan.134 ¶ The source of the blood to be drawn is debated and some authors perform BC only from a peripheral vein or from TIVAP.102 To note, some authors consider that the presence of intracardiac or intravascular devices should preclude the use of ALT, even if this situation is not mentionned in IDSA guidelines.68
**Table 1.** Published studies on antibiotic or ethanol lock therapy for the conservative treatment of bacterial totally implantable venous access port (TIVAP)-related bloodstream infections (BSI) identified with the criteria described in the “search strategy” panel. Of note, most published studies excluded patients with complicated TIVAP-related BSI or infections caused by *S. aureus* or *Candida* spp.

<table>
<thead>
<tr>
<th>Clinical studies, year-reference</th>
<th>No of episodes treated with ALT</th>
<th>Type of catheter†</th>
<th>Micro organisms‡</th>
<th>Catheter use</th>
<th>Systemic antimicrobial treatment, n (%)</th>
<th>ALT or ELT (drug and concentration in mg/mL)</th>
<th>Association with heparin*, IU/mL</th>
<th>No of days of locks</th>
<th>Cure rate, n (%)</th>
<th>Success criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999-Domingo P. et al.¹⁴⁴</td>
<td>27</td>
<td>100-0-0</td>
<td>57-3-3-6-30</td>
<td>Antiinfectious CT in AIDS patients 9 (33)</td>
<td>VAN (1), AMK (1)</td>
<td>No</td>
<td>5</td>
<td>22 (81)</td>
<td>Clinical + negative paired BC at the end of ALT Clinical. No systematic BC</td>
<td></td>
</tr>
<tr>
<td>1999-Piketty C. et al.¹⁴³</td>
<td>31</td>
<td>100-0-0</td>
<td>100-0-0-0-0</td>
<td>Antiinfectious CT in AIDS patients 31 (100)</td>
<td>VAN (40), AMK (60)</td>
<td>Yes, ND</td>
<td>3 [1-5]</td>
<td>13 (42)</td>
<td>Clinical + negative paired BC 2-7 days after the end of ALT</td>
<td></td>
</tr>
<tr>
<td>2001-Longuet P. et al.¹⁴¹</td>
<td>16</td>
<td>100-0-0</td>
<td>41-24-0-12-23</td>
<td>Antiinfectious or antineoplastic CT 16 (100)</td>
<td>VAN (5) or TEC (5) +/- AMK (ND)</td>
<td>No</td>
<td>8 [3-15]</td>
<td>7 (44)</td>
<td>Undefined</td>
<td></td>
</tr>
<tr>
<td>2002-Santarpia L. et al.⁷</td>
<td>60</td>
<td>86-14-0</td>
<td>67-15-0-6-12</td>
<td>TPN 60 (100)</td>
<td>TEC (33-100), PIP (166-500), NET (50-150) or CLI (100-300)</td>
<td>Yes, ND</td>
<td>7</td>
<td>50 (83)</td>
<td><em>defined</em></td>
<td></td>
</tr>
<tr>
<td>2002-Reimund J.M. et al.¹⁴⁶</td>
<td>25</td>
<td>64-36-0</td>
<td>61-24-0-12-3</td>
<td>TPN 39 (100)</td>
<td>VAN (1), AMK (1.5) or MIN (0.2)</td>
<td>No</td>
<td>ND</td>
<td>undefined</td>
<td>undefined</td>
<td></td>
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<tr>
<td>2003-Viale P. et al.¹⁴⁷</td>
<td>30</td>
<td>37-40-23</td>
<td>35-9-9-28-22</td>
<td>Antiinfectious or antineoplastic CT, TPN 15 (50)</td>
<td>VAN (20), TEC (20), AMK (10), IMP (ND)</td>
<td>No</td>
<td>14</td>
<td>28 (93)</td>
<td>Clinical + negative paired BC 14 and 28 days after the beginning of ALT</td>
<td></td>
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<tr>
<td>2004-Koldehoff M. et al.¹⁴⁸</td>
<td>11</td>
<td>100-0-0</td>
<td>46-8-8-8-30</td>
<td>Antineoplastic CT 11 (100)</td>
<td>Taurolidine (5)</td>
<td>No</td>
<td>1 [1-3]</td>
<td>11 (100) §</td>
<td>undefined</td>
<td></td>
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<tr>
<td>2005-Rijnders B.J. et al.⁷⁰</td>
<td>22</td>
<td>91-9-0</td>
<td>63-14-0-0-23</td>
<td>Mostly antineoplastic CT 22 (100)</td>
<td>VAN (0.5) or CAZ (0.5)</td>
<td>Yes, 100</td>
<td>11 [7-14]</td>
<td>14 (67)</td>
<td>Clinical. No systematic BC</td>
<td></td>
</tr>
<tr>
<td>2006-Fortún J. et al.¹⁴⁹</td>
<td>19</td>
<td>74-26-0</td>
<td>74-0-10-16-0</td>
<td>Antineoplastic CT and TPN 19 (100)</td>
<td>VAN (2), GEN (2) or CIP (2)</td>
<td>Yes, 20</td>
<td>12 [5-14]</td>
<td>16 (84)</td>
<td>Clinical + negative catheter BC 2-5 days after the end of ALT</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Years</td>
<td>50-100</td>
<td>0-50</td>
<td>0</td>
<td>Ethanol %</td>
<td>Gen</td>
<td>No</td>
<td>5</td>
<td>End of ALT</td>
<td>BC</td>
</tr>
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<td>---------------------------</td>
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<tr>
<td>2006-Onland W. et al.</td>
<td>91</td>
<td>21-79</td>
<td>52-11</td>
<td>10-14-23</td>
<td>Mostly antineoplastic CT</td>
<td>51 (100)</td>
<td>Ethanol 70%</td>
<td>No</td>
<td>5</td>
<td>45 (88)</td>
</tr>
<tr>
<td>2008-Souza Dias M.B. et al.</td>
<td>91</td>
<td>78-22</td>
<td>0-0</td>
<td>100-0-0</td>
<td>Mostly antineoplastic CT</td>
<td>17 (100)</td>
<td>CEF (ND), AMK (2) or LVX (ND)</td>
<td>Yes</td>
<td>100</td>
<td>ND</td>
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<tr>
<td>2008-Broom J. et al.</td>
<td>103</td>
<td>11-89</td>
<td>25-21</td>
<td>21-0-33</td>
<td>Antineoplastic CT</td>
<td>17 (100)</td>
<td>Ethanol 70%</td>
<td>No</td>
<td>5</td>
<td>15 (88)</td>
</tr>
<tr>
<td>2009-Del Pozo J.L. et al.</td>
<td>91</td>
<td>44</td>
<td>100-0</td>
<td>0-0-0-0</td>
<td>Antineoplastic CT and TPN</td>
<td>44 (100)</td>
<td>VAN (2), TEC (10)</td>
<td>Yes</td>
<td>100</td>
<td>10</td>
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<tr>
<td>2009-Del Pozo J.L. et al.</td>
<td>91</td>
<td>18</td>
<td>5-35</td>
<td>0-0-0-60</td>
<td>Antineoplastic CT</td>
<td>18 (100)</td>
<td>VAN (2) +/- GEN (2) (if E. faecium), TEC (10), TZP (10), LVX (5), TMP/SXT (16/3.2)</td>
<td>Yes</td>
<td>100</td>
<td>12</td>
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<tr>
<td>2009-Rajpurkar M. et al.</td>
<td>94</td>
<td>3</td>
<td>66-33</td>
<td>0-0-0-60</td>
<td>Hemophilia</td>
<td>3 (100)</td>
<td>Ethanol 70%</td>
<td>No</td>
<td>3</td>
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<td>2011-McGrath E.J. et al.</td>
<td>94</td>
<td>80</td>
<td>24</td>
<td>2-9-8-0-30</td>
<td>Antiinfectious or antineoplastic CT, TPN</td>
<td>80 (100)</td>
<td>Ethanol 70%</td>
<td>No</td>
<td>1</td>
<td>59 (75)</td>
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<td>2011- Funalleras G. et al.</td>
<td>93</td>
<td>46</td>
<td>28</td>
<td>2-6-9-15</td>
<td>Antineoplastic CT, hemodialysis</td>
<td>46 (100)</td>
<td>AMK (2) or CIP (2)</td>
<td>Yes</td>
<td>20</td>
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<td>2011- Valentine K.M. et al.</td>
<td>153</td>
<td>26</td>
<td>15-54</td>
<td>3-3-11</td>
<td>Antineoplastic CT, ICU</td>
<td>26 (100)</td>
<td>Ethanol 70%</td>
<td>No</td>
<td>1.5</td>
<td>24</td>
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<td>2012-Del Pozo J.L. et al.</td>
<td>94</td>
<td>13</td>
<td>46-54</td>
<td>87-0-0-13</td>
<td>Antineoplastic CT, hemodialysis</td>
<td>11 (85)</td>
<td>DAP (5)</td>
<td>Yes, 100 if TIVAP and 5000 if dialysis</td>
<td>14</td>
<td>10-14</td>
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</tbody>
</table>

*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. CLA=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.