INFECTIOUS COMPLICATIONS OF ARTERIOVENOUS ePTFE GRAFTS FOR HEMODIALYSIS

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Background. Insufficient venous vasculature disallows autologous arteriovenous fistula creation. In this case an arteriovenous conduit of expanded polytetrafluoroethylene (ePTFE) interposed between artery and vein is used for hemodialysis. Although arteriovenous graft infection is an infrequent complication, infected grafts cannot be used for hemodialysis and can cause infection, sepsis and bleeding. Treatment options remain limited but the general approach is to maintain functional angioaccess and to eradicate infection.

Aim. to summarize current knowledge of the prevention and treatment of arteriovenous graft infection.

Methods. literature review

Conclusions. ePTFE graft present an unreplaceable material used for angioaccess in patients with an insufficient venous vasculature. A number of risk factors causing graft infection is known. Since hemodialysis patients are a high-risk group, an effective strategies for graft infection prevention and early diagnosis should be determined. Among the most important risk factors belong surgical procedure, recurrent venipuncture and other infection disease. The prostheses should be removed when infected, especially in the presence of sepsis. In case of “localized infection”, the prostheses can be removed partially only under the condition of careful patient selection and subsequent follow-up.

INTRODUCTION

Chronic hemodialysis treatment requires vascular access. This can be provided by central venous catheter, native arteriovenous fistula or arteriovenous graft interposed between arterial and venous blood vessel. A native arteriovenous fistula is considered the most favourable in terms of function, duration and absence of complications. There are always however, a number of patients with insufficient autologous venous vasculature where the native superficial venous vessels are hypoplastic or attrited due to previous surgical procedures. For this reason a central venous catheter is introduced or an arteriovenous conduit is implanted in these patients. Various materials – autologous, homologous and heterologous – are used as a graft. Various evaluations of these materials have been reported but the common view is that all are associated with a large number of complications. Currently, the ePTFE conduit is preferred for its availability. A central venous catheter vascular access is indicated if acute hemodialysis procedure is necessary and all other possibilities for angioaccess have been exhausted. Despite associated complications, central venous catheters are increasingly common in Europe as well as in USA and Canada.

Initially, natural materials were used as autologous, homologous and heterologous vein and arteries and later artificial materials such as modified polyester and ePTFE vascular prostheses began to be used. Of these, ePTFE interponate best meets the requirements of sufficient arteriograft: availability and handling, material inertness, rapid healing, low incidence of post venipuncture bleeding, resistance to infectious complications and thrombosis, and long term good cumulative access function. Conduits made of ePTFE have been used for some time. Initially they were used in surgical procedures performed on the venous system. The first experience with ePTFE conduits in human arterial circulation were published in 1975 (ref.). In 1973, Volder was the first to use the ePTFE conduit as an arteriovenous graft for hemodialysis. In the course of time ePTFE conduit has became the gold standard for arteriovenous graft. Currently, there are many ePTFE conduits producers and various product modifications are available. The ePTFE conduits vary in length of fibrils, wall thickness and wall reinforcement, number of wall layers, the cover of the internal surface and shape of the conduit. Conduits have been compared in a number of studies but no substantial benefits between different types have been reported.

Above all, the function and duration in terms of the emergence of stenotic and thrombotic complications have been monitored. These complications are essentially reparable. A more serious complication is graft infection whose spread in the organism can cause general infection. In hemodialysis patients infection is associated with high
morbidity and is the second most common cause of death in this group of patients\textsuperscript{10–21}.

Studies have shown that a vascular access is one of the most important risk factors for infection and bacteremia in hemodialysis patients\textsuperscript{22,23}. The hospitalization rate for these patients is double the general population and in 20\% of cases the cause for hospitalization is infection\textsuperscript{24,25}. Epidemiologic studies have shown that angioaccess type affects the risk of infection or bacteremiac emergence\textsuperscript{22,26}. At highest risk are patients with central venous catheter followed by patients with tunneled catheter and arteriovenous graft, while native arteriovenous fistula present low risk of infection\textsuperscript{23,26,27}. In patients with central venous catheter infection, complications occur in 20 to 50\% and the risk of infection is associated with the duration of catheter positioning\textsuperscript{28–31}. The lowest risk of infectious complications is in patients with native arteriovenous fistula, where the incidence is from 2 to 3\% (ref.\textsuperscript{13,29,32}). In patients with arteriovenous graft the incidence of infection is from 11 to 35\% (ref.\textsuperscript{13,32–35}), and infection complications associated with arteriovenous graft are approximately one third more than arteriovenous fistula\textsuperscript{33}. Also later published studies have shown that the incidence of infection in arteriovenous graft is ten times more common than autologous fistula and significantly lower than central venous catheter\textsuperscript{31,36}. In Europe, infected graft present a problem of catheter localization – infection is more common in lower extremity – infections occur in 20 to 60\% (ref.\textsuperscript{36,53}).

A number of risk factors for arteriovenous graft infection have been found in 20 to 60\% (ref.\textsuperscript{36,53}). The morbidity rate in patients with bacteremia caused by methicillin resistant \textit{Staphylococcus aureus} (MRSA) is an increasing problem in dialysis centers. A risk factor for MRSA is a previous use of antibiotics\textsuperscript{58,59}. An infection caused by MRSA increases the risk of 90-days mortality of 70\% in comparison with an infection caused by methicillin sensitive pathogen\textsuperscript{60}. The use of linezoloid may be beneficial in MRSA soft-tissue infection treatment\textsuperscript{61}. The morbidity rate in patients with bacteremia caused by \textit{Staphylococcus aureus} ranges from 13 to 44\% (ref.\textsuperscript{38,36,37}). Methicillin resistant \textit{Staphylococcus aureus} (MRSA) is an increasing problem in dialysis centers. A risk factor for MRSA is a previous use of antibiotics\textsuperscript{58,59}. An infection caused by MRSA increases the risk of 90-days mortality of 70\% in comparison with an infection caused by methicillin sensitive pathogen\textsuperscript{60}. The use of linezoloid may be beneficial in MRSA soft-tissue infection treatment\textsuperscript{61}. The eventual drug penetration into infected grafts has not been confirmed and needs to be evaluated in further studies. Vancomycin resistant enterococci infections are also more often diagnosed in hemodialysis patients. In the USA the incidence of such infection has at least doubled\textsuperscript{62,63}. The possible cause is excessive use of antibiotics, especially vancomycin and the third generation of cephalosporins\textsuperscript{64,65}.

**Microbiology**

Usually an angioaccess is infected with common skin microorganisms represented by grampositive bacteria. In most cases, the causative organism of the angioaccess infection is \textit{Staphylococcus aureus} or other grampositive pathogens, like coagulase-negative staphylococci. \textit{Staphylococcus aureus} is demonstrated in almost 68\% cases of angioaccess infection. Other grampositive bacteria have been found in 20 to 60\% (ref.\textsuperscript{36,53}).

Less commonly, gramnegative bacteria are the cause of infection with the demonstration in 28\% of cases\textsuperscript{36,54}. Their occurrence is associated with the transmission from hemodialysis machines\textsuperscript{55}. The most common route of infection entry is an angioaccess, followed by urinary tract, gastrointestinal tract and respiratory tract.

Infections caused by \textit{Staphylococcus aureus} occur frequently often and are associated with more complications and worse outcomes than other infections. Metastatic skeletal infections, endocardial infections and brain abscesses are among the most serious infectious complications. Infected arteriovenous graft is the source for septic emboli as has been confirmed in 12\% of infected grafts\textsuperscript{36}.

Serious overall symptoms of infection are sepsis, metastatic infectious complications such as endocarditis, arthritis, pulmonary embolism and osteomyelitis\textsuperscript{36}. Hospitalization due to sepsis is associated with increased incidence of myocardial infarction, congestive heart failure, cerebral stroke and peripheral artery ischemic disease in the following years\textsuperscript{19}. Arteriovenous graft infection management includes treatment of local and general complications as well as maintaining the angioaccess. The task is to maintain functional arteriovenous graft through local treatment and antibiotics administration as long as possible.

A number of risk factors for arteriovenous graft infection have been recognized. Risk factors result from graft localization – infection is more common in lower extremities\textsuperscript{40,41}, insufficient antisepsis during surgical procedure\textsuperscript{49}, technique of venipuncture with risk of hematoma creation or infection contamination\textsuperscript{47}. Clearly, the longer the arteriovenous graft is used for hemodialysis the higher is the risk of graft infection emergence\textsuperscript{35,36,41}.

The incidence of arteriovenous graft infection is affected by a large number of factors such as: impaired immuno-surveillance in hemodialysis patient caused by neutrophils dysfunction in uremia\textsuperscript{44–46}, obesity, diabetes mellitus\textsuperscript{47}, hypalbuminemia\textsuperscript{48,49}, insufficient personal hygiene\textsuperscript{49}. Another risk factor is HIV infection\textsuperscript{50,51}. The arteriovenous graft as well as all vascular prostheses are compromised by other infectious diseases that can spread through blood circulation and colonize the conduit\textsuperscript{52}. As in vascular surgery, the administration of antibiotics can suppress symptoms of arteriovenous graft infection. However, infection cannot be eradicated and presents a permanent risk as source for local or general infection. A considerable risk factor for bacteremia is its existing presence\textsuperscript{17}.

**Prevention**

Compliance with the rules of aseptic surgical techniques and accurate operating technique are the main prevention of early infectious complications following graft implantation\textsuperscript{65}. An early infection complication is almost always associated with microbial contamination. Early infection in association with hematogenous contamina-
tion is extremely rare: an incidence of 1.1% is reported\(^42,66\). Besides inadequate asepsis practices in the operating room, an unqualified wound dressing can cause infection. Such complication is prevent by prophylactic use of antibiotic, e.g. cefazolin\(^57\). Vancomycin single administration after graft implantation was found to lead to significant decrease in early infectious complications\(^34\). However, the use of vancomycin increases the incidence of the vancomycin resistant enterococci\(^68,69\). Also prophylactic use of rifampicin decreases the incidence of *Staphylococcus aureus* infection, but its administration is associated with the risk of toxic reactions and with bacterial resistance after short-term administration\(^70,71\). The perigraft reaction needs to be distinguished from infectious complication. The former manifests with edema, skin erythema and heat and the presence of pain around the vascular prosthesis. The local finding can mimic graft infection. Initially, fluid collects around the prosthesis, cyst formations and later, infiltrates having a fish meat structure on the cut can occur. The perigraft reaction can arise anytime after prosthetic implantation (a few days to months). Histologically it has the structure of a chronic seroma\(^72-74\). In patients with renal end-stage disease the perigraft reaction incidence is higher\(^46\). Due to the local finding graft cannulation is not possible. The perigraft reaction was present in the type of prosthesis Diastat\(^75\).

In practice, the usual rules for medical personnel apply. These include hand washing and, scrubbing, rinsing and disinfection of the forearms. The aseptic technique for the cannulation is also important\(^44\).

**Diagnosis**

Clinical findings such as warmth and redness of the skin, local pain, edema, serous or purulent secretion from the wound (after cannulation) or abscess usually lead to a diagnosis of infection. There may also be general symptoms of temperature and chill. Tunnel infection is extremely serious. It is associated with pus meat structure on the cut can occur. The perigraft reaction can arise anytime after prosthetic implantation (a few days to months). Histologically it has the structure of a chronic seroma\(^72-74\). In patients with renal end-stage disease the perigraft reaction incidence is higher\(^46\). Due to the local finding graft cannulation is not possible. The perigraft reaction was present in the type of prosthesis Diastat\(^75\).

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**Graft Infection Therapy**

Treatment for the graft infection can be conservative, surgical or, most commonly, a combination of both. In terms of surgical treatment, the principal is removal of the infected prosthesis or infected part of the prosthesis – total graftectomy (TGE), subtotal graftectomy (SGE) or partial graftectomy (PGE)\(^53\). In the presence of sepsis, tunnel infection or bleeding from the anastomosis, total graftectomy is indicated\(^81,82\). After removal of the graft, surgical treatment of the anastomosis is required – venous anastomosis is re-sewn and arterial anastomosis is treated with a venous patch. Brachial artery ligature is indicated only when there is bleeding from the anastomosis. Exceptionally, brachial artery ligature can lead to hand ischemia. In such cases, venous bypass performed on the intact subcutis may be necessary to maintain sufficient hand circulation.

If the autologous venous circulation is extremely sclerotic, the bypass cannot be performed. Hand ischemia is preferable to life-threatening arterial bleeding. We know from practice, that the artery can be ligated, if the hand had not been in danger of ischemia while the graft was functional\(^83,84\). The brachial artery can be ligated below the branching point of the deep brachial artery. The ligation is performed on the intact tissue: Generally it is safe and the results are good without ischemic complications or bleeding\(^85\). When the arterial anastomosis is not affected by infection, it is acceptable to leave a small piece of the prosthesis (2 to 3 mm) at the side of the arterial anastomosis and sew the lumen of the prosthesis\(^86,87\). This procedure is also known as subtotal graftectomy. It is indicated in patients with infected prosthesis, but without clinical symptoms of sepsis. The procedure is beneficial as it reduces the risk of arterial and nerve injury and the risk of arterial bleeding. After the graft removal, the necrotic tissue must be removed and lavages are performed\(^83\).

The procedure, when the brachial artery is sutured end-to-end, or when small pieces of left prosthesis are sutured, is not always radical, while the potentially infected tissue surrounding the graft in left in situ. From here the infection can spread and can cause arterial bleeding. The risk of new arterial bleeding in patients with positive hemoculture is 20%. The resection of the artery at the site of anastomosis and the replacement with a venous graft is recommended. Thus a complete infected tissue debridement is allowed. This procedure is radical in the elimination of infection and it also prevents arterial stenosis\(^88\). It should be followed by a microbiological examination of the prosthesis and, subsequently by targeted antibiotic treatment\(^19\). Before the microbiological test results are known, patients are treated empirically, usually with a combination of gentamicin or vancomycin and the third generation of cephalosporins\(^50,53,54\). Sequential antibiotic therapy is set up according to the test results. The dosage of antibiotics is renal function dependent and the treatment duration is 3 to 6 weeks on average\(^50,53\).

Partial graftectomy is indicated if only a part of the prosthesis is infected. The intraoperative finding is fundamental – all the parts of prosthesis, except the affected
part, must be fixed in the subcutis and free of infection. In such situations, the affected part of the prosthesis is removed, the intact parts of the prosthesis are ligated and the subcutis is oversewn through-and-through at the side of the anastomosis. The infected subcutis is partitioned and a new prosthesis is implanted in the intact subcutis, connected only with the unaffected sections of the original prosthesis. This procedure allows us to dialyse the patient through the original vasculature so he or she does not need to be catheterized. However, this procedure remains controversial, while the original graft often works as a source of infection. The infection involvement is not exactly clear during the surgery and the PGE carries a risk of further infectious complications and bleeding. The PGE has been evaluated in many single-centre series and good results have been reported in 74–80% (ref.37, 53, 81, 82, 88). Although, this approach is not generally accepted. Some centers prefer the TGE since the PGE is associated with a large number of infectious complications.

In some cases there is only a “local infection” presented as a skin necrosis, abscess or fistula at the point of entry of infection. The patient is generally symptom free. A graft may be infected, but the local finding is discreet and can be treated with local surgical therapy using drainage, elution and suitable antibiotic administration. With this approach, the majority of infections can mitigate but are not treated.

In general, prompt treatment of skin or distant infection is fundamental for preservation of the graft. Only well-timed and potent antibiotic therapy can positively affect the incipient skin and subcutis involving local infection. The infected graft that cannot be treated by antibiotic therapy, must be resected or completely removed. The next step is to provide an alternative angioaccess, usually catheterization of the central venous system, and intravenous antibiotic therapy. After the resolution of infection, a sequential procedure providing a permanent angioaccess by graft placement is scheduled. Preferably the graft is placed in another location than the previous one. Treatment of the infected graft is associated with hospitalization and thus high care cost.

Typical therapeutic models for graft infection treatment mentioned above have obvious disadvantages. The main disadvantage is that no alternative localization exists for the placement of the graft. This is the situation when attempts for angioaccess have been repetitively performed on the opposite upper extremity and all have failed, or the central venous system is obstructed. Other materials were used as a substitution for autologous vessel circulation to solve this problem.

In 2000 Matsura et al. published a prospective study outcome. The authors used a cryopreserved femoral vein instead of prosthesis in the infected field, or when all others modalities for angioaccess were attrited. The relative resistance to infection of this material was confirmed. The material was used in the field of infection in 38 patients. In 20 patients, infected ePTFE prosthesis was replaced by the cryopreserved vein in one session. No new infection nor any other complication such as bleeding or pseudoaneurysm of the cryopreserved graft appeared. One year primary cumulative function was 49% and secondary patency was 75%. In comparison with a group of 68 patients with implanted ePTFE prosthesis, the patency of the graft was similar and the resistance to infection was higher in the group with the cryopreserved graft.

In 20 patients at high risk for infection Bolton et al. used the cryopreserved femoral vein. The localization of the vein was the thigh, the upper extremity and the chest. They failed to confirm the positive results of Matsura et al. There was sepsis in 15% of patients in their group, local infection in 40% and 6 patients experienced massive hemorrhage from infection. Bolton et al. consider the risk of infection in the cryopreserved vein high, especially when placed in the subcutis of the thigh. They believe that replacement of the infected ePTFE graft by the cryopreserved vein is indicated only if there is no other option available.

In another study published in 2002 further experiences with cryopreserved femoral vein or great saphenous vein harvested from the regularly examined organ transplant donors were discussed. The vein was used in 38 patients and the one year cumulative function was 68%. In this group of patients, no infection of the cryopreserved vein was seen, the aneurysmatic dilatation of the vein was found twice. The clinical signs of allograft rejection did not occur. The potential of cryopreserved vein grafts were also evaluated in 2004 and 2005 by Madden et al. In their first work they compared the outcomes of ePTFE grafts and cryopreserved veins in infection-free field. The graft patency was similar, cryopreserved veins were more resistant to infection but tended more to pseudoaneurysm creation. The study followed up with emphasis on stenotic and thrombotic complications since the authors expected the cryopreserved grafts to be more resistant in this respect than ePTFE grafts. The study was interrupted in 2003 when FDA (Food and Drug Administration) imposed security restrictions on tissue processing to the producer. The study showed similar outcomes in terms of stenotic and thrombotic complications in both groups but no infectious complications.

Since cryopreserved veins are more expensive they were not recommended for usage, irrespective of the FDA restriction.

Considering the expense of ePTFE grafts, formaldehyde-fixed arterial allografts began to be used. Femoral arteries were harvested from cadaver organ transplant donors. Graft patency was comparable to other materials, the incidence of infectious complications was low – one patient out of 43, in a total of 68 grafts.

Data shown suggest that ePTFE prosthesis remains the only material for use. The cryopreserved graft appeared to be acceptable for complicated angioaccess in hemodialysed patients with infection complications. It is not clear from current literature findings if cryopreserved veins were further developed or utilized after the FDA restriction. Clinical importance of the cryopreserved veins is related only to single-centre experience.
CONCLUSION

The arteriovenous graft infection has a significant impact on the morbidity and mortality in hemodialysed patients. A complex approach is required, including prevention, diagnosis and therapy. All measures to decrease the incidence of infection are beneficial and lower the costs of angioaccess care. Observations made during the last thirty years have brought nothing substantially new.

The ePTFE prosthesis remains the most appropriate substitute. Prior to implantation, it is necessary to suppress all source of infection. Prosthesis implantation requires compliance with sterile safeguards. Diagnosis of infection is usually established according to clinical findings. The specification in accordance with PET CT examination seems to be a perspective. The principal of therapy remains unchanged. The surgical procedure is fundamental. Type of surgical procedure depends on experience. Apparently it is safer to remove all the infected prosthesis and provide access to dialysis using a central venous catheter. Functionality and length of use of prosthesis can also influence decisions. Prostheses that are repeatedly examined for stenotic and thrombotic complications with suspicion of infection should be removed. Simultaneous antibiotic therapy should correspond to the results of the susceptibility tests.

REFERENCES


Infectious complications of arteriovenous ePTFE grafts for hemodialysis
