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

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Use of totally implantable venous-access ports (TIVAPs) is standard practice for patients with diseases such as solid-tumour cancers, haematological malignancies, and chronic digestive diseases. Use of TIVAPs allows long-term administration of venotoxic compounds, improves patients' quality of life, and reduces the risk of infection. Microbial contamination, formation of pathogenic biofilms, and infection, however, are associated with morbidity, mortality, and increased health-care costs. Local and systemic complications or infections related to specific pathogens might lead to device removal. Alternatively, conservative treatment with combined systemic antibiotics and antibiotic lock therapy might be useful. We discuss in-vitro and in-vivo basic and clinical research findings on the epidemiology, diagnosis, and prevention of TIVAP-related infections, the current challenges to management, promising strategies, and some treatments in development that are likely to improve outcomes of TIVAP-related infections, with a particular focus on antibiotic lock therapy.

Introduction

Some chronic diseases, such as solid-tumour cancers, haematological malignancies, digestive diseases, cystic fibrosis, and HIV, require long-term administration of potentially venotoxic compounds.[1,2] Long-term intravascular catheters (LTIVCs) were developed to reduce the risk of toxic effects and bacterial or fungal colonisation by use of a subcutaneous route or tunnel that impedes the migration of microorganisms present on the surface of the skin.[3,4] In the early 1980s a new type of LTIVC called a totally implantable venous-access port (TIVAP) was developed.[5] A TIVAP comprises a subcutaneously implanted port (or reservoir) connected to a central venous catheter, most frequently inserted into the internal jugular, subclavian, or cephalic vein.[2] Use of TIVAPs has become standard clinical practice and has greatly increased patients' comfort and quality of life compared with other LTIVCs.[2] TIVAPs are inserted for the administration of antineoplastic chemotherapy, parenteral nutrition, blood products, and long-term antimicrobial treatment (eg, in cyctic fibrosis).[2,6,7] The number of TIVAPs implanted is increasing, with more than 400 000 sold each year in the USA.[8] Nevertheless, despite the reduced risk of microbial contamination, 3–10% of TIVAP carriers experience a related infection, which is the most frequent indication for TIVAP removal.[9–14] Thus, infections have a notable effect on the care of patients and require focused research.

In this Review we aim to provide insights into challenges associated with TIVAP-related infections, including diagnosis, and prevention, and discuss novel approaches that might improve management.

Epidemiology

Dependent on the indication for TIVAP insertion, patients' risk factors for infection differ and, therefore, infection rates also differ. For instance, with use of TIVAPs for antineoplastic chemotherapy or in patients with cystic fibrosis, the infection rate ranges from 0·11 to 0·37 per 1000 catheter-days.[6,9,10,13–17] In patients with cancer, the risk of TIVAP-related infection seems to have remained unchanged over time, with infection rates of 0·21 and 0·20 per 1000 catheter-days being reported, respectively, in 1993 and 2011.[9,13] For TIVAPs used for total parenteral nutrition, the infection rate rises to between 0·33 and 3·20 per 1000 catheter-days, dependent on the indication.[7,18,19] In HIV-infected patients, infection rates range from 1·50 to 3·81 per 1000 catheter-days, probably because these patients combine multiple risk factors.[20,21] Mean reported times to infection from TIVAP insertion are 80–192 days (range 2–1406).[10,13,20,21]

Routes of contamination and risk factors

The discrepancies between different groups of patients probably reflect exposure to different risk factors. A prospective study showed that frequency of handling was one of the most important associated risk factors (panel 1).[21] Unsurprisingly, therefore, coagulase-negative staphylococci, which are frequent colonisers of the human skin and mucosal flora, lead to a substantial proportion of TIVAP-related infections.[27] For instance, among 29 cases of TIVAP-related infections, 57% were caused by coagulase-negative staphylococci, 20% by Gram-negative rods, 7% by *Staphylococcus aureus*, and 3% by *Candida albicans*.[13] In later studies higher rates of infections with Gram-negative rods (up to 40%) and yeasts (up to 23%) have been reported.[10,20,25] These differences might be related to various factors, such as intensification of antineoplastic chemotherapy because of increased neutropenia, which could lead to translocation of microorganisms from the gut to the bloodstream, increased frequency of total parenteral nutrition, or administration of broad-spectrum antibiotics.[10] Early TIVAP-related infections (30 days or earlier) are more frequently caused by *S aureus* than late infections (50% *vs* 12%).[28]

Antibiotic resistance requires some consideration. In a French cohort of patients with cancer, 58% of coagulase-negative staphylococci and 25% of *S aureus* were meticillin resistant.[28] In the USA, 37–55% of *S aureus* responsible for catheter-related bloodstream infections are resistant to meticillin.[29,30]

The total implantation of TIVAPs means that the risk of extraluminal colonisation is low and mostly occurs during insertion, which results in surgical-site infection. After insertion, repeated punctures with Huber needles might lead to contamination if the skin has not been completely cleaned. In these cases, microorganisms in an intraluminal colonisation can be spread from the port to the catheter tip.[31–33] If a bloodstream infection arises from another source, bacteria might adhere to the catheter tip. These haematogenous colonisations are rare and are caused mostly by *S aureus*. Bacteria use proteinaceous stalks called adhesins to adhere to the internal or external surface of the TIVAP, dependent on the source of contamination.[34]

Bacterial adhesion is affected by the catheter materials or bacterial characteristics or by the presence of a layer of host blood components, called a conditioning film. The conditioning film develops within a few days and comprises components such as fibrin and platelets.[31,35,36] These deposits might increase or lessen the risk of bacterial adhesion or the efficacy of any antibiotic-releasing surface. After adhesion, bacteria multiply to form a surface-associated microbial community called a biofilm, which is embedded in a matrix of extracellular polymeric substances produced by the bacteria and the host.[11,34] Biofilm bacteria can survive high concentrations of antibiotics.[37] Thus, systemic antibiotics might cure TIVAP-related bloodstream infections, but the source of infection might not be eradicated unless the device is removed or intraluminal treatment used, and infection relapse is possible. Preventive approaches are crucial to avoid microbial contamination and biofilm formation.

Prevention of colonisation

Owing to the reduced risk of infection, TIVAPs are favoured over other LTIVCs for use in treatment of solid tumours and haematological malignant disease in children.[13,25,38] By contrast, because of the high risk of infection associated with TIVAPs used for total parenteral nutrition, a tunnelled catheter might be preferable if daily vascular access is required.[1,7] If a TIVAP is chosen for patients with oncological or haematological diseases, it should be inserted as early as possible because the risk of infection is increased by neutropenia.[26,39] Preventive strategies must be applied in all patients during and after TIVAP insertion.

Insertion

Trained staff should perform TIVAP insertion, taking maximum sterile barrier precautions, including gloves, cap, mask, gown, and full-body drape.[2,40,41] For skin preparation, alcohol-based chlorhexidine or alcohol-based povidone-iodine should be applied at least 30 s and left to dry before insertion.[41] The chlorhexidine concentration should be higher than 0·5% (2% is used in most clinical trials). Whether skin cleaning (or scrubbing) before antiseptic application is relevant is debated,[42] but is recommended in France. Furthermore, no randomised, prospective clinical trial has directly compared these two alcohol-based antiseptic solutions.[42]

The choice of venepuncture site is not associated with different infection rates, as shown by a prospective study of 403 patients randomly allocated to insertion via the internal jugular vein or subclavian vein or by a surgical cutdown through the cephalic vein.[43] If the superior vena cava is not accessible, for instance because of thrombosis, a TIVAP can be inserted in the femoral vein (infection rate 0·69 per 1000 catheter-days[44]). Use of ultrasound-guided catheter insertion does not reduce the rate of TIVAP-related infections, but does significantly lower the number of attempts required for successful insertion and increases patients' comfort.[43,45] Systemic antibiotic prophylaxis during TIVAP insertion has no benefit and is not indicated.[46–48]

After insertion

Training of patients, nursing teams, and physicians in how to handle TIVAPs after insertion is mandatory to minimise the risk of bacterial contamination.[7] Huber needles used to

***Panel 1*: Risk factors for TIVAP-related infections**

Modifiable risk factors

- Frequency of TIVAP handling: OR 1·15 (95% CI 1·03–1·3) for each 10% increase in frequency of LTIVC handling, especially in patients with HIV[21]
- Use of TPN, where frequent access to TIVAP and the use of fluids such as lipid products can increase microbial growth[7] (OR 28·5, 95% CI 4·2–200·0)[22]
- Difficulties during insertion (ie, several punctures are required) leading to formation of local thrombus or haematoma that increase the risk of bacterial colonisation (OR 25·6, 95% CI 4·2–106)[22]

Non-modifiable risk factors

- Age, although thresholds depend on the study: <7 years,[13] <10 years (OR 18·4, 95% CI 1·9–106·7),[22] and <40 years[10]
- Chemotherapy for haematological malignancies rather than for solid tumours[13,23] (OR 5·1, 95% CI 1·5–17·5)[24]
- Haemopoietic stem-cell transplantation (OR 1·74, 95% CI 1·1–2·4)[25]
- Reduced autonomy (Karnofsky performance status ≤80%) in patients with cancer (OR 5·3, 95% CI 1·5–19·3)[21]
- Presence of metastases in patients with cancer (OR 4·1, 95% CI 0·9–19·5)[21]
- Bacterial infection within the previous month (OR 2·1, 95% CI 1·1–3·8 in patients with HIV, 5·4, 1·2–25·3 in patients with cancer)[21]
- Neutropenia in patients with HIV (OR 1·8, 95% CI 1·1–3·1)[21] or haematological malignancies (15·1, 2·6–86·5)[26]
- Diabetes in patients with cystic fibrosis[6]

No study identified a specific class of antineoplastic chemotherapy or radiation therapy as being a risk factor of TIVAP-related infection. TIVAP=totally implantable venous-access ports. OR=odds ratio. LTIVC=long-term intravascular catheter. TPN=total parenteral nutrition.

access the TIVAP must be inserted by trained nurses, and operators must wear facial masks, caps, and sterile gloves. Skin must be disinfected with an alcoholic antiseptic (alcohol-based chlorhexidine or povidone-iodine) before every needle insertion.[41] The Huber needle should be changed every 7 days if vascular access is maintained continuously.[10] During needle withdrawal, positive pressure with saline injection might reduce the risk of blood reflux and so prevent catheter-tip occlusion.[49] A heparin lock or flush should not be used after TIVAP; use sterile saline locks after TIVAP are equally efficient to prevent functional or infectious complications.[41,50] The use of chlorhexidine-impregnated sponges or dressings for the prevention of catheter-related bloodstream infections in intensive care has been assessed,[51] but no studies has specifically addressed their use in relation to TIVAP insertion and, therefore, use is not recommended.

Lock solutions and coatings

Preventive antibiotic lock therapy is achieved by injection of a highly concentrated antibiotic solution into the TIVAP lumen. The principle is that this solution will dwell in the lumen for an extended period of time and eradicate any bacteria that might be injected afterwards. Nevertheless, preventive antibiotic lock therapy only prevents intraluminal contamination. The chosen volume of antibiotic must enable coverage of the whole internal surface and, therefore, depends on the type of device. Antibiotic flushes of the catheter may also be applied. During antibiotic flushes the volume of antibiotic solution is injected whenever the device is used but is not left to dwell. A meta-analysis showed that antibiotic lock or flush with vancomycin reduced the risk of catheter-related bloodstream infections.[52] Minocycline combined with a chelator, such as EDTA (edetic acid), has also been assessed.[53] Two paediatric oncology studies showed that antibiotic lock therapy with combined minocycline and EDTA was more effective than heparin for the prevention of catheter-related bloodstream infections.[54,55] Nevertheless, systematic use of antibiotic lock therapy could increase antibiotic resistance.[35,56] Thus, guidelines recommend that the use of preventive antibiotic lock therapy be restricted to patients with LTIVCs who have had multiple catheter-related bloodstream infections despite optimum aseptic techniques.[41]

Limited data are available for non-antibiotic lock solutions, such as ethanol or taurolidine. One preliminary paediatric study of ethanol locks that included 12 patients was interrupted because of TIVAP occlusion in three.[57] A meta-analysis showed that ethanol lock therapy reduces the incidence of catheter-related bloodstream infection in paediatric total parenteral nutrition when tunnel catheters are used, but increases the risk of thrombosis,[58] and, therefore, should be restricted to high-risk patients with tunnel catheters.[59] Mild and self-limiting adverse effects, such as dizziness, nausea, headaches, facial flushing, and eventually an alcohol taste in the mouth, have been reported, especially after flushing.[60,61]

Taurolidine, a derivative of the aminoacid taurine, has been proposed as a lock therapy because of its antimicrobial effect against a broad range of micro-organisms in vitro.[62–64] Studies done in patients receiving haemodialysis are encouraging, but data supporting its use as a lock in TIVAP are limited.[65,66] An initial study in 179 children with cancer, around 75% of whom had TIVAPs, showed no significant reduction in catheter-related bloodstream infections with taurolidine and sodium citrate when compared with heparin.[67] A later study in children with haematological disease showed a significant reduction in catheter-related bloodstream infections with use of taurolidine and sodium citrate locks compared with heparin, but the locks were only assessed in tunnel catheters.[63] A randomised study in patients receiving total parenteral nutrition showed that a taurolidine and sodium citrate lock reduced the rate of catheter-related bloodstream infections when used after the first episode of infection, compared with heparin (TIVAPs represented around 40% of LTIVCs).[68] These results indicate that larger comparative studies with TIVAP are needed to define the precise roles and indications of ethanol or taurolidine as preventive locks.

The use of coatings on central venous catheters has been extensively studied for short-term use, and has been associated with significant reductions in the risk of catheter-related bloodstream infections.[69,70] In LTIVCs, however, which dwell in the blood flow for longer periods, the formation of the conditioning film might lessen the antimicrobial action of the coating.[31] Furthermore, if made with antibiotic-releasing surfaces, the effect will stop once the device is exhausted. In a study of LTIVCs coated with minocycline and rifampicin, in place for a mean period of 66 (SD 31) days, the rate of catheter-related bloodstream infections was significantly reduced.[71] Drug delivery was maintained for at least 35 days after catheter insertion. Thus, the development of surface modifications or antibiotic coatings that would prevent colonisation for a longer time remains an important challenge.

Diagnosis of infections

TIVAP-related infection should be suspected if a patient exhibits local signs of infection, such as pain or erythema, at the site of implantation. If, however, patients have isolated fever, chills, or severe sepsis, diagnosis is more difficult. Guidelines have proposed classification of TIVAP-related infections into three subtypes: local complicated infections, defined as infection of the tunnel or port pocket with extended erythema or induration (more than 2 cm), purulent collection, skin necrosis, and spontaneous rupture and drainage (figure 1); TIVAP-related bloodstream infections, defined as a positive blood culture drawn from a peripheral vein associated with corroborating evidence from paired blood cultures or culture of components of the removed TIVAP (ie, infections can be identified with or without device removal); and catheter-related infections, defined by the

association of local or general signs of infection and positive culture of the catheter tip.[72] On the basis of these criteria, we propose a diagnostic algorithm that includes clinical signs and microbiological tests (figure 2).

Local infections

Clinical signs of local infection at the site of TIVAP implantation, such as erythema or purulent exudate, have high specificity but little sensitivity for the diagnosis of TIVAP-related infection.[72] Local signs are reported in only 7–12% of TIVAP-related bloodstream infections. On the other hand, because local infections are caused by extraluminal contamination, they frequently occur without any concomitant bloodstream infection.[28,73,74] 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 or necrotic skin, or by swabbing of the port surface is mandatory.[28,75] Culture of peripheral blood should also be done to rule out associated bloodstream infection (figure 2).

Bloodstream infections

Device in situ

To diagnose infection without removal of the TIVAP relies on the identification of the same microorganism in paired blood cultures.[72] To correctly interpret the results, consecutive blood samples should be tested, with the same volume of blood drawn from a peripheral vein and from the TIVAP through a Huber needle, ideally before the start of antibiotic treatment.[72,76,77] Another crucial point is to precisely label the origin of each blood culture bottle.[71] The two most frequently used methods for diagnosis of catheter-related bloodstream infections are simultaneous quantitative blood cultures and the differential time to positivity of qualitative blood cultures.[76,78–80] If a TIVAP is the source of a bloodstream infection, the inoculum will be higher in the blood drawn from TIVAP than in that drawn from the peripheral vein and, therefore, the number of bacteria will be higher and the differential time to positivity longer; differences of four times the level of bacteria or at least 2 h between times to positivity are relevant results (figure 2).[72,76,77,79,80] When used for the diagnosis of LTIVC-related bloodstream infection, these two methods have sensitivity of more than 90% and specificity close to 100% for quantitative paired blood cultures and 75–91% for differential time to positivity,[76,79,80] although they are deemed of equivalent usefulness in guidelines.[72] Therefore, the choice of technique will rely mostly on local equipment and training.

To reduce the risk of contamination when blood is drawn from TIVAP, rigorous skin disinfection is mandatory before sampling.[72]

After device removal

To show that a bloodstream infection originates from a TIVAP relies on the identification of the same microorganism in a TIVAP component and peripheral blood cultures (figure 2). The catheter tip (4 cm distal part) can be cultured with semiquantitative or quantitative methods, with thresholds for clinically relevant colonisation of 15 colony-forming units (cfu) and 10^3 cfu/mL, respectively.[81,82] Both methods, however, have sensitivity lower than 50% for the diagnosis of TIVAP colonisation and, therefore, should be used in conjunction with other techniques.[72,73,75,83] For instance, an adapted Brun-Buisson method has been suggested for quantitative culture of the TIVAP septum. When a threshold of 10^3 cfu/mL was used, this method was associated with 93% sensitivity and 100% specificity for the diagnosis of TIVAP-related bloodstream infections.[73]

Any macroscopic debris or clots present after septum removal should also be sampled and cultured. Sensitivity and specificity are both 100% for TIVAP-related bloodstream infections.[75] The internal surface of the port can be swabbed.[84,85] In clinical microbiology laboratories not permitted to use cutting blades, sterile saline (0·2 mL) may be injected inside the reservoir, aspirated, and plated.[28]

The main limitations to culture of the port septum and port deposits are a lack of standardisation for technical procedures and the absence of a consensus threshold.[72] Therefore, testing of the catheter tip and of a component of the port reservoir is advisable.[72] Careful handling of explanted materials will reduce the risk of contamination in the laboratory.

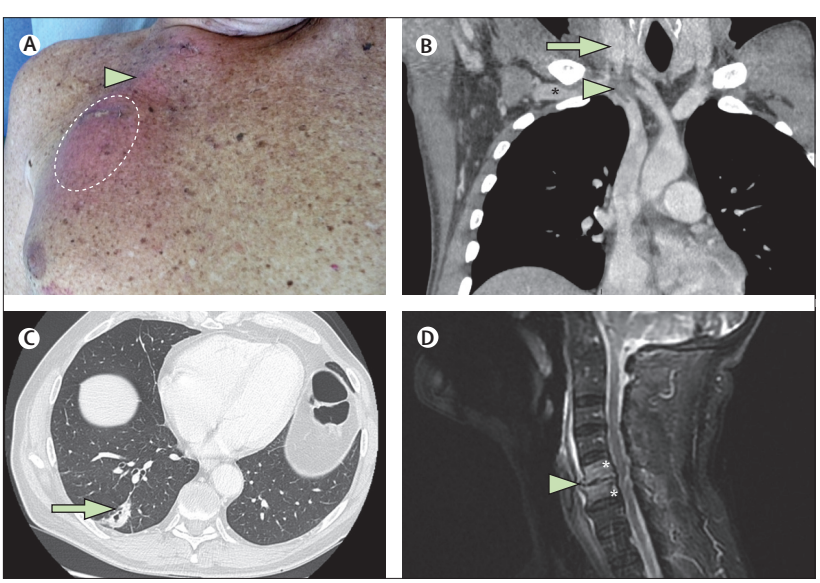

***Figure 1*: Complications of infections related to totally implantable venous access ports**
(A) Port-pocket infection (surrounded by white dashed line) and tunnel infection (green arrow) caused by *Staphylococcus aureus*. (B) Thrombophlebitis after a bloodstream infection related to a totally implantable venous access port, caused by *S aureus*. A thrombus (green arrowhead) developed at the junction of the internal jugular vein (green arrow) and subclavian vein (asterisk). (C) Right pulmonary abscess (green arrow) with cavitation secondary to a bloodstream infection related to a totally implantable venous access port, caused by *S aureus*. (D) C5–C6 spondylitis caused by *Staphylococcus lugdunensis* after a bloodstream infection related to a totally implantable venous access port. Sagittal view of the cervical spine with T2-weighted MRI shows narrowing of the disc space (green arrowhead) and vertebral oedema (asterisks). Panel A was reproduced by permission of Chantal Dreyer, Hôpital Beaujon, Clichy, France.

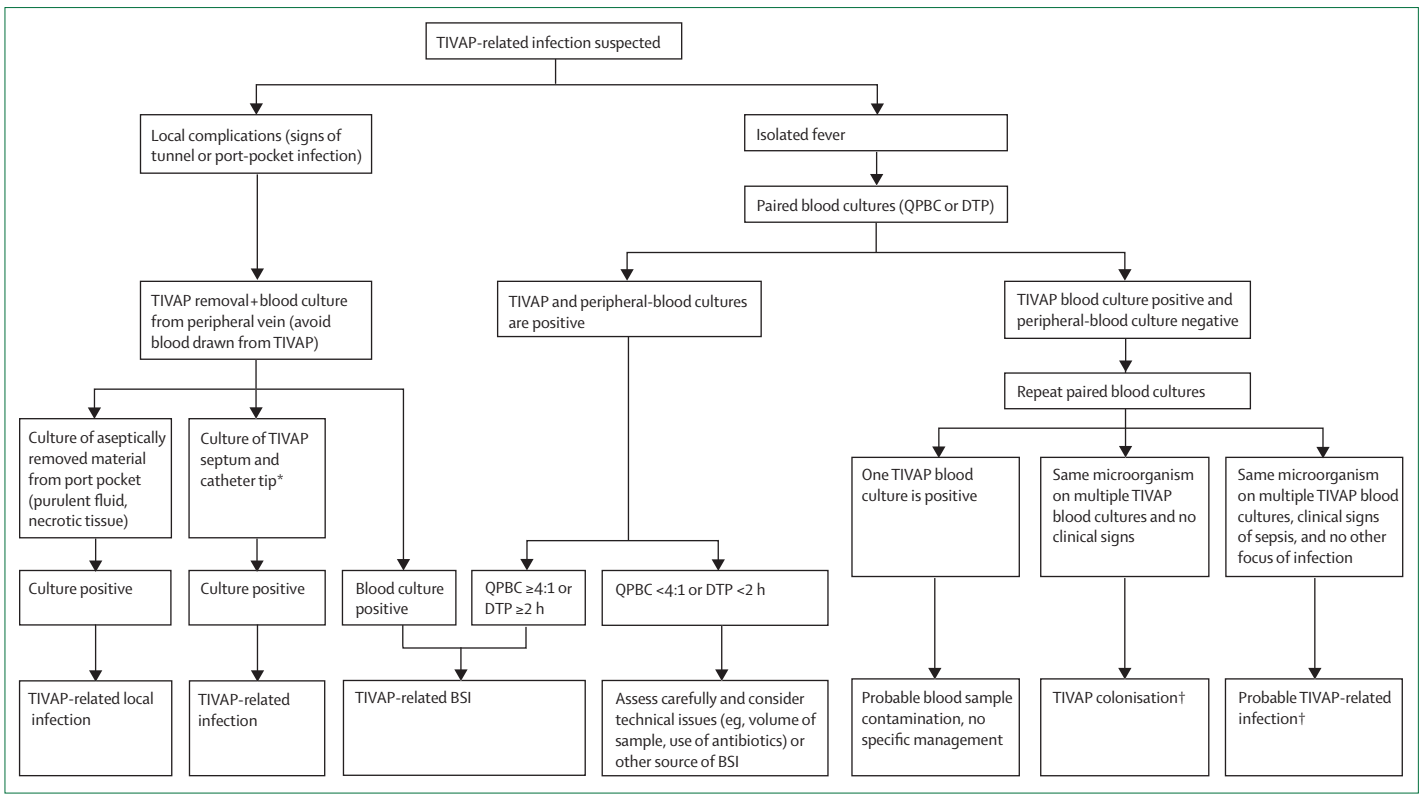

***Figure 2*: Diagnostic algorithm to guide assessment of suspected TIVAP-related infections**
TIVAP=totally implantable venous-access port. QPBC=quantitative paired blood cultures. DTP=differential time to positivity. BSI=bloodstream infection. *Use quantitative or semiquantitative methods.[4,72] †TIVAP colonisation differentiated from probable TIVAP-related infection by the presence of clinical signs of sepsis. Another focus of infection must be ruled out.

Fungal bloodstream infections

Without TIVAP removal, diagnosis of fungal infections is challenging. Studies of paired blood cultures have seldom included fungal infections.[76,78,79,86] The time taken to detect *Candida* spp growth in peripheral blood cells has been suggested as a diagnostic tool, because in one study time to positivity was shorter in cases of catheter-related candidaemia (mean 17 [SD 2] h) than candidaemia from another source (38 [3] h).[87] Thus, times longer than 30 h would rule out the catheter as the source of candidaemia. If the TIVAP is removed, microbiological methods and thresholds are the same as for bacterial infections. Culture on blood agar is sensitive enough to detect the growth of fungi involved in TIVAP-related infections, even if a longer incubation time is required than for bacteria (24–72 h).[88]

Workup for complications

When TIVAP-related bloodstream infection is suspected, clinicians should assess patients for complications, such as severe sepsis, endocarditis, or other haematogenous effects (figures 1, 3).[28] Guidelines recommend systematic transoesophageal echocardiography in patients with *S aureus* TIVAP-related bloodstream infections.[72] Nevertheless, in selected patients without intracardiac devices and with rapid clearance of bloodstream infection, transthoracic echocardiography at least 5 days after infection onset can probably safely rule out infective endocarditis.[91–95] If patients develop clinical signs of thrombophlebitis or persistent bloodstream infection despite appropriate systemic antimicrobial therapy, venous ultrasonography should be used, especially in cases of *S aureus* TIVAP-related bloodstream infections (figure 1).[72,96]

Whatever the microorganism, persistent bloodstream infection after 3 days of adequate antimicrobials should prompt a complete workup, including echocardiography and venous ultrasonography, with or without CT.[72]

Treatment

Removal or retention of the device

In the case of catheter-related bloodstream infection, the treatment of choice is systemic antimicrobial therapy in conjunction with removal of the colonised device.[4] Nevertheless, reduced venous access, the potential for coagulation disorders, and the cost of a new procedure all support catheter salvage if the clinical situation allows it.[72]

TIVAP removal is mandatory, irrespective of the microbial cause, in complicated infections, which are defined by tunnel or port-pocket infections, severe sepsis, or septic shock, endocarditis, septic thrombophlebitis, osteomyelitis, or other haematogenous seeding (figures 1, 3).[72] Furthermore, complicated and

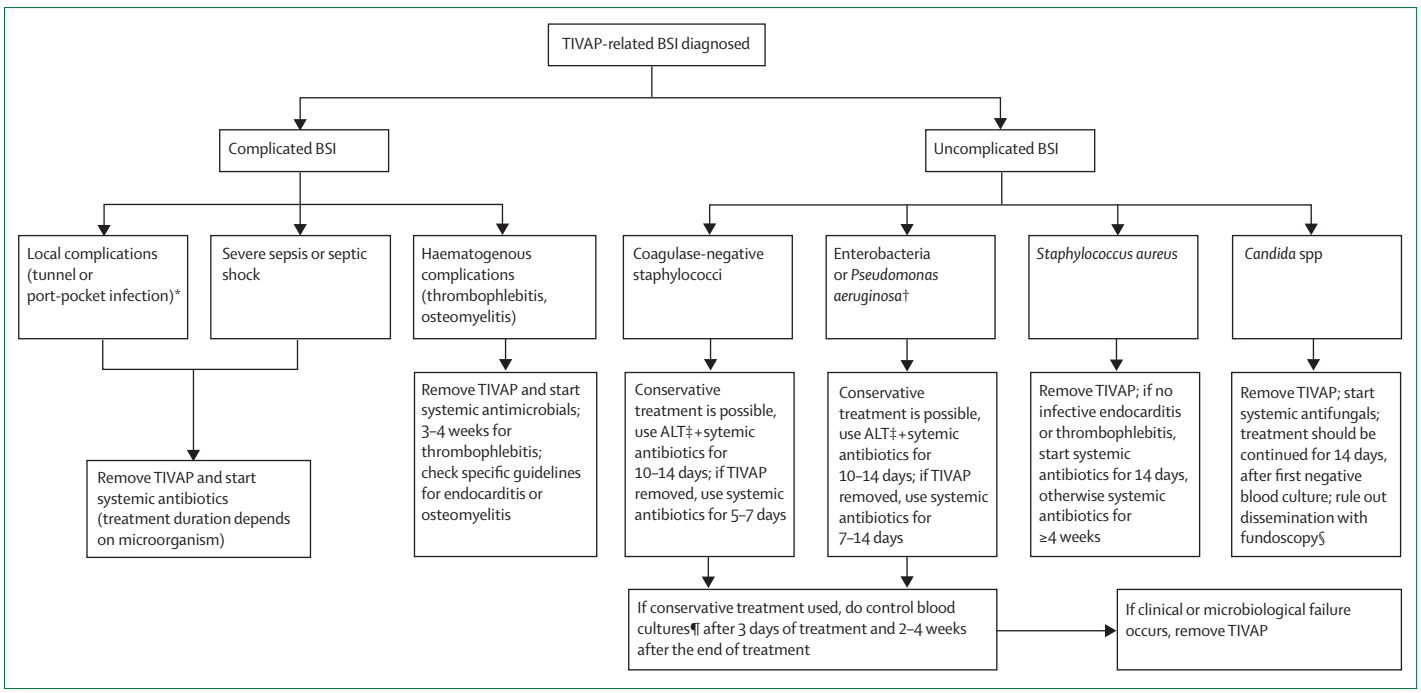

***Figure 3*: Treatment of TIVAP-related bloodstream infection[71]**

TIVAP=totally implantable venous-access port. BSI=bloodstream infection. ALT=antibiotic lock therapy. *In case of tunnel or port-pocket infection without BSI, TIVAP removal is also required with 5–7 days of systemic antibiotics.[4,72,89] †In case of *Pseudomonas aeruginosa* TIVAP-related BSI, guidelines suggest that TIVAP removal is the first-line option.[72] ‡The presence of intracardiac or intravascular devices is purported to preclude the use of ALT, although this contraindication is not mentioned in guidelines.[72] §Only ophthalmological examination is recommended for all patients in guidelines, although some clinicians also propose echocardiography and CT.[89] ¶The source of the blood to be drawn is debated; some authors recommend blood culture only on samples from a peripheral vein or from TIVAP.[90]

non-complicated infections caused by *S aureus* or *Candida* spp generally warrant TIVAP removal (figure 3), although there are some exceptions, as discussed in the section on adaptations of treatment.[72,90] If a conservative strategy is decided upon, the TIVAP should be removed if blood cultures are persistently positive 72 h after antibiotics are started.[72]

In cases of uncomplicated TIVAP-related bloodstream infection not caused by *S aureus* or *Candida* spp, conservative treatment with a combination of systemic antimicrobials and antibiotic lock therapy can be considered.[72] Most infections are associated with intraluminal colonisation and, therefore, administration of high concentrations of antimicrobial solution that fills and remains in the entire volume of the lumen for an extended period of time might sterilise the device.[97–99] Despite several limitations, evidence supports the use of antibiotic lock therapy. For instance, in a randomised, placebo-controlled study antibiotic lock plus systemic antibiotic therapy was more effective than systemic antibiotic therapy alone for the treatment of LTIVC-related bloodstream infections, although the difference did not reach significance because of the small sample size.[74] Additionally, large uncontrolled studies (table) showed high cure rates in patients with uncomplicated LTIVC-related bloodstream infections due to coagulase-negative staphylococci (89%) or Gram-negative rods (95%).[90,98,113]

Antibiotic lock preparations

Head-to-head comparisons of antibiotic lock drugs are lacking and some in-vitro studies have yielded conflicting results.[115,116] The most frequently used antibiotics are glycopeptides, aminoglycosides, and fluoroquinolones, which have been associated with high rates of good outcomes (table). The chosen antibiotic must be active against the identified microorganism in vitro. Ideally, antimicrobials should be administered at a concentration at least 1000 times greater than the minimum inhibitory concentration (frequently 1–5 mg/mL) with a volume that fills the entire TIVAP lumen. In most studies, antibiotic lock therapy is prescribed for 10–14 days (figure 3, table) with change of the lock solution every 12–24 h, dependent on the necessity for vascular access.[72] Replacement of the solution every 48–72 h is also safe.[113] In patients with TIVAP-related bloodstream infections, systemic antimicrobials should be administered for 10–14 days.[72] The addition of heparin to antibiotic lock therapy has been proposed to avoid thrombosis of the catheter,[72] although no comparative data support this approach and adverse effects have been reported, such as bleeding or increased *S aureus* biofilm formation in vitro.[117,118] Antibiotic lock therapy can, therefore, be administered in saline or heparin, at 10–100 IU/mL (table).[72] When conservative treatment is used, close follow-up is mandatory to assess for treatment failure. At the very least blood samples

should be cultured 3 days after the start of treatment and 2–4 weeks after the end of the treatment (figure 3).

Adaptation of treatment according to the identified microorganism

In infections with coagulase-negative staphylococci and without complications, the cure rate of antibiotic lock therapy is high (more than 80%), and failures are due mainly to relapses during the first month of follow-up.[90,98] If treatment fails or infection recurs, removal of the TIVAP should be considered. Glycopeptides given for 10–14 days have been used extensively. A prospective uncontrolled study identified a trend towards better outcomes with teicoplanin than

	Number of episodes treated with ALT	Percentage of catheters that were TIVAP (%)*	Microorganisms (%)	Catheter use	Systemic anti-microbial treatment (n [%])	ALT or ELT	Association with heparin† (concen-tration)	Duration of ALT or ELT (days)	Cure rate	Success criteria
Domingo et al, 1999[100]	27	100%	CNS 57%, *Enterobaceriaceae* spp 3%, *Pseudomonas* spp 3%, *Staphylococcus aureus* 6%, others 30%	Anti-infective chemotherapy in patients with AIDS	9 (33%%)	Vancomycin (1 mg/mL), amikacin (1 mg/mL)	No	5	22 (81%)	Clinical plus negative paired blood cultures at the end of ALT
Piketty et al, 1999[101]	31	100%	CNS 100%	Anti-infective chemotherapy in patients with AIDS	31 (100%)	Vancomycin (40 mg/mL), amikacin (60 mg/mL)	Yes (ND)	3 (1–5)	13 (42%)	Clinical (no systematic blood culture)
Longuet et al, 2001[102]	16	100%	CNS 41%, *Enterobaceriaceae* spp 24%, *Staphylococcus aureus* 12%, other 23%	Anti-infective or antineoplastic chemotherapy	16 (100%)	Vancomycin (5 mg/mL) or teicoplanin (5 mg/mL) with or without amikacin (ND)	No	8 (3–15)	7 (44%)	Clinical plus negative paired blood cultures 2–7 days after the end of ALT
Santarpia et al, 2002[7]	60	86%	CNS 67%, *Enterobaceriaceae* spp 15%, *Staphylococcus aureus* 6%, other 12%	TPN	60 (100%)	Teicoplanin (33–100 mg/mL), piperacillin (166–500 mg/mL), netilmicin (50–150 mg/mL) or clindamycin (100–300 mg/mL)	Yes (ND)	7	50 (83%)	Undefined
Reimund et al, 2002[103]	25	64%	CNS 61%, *Enterobaceriaceae* spp 24%, *Staphylococcus aureus* 12%, other 3%	TPN	39 (100%)	Vancomycin (1 mg/mL), amikacin (1·5 mg/mL) or minocycline (0·2 mg/mL)	No	ND	25% if TIVAP, 50% if tunnelled	Undefined
Viale et al, 2003[104]	30	37%	CNS 35%, *Enterobaceriaceae* spp 9%, *Pseudomonas* spp 9%, *Staphylococcus aureus* 28%, other 22%	Anti-infective or antineoplastic chemotherapy and TPN	15 (50%)	Vancomycin (20 mg/mL), teicoplanin (20 mg/mL), amikacin (10 mg/mL), imipenem (ND)	No	14	28 (93%)	Clinical plus negative paired blood cultures 14 and 28 days after the beginning of ALT
Koldehoff et al, 2004[105]	11	100%	CNS 46%, *Enterobaceriaceae* spp 8%, *Pseudomonas* spp 8%, *Staphylococcus aureus* 8%, other 30%	Antineoplastic chemotherapy	11 (100%)	Taurolidine (5 mg/mL)	No	1 (1–3)	11 (100%)‡	Undefined
Rijnders et al, 2005[74]	22	91%	CNS 63%, *Enterobaceriaceae* spp 14%, other 23%	Mostly antineoplastic chemotherapy	22 (100%)	Vancomycin (0·5 mg/mL) or ceftazidime (0·5 mg/mL)	Yes (100 IU/mL)	11 (7–14)	14 (67%)	Clinical (no systematic blood culture)
Fortún et al, 2006[106]	19	74%	CNS 74%, *Pseudomonas* spp 10%, *Staphylococcus aureus* 16%	Antineoplastic chemotherapy and TPN	19 (100%)	Vancomycin (2 mg/mL), gentamicin (2 mg/mL), or ciprofloxacin (2 mg/mL)	Yes (20 IU/mL)	12 (5–14)	16 (84%)	Clinical plus negative catheter blood culture 2–5 days after the end of ALT
Fernàndez-Hidalgo et al, 2006[90]	115	16%	CNS 49%, *Enterobaceriaceae* spp 18%, *Pseudomonas* spp 5%, *Staphylococcus aureus* 16%, other 12%	Antineoplastic chemotherapy, TPN, and haemodialysis	115 (100%)	Vancomycin (2 mg/mL), amikacin (2 mg/mL) or ciprofloxacin (2 mg/mL)	Yes (20 IU/mL)	12 (8–14)	94 (82%)	Clinical plus negative blood culture 1 month after the end of ALT
Onland et al, 2006[107]	51	21%	CNS 52%, *Enterobaceriaceae* spp 11%, *Staphylococcus aureus* 14%, other 23%	Mostly antineoplastic chemotherapy	51 (100%)	Ethanol 70%	No	5	45 (88%)	Clinical (no systematic blood culture)

(Continues on next page)

	Number of episodes treated with ALT	Percentage of catheters that were TIVAP (%)*	Microorganisms	Catheter use	Systemic anti-microbial treatment (n [%])	ALT or ELT	Association with heparin† (concen-tration)	Duration of ALT or ELT (days)	Cure rate	Success criteria
(Continued from previous page)										
Souza Dias et al, 2008[108]	17	78%	*Pseudomonas* spp 100%	Mostly antineoplastic chemotherapy	17 (100%)	Ceftazidime (ND), amikacin (2 mg/mL) or levofloxacin (ND)	Yes (100 IU/mL)	ND	14 (82%)	Undefined
Broom et al, 2008[109]	17	11%	CNS 25%, *Enterobaceriaceae* spp 21%, *Pseudomonas* spp 21%, other 33%	Antineoplastic CT	17 (100%)	Ethanol 70%	No	5	15 (88%)	Clinical plus negative catheter blood culture 1 day after the end of ALT
Del Pozo et al, 2009[98]	44	100%	CNS 100%	Antineoplastic chemotherapy and TPN	44 (100%)	Vancomycin (2 mg/mL), teicoplanin (10 mg/mL)	Yes (100 IU/mL)	10 (10–14)	39 (89%)	Clinical plus negative catheter blood cultures 7 days after the end of ALT
Del Pozo et al, 2009[110]	18	100%	CNS 5%, *Enterobaceriaceae* spp 35%, other 60%	Antineoplastic chemotherapy	18 (100%)	Vancomycin (2 mg/mL) with or without gentamicin (2 mg/mL) (if *Enterococcus faecium*), teicoplanin (10 mg/mL), piperacillin-tazobactam (10 mg/mL), levofloxacin (5 mg/mL), co-trimoxazole (16/3·2 mg/mL)	Yes (100 IU/mL)	12 (5–14)	16 (89%)	Clinical + negative catheter blood culture 30 days after the end of ALT
Rajpurkar et al, 2009[111]	3	66%	CNS 40%, other 60%	Clotting factors in patients with haemophilia	3 (100%)	Ethanol 70%	No	3 (1–3)	3 (100%)	Clinical plus negative catheter blood culture after the end of ALT
McGrath et al, 2011[112]	80	24%	CNS 33%, *Enterobaceriaceae* spp 20%, *Pseudomonas* spp 9%, *Staphylococcus aureus* 8%, other 30%	Anti-infective or antineoplastic chemotherapy and TPN	80 (100%)	Ethanol 70%	No	1	59 (75%)	Clinical plus negative catheter blood culture 30 days after the beginning of ALT
Funalleras et al, 2011[113]	46	28%	*Enterobaceriaceae* spp 59%, *Pseudomonas* spp 26%, other 15%	Antineoplastic chemotherapy and haemodialysis	46 (100%)	Amikacin (2 mg/mL) or ciprofloxacin (2 mg/mL)	Yes (20 IU/mL)	13 (10–16)	44 (96%)	Clinical plus negative catheter blood culture 30 days after the beginning of ALT
Valentine et al, 2011[114]	26	15%	CNS 14%, *Enterobaceriaceae* spp 36%, *Pseudomonas* spp 3%, *Staphylococcus aureus* 11%, other 36%	Antineoplastic chemotherapy in intensive care	26 (100%)	Ethanol 70%	No	1·5 (1–5)	24 (92%)	Clinical plus negative catheter blood culture 2 days after the beginning of ALT
Del Pozo et al, 2012[115]	13	46%	CNS 87%, other 13%	Antineoplastic chemotherapy and haemodialysis	11 (85%)	Daptomycin (5 mg/mL)§	Yes (100 IU/mL if TIVAP and 5000 IU/mL if dialysis)	14 (10–14)	11 (85%)	Clinical plus negative catheter blood culture 30 days after the end of ALT

Most published studies excluded patients with complicated bloodstream infections or infections caused by *Staphylococcus aureus* or *Candida* spp. ALT=antibiotic lock therapy. TIVAP=totally implantable venous-access port. ELT=ethanol lock therapy. CNS=coagulase-negative staphylococci. ND=not determined. TPN=total parenteral nutrition. *Other long-term intravascular catheters were tunnelled or haemodialysis catheters. †Of note, the heparin that is used does not contain antimicrobial preservative. ‡Three re-treatments needed. §In lactated Ringer's solution providing 45 mg of calcium/L.

***Table*: Studies of conservative treatment of bacterial bloodstream infections related to totally implantable venous access ports**

with vancomycin.[90,98] Daptomycin might be suitable as an alternative.[115,116]

Conservative treatment of TIVAP-related bloodstream infection with Gram-negative rods is associated with a cure rate of 87–95% when patients with local or distant complications are excluded.[90,113] Guidelines suggest TIVAP removal if *Pseudomonas aeruginosa* infection is identified,[72] but studies of antibiotic lock therapy have shown similar outcomes for *Pseudomonas* spp and *Enterobacteriaceae* spp. Fluoroquinolones and aminoglycosides are the antimicrobials that have been most frequently tested for these infections.[90,113]

In most cases of *S aureus* TIVAP-related bloodstream infection the catheter should be removed because of the high failure rates of antibiotic lock therapy (45–60%) and possible death.[90,119] Antibiotic lock therapy could, however,

be considered in exceptional circumstances, after exclusion of local or distant complications, such as infective endocarditis.[72] Cefazolin and vancomycin are the antimicrobials most frequently used in this setting. The efficacy of other antimicrobials such as aminoglycosides or daptomycin should be assessed in clinical studies.[90,116,119,120]

Infections due to *Candida* spp should lead to catheter removal. Conservative treatment should be considered only in unusual and extenuating circumstances, after the ruling out of local or distant complications. Although the optimum antifungal lock therapy has not been established for this unusual situation, amphotericin B (liposomal or deoxycholate) and ethanol are the most frequently used compounds.[121] If the catheter is retained, a systemic antifungal with activity against *Candida* spp biofilms should be used, such as lipid-based amphotericin B or echinocandins (panel 2).[122]

If polymicrobial infection develops, antibiotic lock therapy can be proposed if two criteria are met: none of the involved microorganisms is *S aureus* or *Candida* spp, and a one antimicrobial will treat all microorganisms or a combination of antimicrobials with known stability is available.[90,113]

Alternative lock therapies

Aside from commonly used drugs in antibiotic lock therapy, 70% ethanol or daptomycin have been used in conservative treatment. Most ethanol studies have been uncontrolled and done in paediatric patients in whom diagnosis might be inaccurate owing to a lack of peripheral-blood cultures.[107,109,112] A retrospective study of 70% ethanol dwelling for 5 days in the catheters of 51 children reported that the infection was cleared in all patients, with recurrence within 30 days seen in 12%.[107] Daptomycin has been proposed as lock therapy because of its potent in-vitro effect against biofilms.[127,128] A phase 2 clinical study of daptomycin antibiotic lock therapy was done in 13 patients with LTIVC-related infections (50% in TIVAPs) caused by coagulase-negative staphylococci or *Enterococcus faecalis*.[115] After a mean of 14 days of treatment, infections were cleared in 11 (85%) patients.[115] No comparative studies have yet been published on ethanol or daptomycin and clinical studies are now expected to assess whether either is more efficient or more quickly effective than the antibiotics already used.

***Panel 2*: Challenges related to TIVAP-related fungal infections**

- Guidelines recommend early removal of central venous catheters in cases of candidaemia[72,89,122]
- Catheter-related candidaemia needs to be differentiated from non-catheter-related candidaemia
- If the candidaemia is not catheter related, it is plausible that catheter retention will not affect outcomes, especially with use of an antifungal effective against *Candida* spp biofilms[123]
- If the candidaemia is catheter related, it is very likely that catheter removal is required.[124]
- The diagnosis of fungal catheter-related bloodstream infections without catheter removal is challenging, as paired blood cultures in this setting are poorly studied[75,77,78]
- Even if TIVAP removal is recommended, many patients are not candidates for catheter replacement because of poor general condition
- Antifungal lock therapy has been proposed to increase the likelihood of biofilm eradication and reduce the need for TIVAP removal[121]
- Against *Candida* biofilms, azoles have poor activity; lipid formulations of amphotericin B are more effective than amphotericin B deoxycholate, and echinocandins have excellent in-vitro activity[121]
- An overall success rate was reported in 15 of 20 patients with various types of antifungal locks[121]
- Ethanol lock therapy could be a promising alternative to antifungal lock therapy, with successes having been reported on eight of ten patients[125,126]
- Studies of antifungal lock therapy specifically for TIVAP-associated fungal infections are clearly needed

TIVAP=totally implantable venous-access port.

Directions for future developments

In view of limitations of current diagnostic, preventive, and therapeutic measures, many questions still need to be addressed about TIVAP-related infections.

Diagnosis

Despite the usefulness of paired blood cultures in the diagnosis of TIVAP-related bloodstream infections without device removal, false-positive and false-negative results are possible.[73,77,86,129,130] Attempts have been made, therefore, to develop molecular biology tools for the diagnosis of TIVAP-related infections. For example, amplification and sequencing of bacterial DNA in the *16S rRNA* gene has been done in blood drawn from central venous catheters of patients with catheter-related bloodstream infections or in fluid and biofilms from the internal surface of the port after TIVAP removal.[84,131] These methods are more sensitive than cultures in patients who have previously received antibiotics, but specificity is only around 80% because of false-positive results from external DNA contamination during the procedure.

Another approach has been to try to identify biomarkers of biofilm formation inside the port that would enable early identification of colonisation before the onset of bloodstream infections. For instance, some lipopolysaccharide modifications occur only within Gram-negative bacterial biofilms.[132]

In relation to fungal infections, the use of selective blood culture bottles, PCR, or antigen detection on blood samples might increase the speed, sensitivity, or both, of diagnosis, but these methods need to be assessed specifically in TIVAPs.[133,134]

Prevention

Multifactorial initiatives that bundle together strategies to improve adherence to recommended evidence-based practices and achieve optimum hygiene should be

implemented for TIVAP insertion and handling.[4,41,72] Dedicated teams could be involved in the training of health-care workers and patients about infusion therapy.[4]

Other preventive strategies are limited by the effects of the host's conditioning film on any modified surfaces of TIVAPs, and by the decline in effect of antibiotic coatings on catheters over time. A possible solution might be to use antiadhesive compounds that inhibit the deposition of blood components or local thrombosis, which would slow or prevent the formation of the conditioning film. For instance, modification of TIVAP surfaces with non-leaching polymeric sulphobetaine retains water on the catheter surface, which reduces adhesion of proteins, host cells, and microbes and lowers the risk of thrombus formation in vitro and in vivo.[135] Although this and other approaches show encouraging results, longer-term assessment is required.[136]

Biofilm eradication

Antibiotic lock therapy has drawbacks, such as possible treatment failure or long treatment duration.[72] Development of more efficient and faster antibiotic lock therapies has been attempted to resolve these issues. In-vitro and in-vivo studies have identified several potential lock candidates, such as ethanol or daptomycin.[109,115] Another approach is to use an adjuvant to increase the antibiotic efficiency against biofilms. For instance, combined use of an antibiotic and a chelator, such as EDTA or sodium citrate, has been proposed, because divalent cations play a key part in the maintenance of biofilm matrix stability.[137] The addition of chelators destabilises the matrix and, therefore, increases antimicrobial activity.[53] Many in-vitro studies have reported effects against biofilms with EDTA alone or combined with gentamicin or minocycline and 25% ethanol.[138,139] In a rat study, the combination of gentamicin and EDTA led to complete eradication in vivo of biofilms of Gram-positive and Gram-negative bacteria formed inside TIVAP, which suggests that clinical studies are warranted.[140]

Various other compounds have shown promising effects in basic research, although none has yet been assessed as an antibiotic lock therapy. The association of an aminoglycoside and a sugar, such as mannitol or fructose, might increase antibiotic uptake in the most tolerant bacteria inside biofilms. Killing of these cells, called persisters cells, might improve treatment efficacy in vivo.[141]

Quorum sensing is a key component of biofilm communication and, therefore, many investigators have speculated that interfering with relevant signals could alter biofilm maturation, which might improve eradication. For instance, RNAIII inhibiting peptide, a compound that interferes with *S aureus* quorum sensing, efficaciously prevented infection related to central venous catheters in vivo.[142]

Search strategy and selection criteria

We searched PubMed for papers published in English between January, 1980, and July, 2013, reporting on infections related to totally implantable venous-access ports for any indication. We used the search 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", and, related to treatment, we included the terms "sepsis/prevention & control", "catheter-related infections/drug therapy", "bacteremia/drug therapy", "antibiotic lock therapy", "ethanol lock", "antibiotic lock technique", and "antifungal lock therapy". We focused on studies assessing epidemiology, risk factors, microbiology, diagnosis, prevention, treatment, and prognosis. We included epidemiological or therapeutic studies of different types of long-term intravascular catheters if they included specific data about totally implantable venous access ports. We also searched the reference lists of retrieved papers for further relevant articles.

Another approach would be to disperse bacterial biofilms because most of the antibiotic tolerance is lost when the bacteria return to a planktonic state.[37] Dispersion, however, must coincide with use of systemic and local antibiotics, because release might be associated with upregulation of bacterial virulence, which could lead to severe sepsis.[143] Various compounds, such as dispersin B, DNase I, or autoinducing peptides, have been associated with biofilm dispersion in vitro, and to a lesser extent in vivo.[144,145]

Many other compounds or strategies are being investigated, such as vaccination, bacteriophages, or combinations of antibiotic and non-antibiotic compounds selected through the screening of chemical libraries. Substantial research is still required before these approaches could reach clinical studies.[35,146–149]

Conclusions

30 years of intense study of TIVAP-related infections has led to improved delineation of risk factors, which is of key importance owing to the increasing number of TIVAPs being used. Although antibiotic lock therapy has proven to be a pivotal strategy for the conservative treatment of selected uncomplicated TIVAP-related bloodstream infections, much work still needs to be done, particularly because progress has been made on the reduction of antimicrobial tolerance by use of combinations of antibiotics and compounds that affect biofilm integrity. Prevention of TIVAP-related infections will benefit from device development, specifically methods to reduce microbial colonisation such as surface modifications with antiadhesion agents. Finally, although the diagnosis of TIVAP infections remains challenging, identification of biofilm biomarkers could lead to improved preventive or curative

decisions at early stages of TIVAP colonisation. Such timely therapeutic actions could substantially lower the rate of device removal and fundamentally change TIVAP management.

Contributors

DL, NF-H, and BA did the initial literature searches and wrote the first draft of the Review. DL prepared the figures. All authors participated in decisions about the intellectual content, revision, and final approval of the paper.

Conflicts of interest

We declare that we have no conflicts of interest.

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