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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 and formation of pathogenic biofilm in TIVAPs is 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.

Search strategy and selection criteria

References for this review were identified through searches of PubMed for articles published in English between January 1980 and February 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).[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.[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).[5] TIVAP is composed of a subcutaneously implanted port (or reservoir) connected to a central venous catheter, most frequently inserted in the internal jugular, subclavian or cephalic vein.[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.[2] TIVAPs are used for the administration of antineoplastic chemotherapy, parenteral nutrition, blood products and for prolonged antimicrobial treatment in CF.[2,6,7] Of note, the number of implanted TIVAPs is increasing and currently more than 100,000 TIVAPs are inserted each year in the USA alone.[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.[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.[6,9,12,13,15-19] If TIVAP is used for total parenteral nutrition (TPN), incidence density is higher and is comprised between 0·33 and 3·2/1000 catheter-days with heterogeneous data depending on the indication for TPN.[7,20,21] In HIV-infected patients, incidence density is also high and ranges from 1·5 to 3·81/1,000 catheter-days, probably because when they require a LTIVC, these patients combine most of the risk factors of infection identified so far.[8,22] The reported time to infection from TIVAP insertion is variable, but major studies report median occurrence ranging from 80 to 192 days with extreme values of 2 and 1406 days.[8,9,12,22]

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.[22] Additional risk factors have also been described such as:

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

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.[27] 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%).[12] More recent studies described a higher rate of GNR (up to 40%) and yeasts (up to 23%).[8,9,28] This shift has been suggested to result from antineoplastic chemotherapy intensification with more sustained neutropenia allowing translocation of microorganisms from the gut to the bloodstream, but also because of a more frequent use of supportive care such as TPN and use of broad-spectrum antibiotics. Few data regarding antibiotic resistance in this population are available.

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

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 properly cleaned, therefore leading to an intraluminal colonization that can spread from the port to the catheter tip.[32-34] In case of BSI coming from another focus of infection, bacteria may adhere on the catheter tip, therefore defining a hematogenous route of colonization. After device contamination, bacteria adhere to the surface of TIVAP using bacterial appendages called adhesins.[35] Bacterial adhesion is influenced by the type of catheter material, presence of layer of blood products such as fibrin or platelets and bacterial characteristics.[32,36] After adhesion, bacteria multiply and constitute a surface-associated microbial community called a biofilm, which is embedded in an extracellular matrix (ECM).[10,35] While systemic antibiotics can cure TIVAP-related BSI, biofilm bacteria are able to survive high concentrations of antibiotics.[37] This high tolerance towards antibiotics causes infection recurrence unless the device is removed or intraluminal treatment used. 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 LTIVC for treatment of solid tumor and in pediatric hematology patients.[12,28,38] In case of prolonged TPN, due to higher risk of infection associated with TIVAPs, a tunnelled catheter is preferred for daily vascular access.[1,7] If TIVAP is chosen in oncology or hematology patients, it should be inserted as early as possible, due to increased risk of infection in case of neutropenia.[39,40] Then, preventive strategies must be applied during and after TIVAP insertion.

Preventive measures during TIVAP insertion

Trained personnel with maximum sterile barrier precautions, including sterile gloves, cap, mask, sterile gown and a sterile full body drape, must perform TIVAP insertion.[2,41,42] For skin preparation, alcohol-based antiseptics such as alcohol-based chlorhexidine or alcohol-based povidone-iodine ought to be used, but no direct comparative study has been done using these solutions.[42] A >0·5% chlorhexidine preparation with alcohol may be favored based on the result of a prospective study comparing chlorhexidine-based antiseptic solution with alcohol-based povidone-iodine.[43]

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.[44] 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.[45] 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.[44,46] Systemic antibiotic prophylaxis is useless during TIVAP insertion and is not indicated.[47-49]

Preventive measures after TIVAP insertion

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

catheter tip occlusion.[50] It is now recommended that heparin locks or flush after TIVAP use should not be performed, as sterile saline locks are equally efficient to prevent functional or infectious complications.[42,51]

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 incoming bacteria. 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.[52] 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 minocyline-EDTA ALT was more effective than heparin for the prevention of CRBSI.[53,54] Nevertheless, systematic use of ALT could lead to increased antibiotic resistance and should therefore be considered only in high-risk patients, who already experienced TIVAP-related infections.[36,42,55]

Limited data are available for non-antibiotic lock solutions, such as ethanol- or taurolidine-lock. One preliminary pediatric study using ethanol locks including 12 patients with TIVAP was interrupted as 3 patients experienced TIVAP occlusion.[56] 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.[57] Therefore, ethanol lock could be proposed in case of high-risk TPN patients with tunnelled catheters.[58] 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.[59,60]

Taurolidine, a derivative from the aminoacid taurine, was proposed as a lock therapy in 1993 because of its antimicrobial effect against a broad range of microorganisms *in vitro*.[61-63] Although studies conducted in hemodialysis patients are encouraging, data supporting its use as a lock in TIVAP are limited.[64,65] In pediatric cancer patients, an initial study showed no significant reduction of CRBSI with taurolidine/citrate as compared to heparin, with ~75% of TIVAP patients amongst LTIVC.[66] A more recent study in pediatric hematology patients showed a significant reduction of CRBSI with taurolidine/citrate as compared to heparin but included only tunnelled catheters.[62] 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 ~ 40% of LTIVC).[67] 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.[68,69] As LTIVCs dwell for a longer time in the blood flow, their surfaces become covered by a film composed of various blood components, therefore reducing the antimicrobial action of the coating.[32] 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.[70] Thus, developing an efficient surface modification or antibiotic coating that would help preventing colonization is still a major challenge.

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:[71]

-Local 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).[71]

-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.[71]

-Catheter-related infection, defined by the association of local or general signs of infection and a positive culture of the catheter tip.[71]

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.[71] 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.[29,72,73] 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.[29,74] 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.[71] Correct interpretation of the test requires blood samples to be performed at the same moment, 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.[71,75,76] Another critical point is to precisely label the origin of each blood culture bottle.[71] 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.[75,77-79] 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).[71,75,76,78,79] 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.[75,78,79] They are nevertheless considered equivalent in recent guidelines and the choice of a technique will mostly rely on local equipment and training.[71]

Diagnosis of TIVAP-related BSI after device removal

The demonstration that a BSI originates from a TIVAP relies on the identification of the same microorganism in a TIVAP component and peripheral blood cultures. The catheter tip (four-cm distal part) can be cultured using the semiquantitative or quantitative methods with thresholds defining a significant colonization of >15 CFU and $\geq 10^3$ CFU/mL, respectively (Figures 3A and B).[80,81] 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.[71,72,74,82] For instance, it has been proposed to perform quantitative culture of the TIVAP septum using an adapted Brun-Buisson method (Figures 3A and C).[72] With a threshold of 10^3 CFU/mL, this method was associated with 93% sensitivity and 100% specificity for the diagnosis of TIVAP-related BSI.[72] 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.[74] The main limitations of port septum and port deposit cultures are lack of technical standardization and absence of a consensus threshold.[71] Therefore, performing both catheter tip culture and a culture of a component of the port reservoir is advisable.[71]

Diagnosis of fungal TIVAP-related BSI

Without TIVAP removal, such a diagnosis is challenging as studies assessing paired blood cultures infrequently included fungal infections[75,77,78,83] Authors 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).[84] 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 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).[85]

Workup to rule out complications

Once TIVAP-related BSI has been diagnosed, clinicians should look for infectious complications such as severe sepsis, endocarditis, or other hematogenous complications (Figures 1B, C and D).[29] Recent guidelines recommend systematic transesophageal echocardiography in case of *S. aureus* TIVAP-related BSI.[71] 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.[86-90] 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).[71,91]

Treatment: should TIVAP be removed or retained?

In the case of CRBSI, the treatment of choice is systemic antimicrobial therapy in conjunction with removal of the colonized device.[4] However, in case of TIVAPs, reduced venous access, potential presence of coagulation disorders, the need for a new procedure and its cost, all argue in favor of attempting a catheter salvage, if the clinical situation allows it.[71] TIVAP removal is mandatory in case of local or distant complications, or in case of infection caused by *S. aureus* or *Candida* spp., based on the high failure rates of treatment when the colonized catheter is retained (Figure 1 and 4).[71,92] 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.[71]

In other cases, conservative treatment using a combination of systemic antimicrobials and ALT can be considered.[71] 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.[93-95] 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.[73] 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).[92,94,96]

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.[97,98] 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. 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.[71] Replacing the solution every 48 or 72 hours has also been performed safely.[96] In case of TIVAP-related BSI, systemic antimicrobials should always be administered for 10 to 14 days.[71] Addition of heparin in ALT has been proposed to avoid thrombosis of the catheter

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

Adapting treatment to the identified microorganism (Figure 4)

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

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

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.[92,101] ALT can nevertheless be considered in exceptional circumstances after having excluded local or distant complications, such as infective endocarditis with transesophageal echocardiography.[71] 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.[92,98,101,102]

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

Recently developed locks

Aside from commonly used antimicrobials in ALT, 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.[105-107] 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.[107] More recently, daptomycin has been proposed as lock therapy because of its potent *in vitro* effect against biofilms.[108,109] 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.[97] After a mean of 14 days of treatment, cure rate was 85% (11/13 patients).[97] 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.[72,76,83,110,111] 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.[112,113] These methods are more sensitive than cultures in case of previous antibiotic administration. Beside, 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.[114]

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 still need to be assessed in the setting of TIVAP.[115,116]

Prevention

Improvement of hygiene measures should always be attempted through definition and implementation of local clinical bundles for TIVAP insertion and handling.[4,42,71] Dedicated infusion therapy teams could be involved in the education of healthcare workers and patients.[4] Other preventive strategies are limited by the long-term implantation of TIVAP leading to coverage by host blood components of any modified surface, and reduction of the effect of antibiotic-coated catheters over time. One possible solution would be to use anti-adhesive compounds inhibiting the deposition of blood components or inhibiting local thrombosis that would delay or reduce the risk of formation of the protein film. For instance, a surface modification using nonleaching polymeric sulfobetaine (polySB) is associated with a significant reduction of adherence and activation of platelets and white blood cells.[117] Using an *in vivo* canine model, this surface modification has been demonstrated to reduce thrombus accumulation and bacterial adhesion.[117] 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.[71] Several investigators have attempted to develop more efficient and faster ALT to face these challenges. Use of *in vitro* and *in vivo* models led to the identification of several potential lock candidates for clinical studies; for instance, ethanol or daptomycin are now being clinically assessed.[97,105] 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 ECM stability.[118] Addition of chelators destabilize ECM and therefore increase antimicrobial activity.[119] Many *in vitro* studies have reported an antibiofilm effect of EDTA alone and a synergistic effect when combined with gentamicin or minocycline/25% ethanol.[120,121] *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.[122]

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 persister cells may lead to a more efficient treatment of *in vivo* biofilm.[123] 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 authors 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 is efficiently preventing CVC-related infection *in vivo*.[124] Other compounds interfering with *S. epidermidis* QS such as farnesol have also demonstrated synergy with antibiotics *in vitro* and *in vivo* and should be considered as potential locks.[125]

-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.[37] However, the dispersal approach needs to be associated with antibiotics as released bacteria from the biofilm into the bloodstream may express virulence genes and lead to severe sepsis.[126] 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* but none of them have been proposed as ALT yet.[127,128]

-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.[36,129-132]

Treatment of fungal infections

All published international guidelines so far strongly recommend the early removal of CVC in case of candidemia whether or not it is CR.[71,104,133] Two situations should be distinguished. On one hand, if the candidemia is not CR, it is plausible that catheter retention does not influence outcome, especially if an antifungal efficient against *Candida* biofilm is used.[134] 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.[135] 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.[75,77,78]

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.[103] *In vitro* and *in vivo* studies reveal that against *Candida* biofilms: i) azoles have poor activity; ii) lipid formulations of amphotericin B are more effective than amphotericin B deoxycholate; and iii) echinocandins have excellent *in vitro* activity.[103] Non-antifungal lock therapy against *Candida* biofilms have also been proposed such as EDTA in combination with antifungals or minocycline, ethanol, heparin and even highly concentrated antibiotics like doxycyline.[103,136-139] Although from a clinical point of view 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.[103] Hence, ethanol lock therapy could be a promising candidate with eight successes among ten reported patients.[138,139] Of note, most of these published cases are of pediatric patients with the limitation of diagnostic criteria, frequently based only 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.

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 antibiofilm 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.

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.** Complicated local infection caused by *S. aureus* occurring six days after TIVAP surgical insertion with port-pocket infection (surrounded by black dashed line) and tunnel infection (white arrowhead). **B.** Thrombophlebitis diagnosed after TIVAP-related bloodstream infection (BSI) caused by *S. aureus*. Thrombus (black arrowhead) developed at the junction of internal jugular vein (black arrow) and subclavian vein (black star). TIVAP was inserted in the right subclavian vein. Coronal view of computed tomography (CT) scan of the chest after iodine-based contrast agent injection. **C.** Right pulmonary abscess (white arrow) with cavitation secondary to a *S. aureus* TIVAP-related BSI. Axial view of computed tomography (CT) scan of the chest. **D.** C5-C6 spondylitis caused by *S. lugdunensis* after an episode of TIVAP-related BSI. Sagital 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.[29]

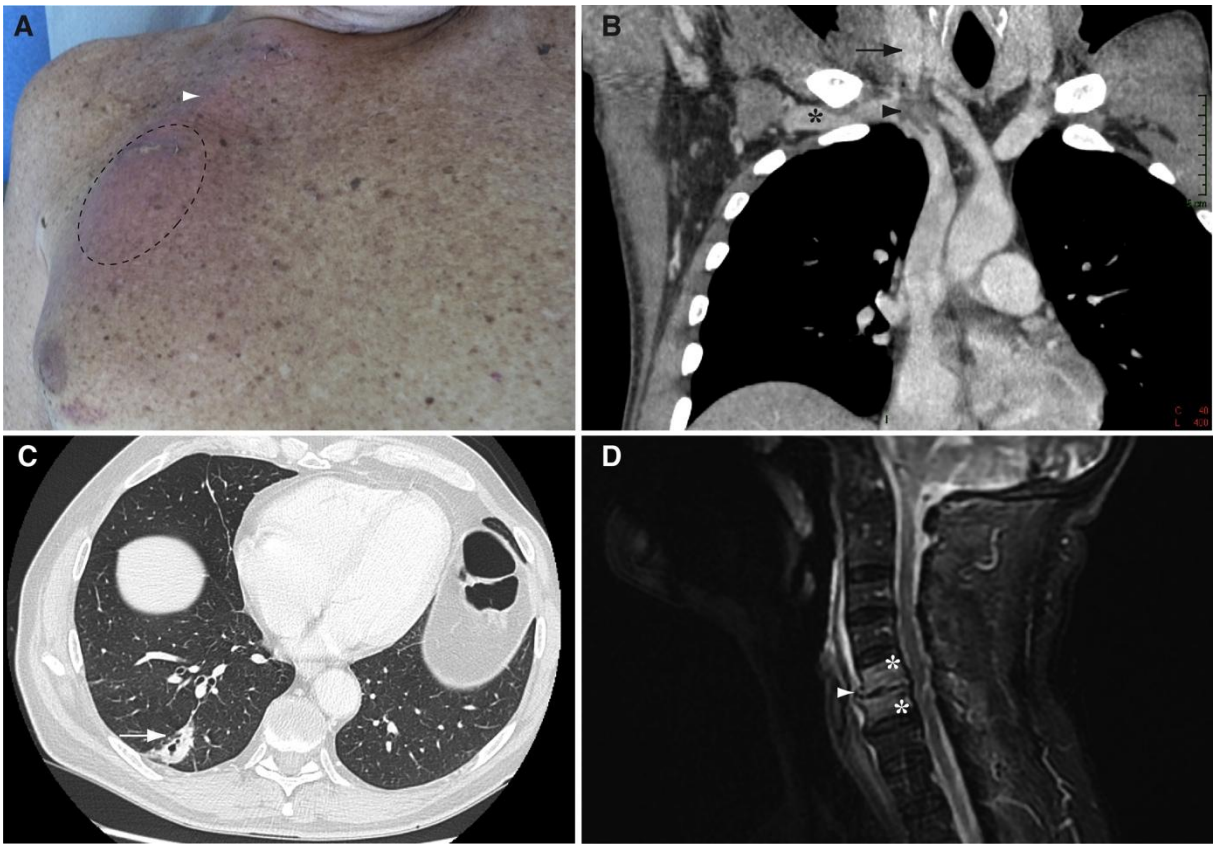

Figure 2. **Diagnostic algorithm in case of suspicion of totally implantable venous access port (TIVAP)-related infection**. ALT=antibiotic lock therapy. BC=blood cultures. BSI=bloodstream infection. DTP=differential time to positivity. QPBC=quantitative paired blood cultures. *Using quantitative or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

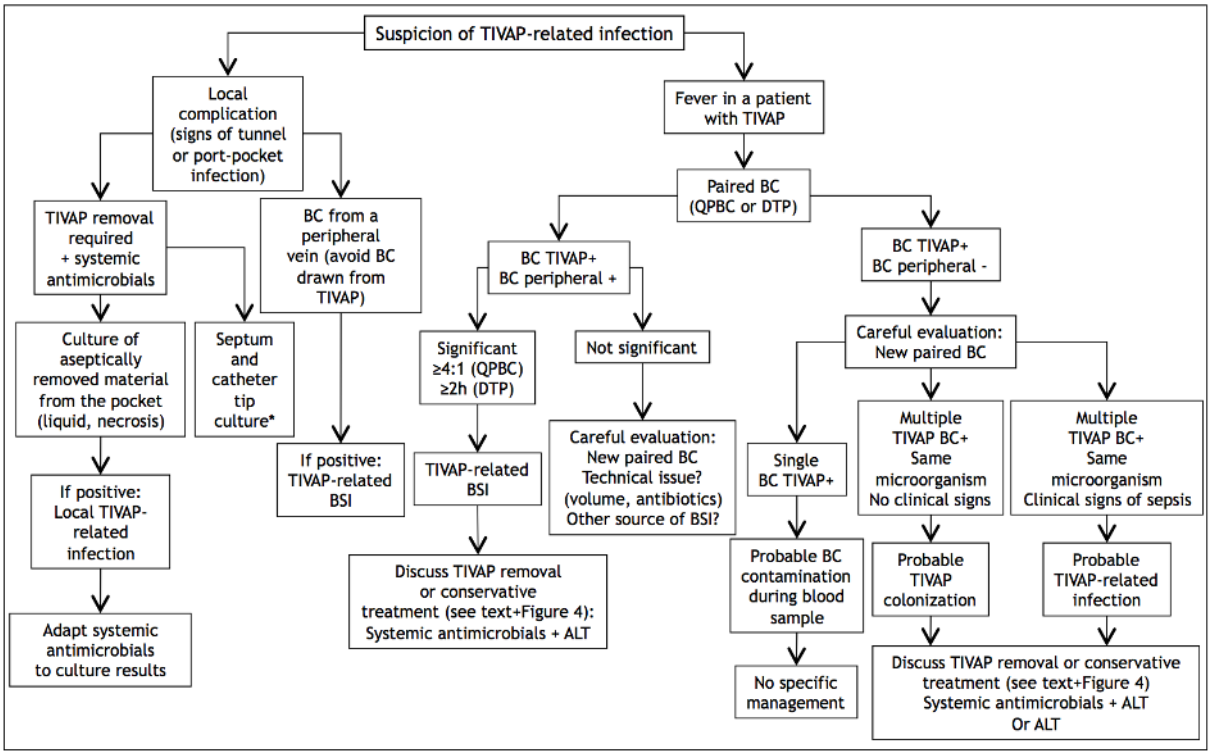

Figure 3. **Microbiological methods for the diagnosis of totally implantable venous access port (TIVAP) colonization**. **A.** Schematic view of a removed TIVAP. Catheter tip (black star) is cut and the septum (white star) removed using sterile blade.[71,72,140] **B.** Culture of the catheter tip can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

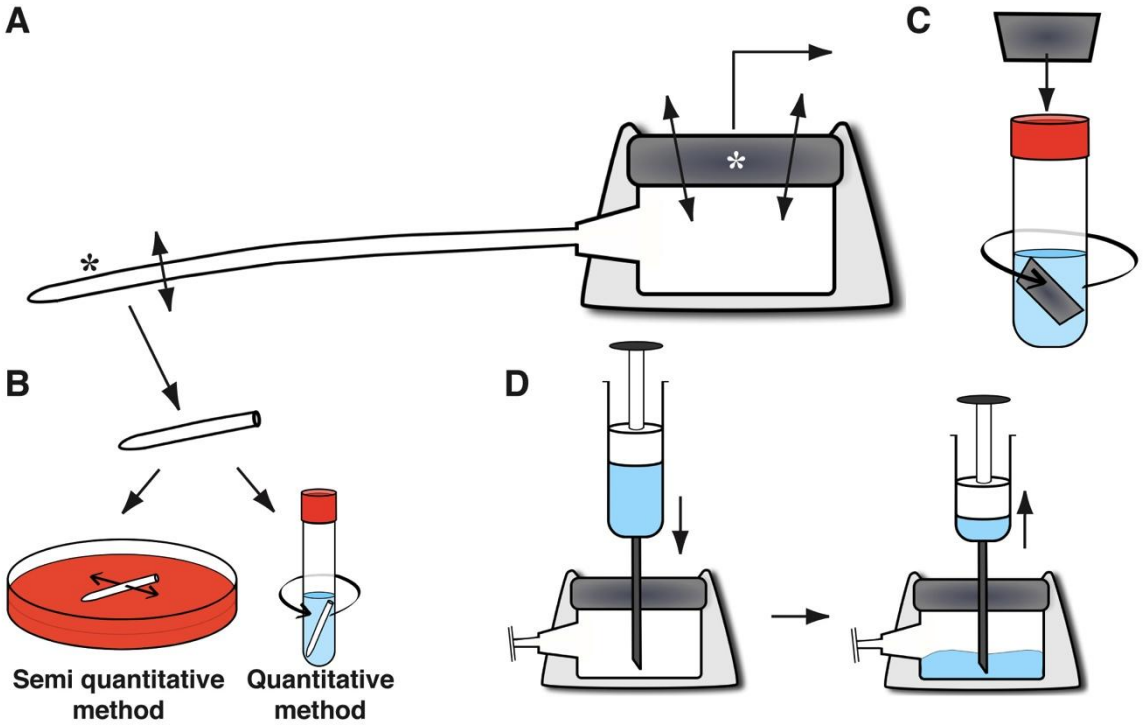

Figure 4. **Treatment of totally implantable venous access port (TIVAP)-related bloodstream infection (BSI)**. AB=antibiotic. AF=antifungal. ALT=antibiotic lock therapy. BC=blood cultures. IE=infective endocarditis. *In case of tunnel or port-pocket infection without BSI, TIVAP removal is also required with five to seven days of systemic antimicrobials.[4,71,133]

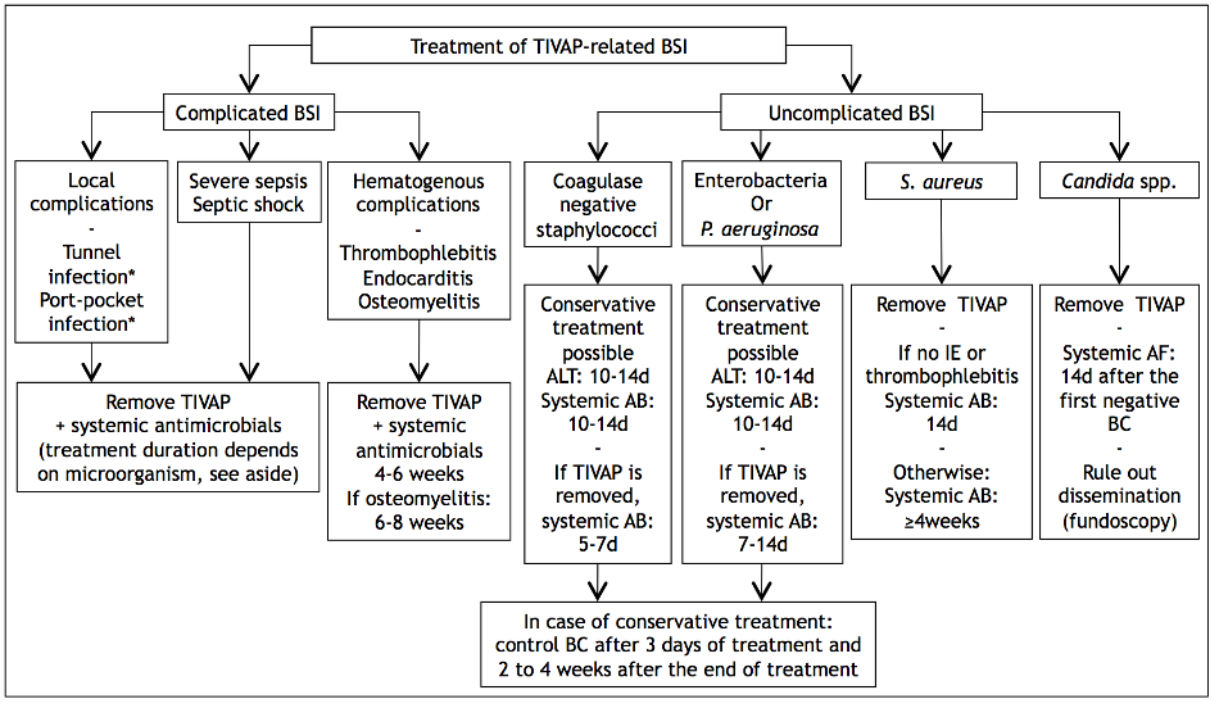

Table 1. Published studies on antibiotic or ethanol lock therapy for the conservative treatment of bacterial totally implantable venous access port-related bloodstream infections.

Clinical studies, year-reference	No of episodes treated with ALT	Type of catheter†	Catheter use	Systemic antimicrobial treatment, n (%)	ALT or ELT (drug and concentration in mg/mL)	Association with heparin, IU/mL	No of days of locks	Cure rate, n (%)	Success criteria
1999-Domingo P. *et al.*[141]	27	100-0-0	Antiinfectious CT in AIDS patients	9 (33)	VAN (1), AMK (1)	No	5	22 (81)	Clinical + negative paired BC at the end of ALT
1999-Piketty C. *et al.*[142]	31	100-0-0	Antiinfectious CT in AIDS patients	31 (100)	VAN (40), AMK (60)	Yes, ND	3 [1-5]	13 (42)	Clinical. No systematic BC
2001-Longuet P. *et al.*[140]	16	100-0-0	Antiinfectious or antineoplastic CT	16 (100)	VAN (5) or TEC (5) +/- AMK (ND)	No	8 [3-15]	7 (44)	Clinical + negative paired BC 2-7 days after the end of ALT
2002-Santarpia L. *et al.*[7]	60	86-14-0	TPN	60 (100)	TEC (33-100), PIP (166-500), NET (50-150) or CLI (100-300)	Yes, ND	7	50 (83)	Undefined
2002-Reimund J.M. *et al.*[143]	25	64-36-0	TPN	39 (100)	VAN (1), AMK (1.5) or MIN (0.2)	No	ND	25% if TIVAP-50% if tunnelled	Undefined
2003-Viale P. e*t al.*[144]	30	37-40-23	Antiinfectious or antineoplastic CT, TPN	15 (50)	VAN (20), TEC (20), AMK (10), IMP (ND)	No	14	28 (93)	Clinical + negative paired BC 14 and 28 days after the beginning of ALT
2004-Koldehoff M. *et al.*[145]	11	100-0-0	Antineoplastic CT	11 (100)	Taurolidine (5)	No	1 [1-3]	11 (100) ‡	Undefined
2005-Rijnders B.J. *et al.*[73]	22	91-9-0	Mostly antineoplastic CT	22 (100)	VAN (0.5) or CAZ (0.5)	Yes, 100	11 [7-14]	14 (67)	Clinical. No systematic BC
2006-Fortún J. *et al.*[146]	19	74-26-0	Antineoplastic CT and TPN	19 (100)	VAN (2), GEN (2) or CIP (2)	Yes, 20	12 [5-14]	16 (84)	Clinical + negative catheter BC 2-5 days after the end of ALT
2006-Fernàndez-Hidalgo N. *et al.*[92]	115	16-73-11	Antineoplastic CT, TPN, hemodialysis	115 (100)	VAN (2), AMK (2) or CIP (2)	Yes, 20	12 [8-14]	94 (82)	Clinical + negative BC 1 month after the end of ALT
2006-Onland W. *et al.*[107]	51	21-79-0	Mostly antineoplastic CT	51 (100)	Ethanol 70%	No	5	45 (88)	Clinical. No systematic BC
2008-Souza Dias M.B. *et al.*[147]	17	78-22-0	Mostly antineoplastic CT	17 (100)	CEF (ND), AMK (2) or LVX (ND)	Yes, 100	ND	14 (82)	Undefined
2008-Broom J. *et al.*[105]	17	11-89-0	Antineoplastic CT	17 (100)	Ethanol 70%	No	5	15 (88)	Clinical + catheter BC negative 1 day after the end of ALT
2009-Del Pozo J.L. *et al.*[94]	44	100-0-0	Antineoplastic CT and TPN	44 (100)	VAN (2), TEC (10)	Yes, 100	10 [10-14]	39 (89)	Clinical + catheter BC negative 7 days after the end of ALT

2009-Del Pozo J.L. *et al.*[148]	18	100-0-0	Antineoplastic CT	18 (100)	VAN (2) +/- GEN (2) (if *E. faecium*), 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. *et al.*[149]	3	66-33-0	Hemophilia	3 (100)	Ethanol 70%	No	3 [1-3]	3 (100)	Clinical + catheter BC negative after the end of ALT
2011-McGrath E.J. *et al.*[106]	80	24-72-4	Antiinfectious or antineoplastic CT, TPN	80 (100)	Ethanol 70%	No	1	59 (75)	Clinical + catheter BC negative 30 days after the beginning of ALT
2011-Funalleras G. *et al.*[96]	46	28-72-0	Antineoplastic CT, hemodialysis	46 (100)	AMK (2) or CIP (2)	Yes, 20	13 [10-16]	44 (96)	Clinical + catheter BC negative 30 days after the beginning of ALT
2011-Valentine K.M. *et al.*[150]	26	15-54-31	Antineoplastic CT, ICU	26 (100)	Ethanol 70%	No	1.5 [1-5]	24 (92)	Clinical + negative catheter BC 2 days after the beginning of ALT
2012-Del Pozo J.L. *et al.*[97]	13	46-54-0	Antineoplastic CT, hemodialysis	11 (85)	DAP (5)*	Yes, 100 if TIVAP and 5000 if dialysis	14 [10-14]	11 (85)	Clinical + catheter BC negative 30 days after the end of ALT

†Expressed as % TIVAP-tunnelled-other.
‡But 3 retreatments needed.
*In lactated Ringer's solution providing 45 mg of calcium/L.
AIDS=acquired immunodeficiency syndrome. ALT=antibiotic lock therapy. AMK=amikacin. BC=blood cultures. CIP=ciprofloxacin. CLI=clindamycin. CT=chemotherapy. DAP=daptomycin. ELT=ethanol lock therapy. GEN=gentamicin. ICU=intensive care unit. IMP=imipenem. MIN=minocycline. ND=not determined. NET=netilmicin. PIP=piperacillin. TMP-SMX=trimethoprim-sulfamethoxazole. TPN=total parenteral nutrition. TZP=piperacillin/tazobactam.