

How to treat aortic graft infection? With a special emphasis on xeno-pericardial aortic tube grafts

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Abstract Infection of a vascular prosthesis or endovascular stent-graft is probably the most serious complication that may occur after implantation and dramatically affects the patient's outcome. The most common etiology of graft and/or prosthetic valve infection is usually wound-related infection, followed by seeding from distant infection sites (lung, urinary tract). Surgical treatment is almost always required but even after surgery, morbidity can be significant. Operative procedure must be tailored according to the individual patient and to the experience of the surgical team. Complete resection of the infected foreign material with débridement of the surrounding tissue gives most probably the best results. Orthotopic reconstruction is the best option for all thoracic and thoraco-abdominal pathologies and the use of coated prostheses, industrially fabricated bio-conduits, homografts or self-made vascular tubes from xenopericardial tissue has to be discussed from case to case. In some exceptional situations, endovascular stent-graft can be performed as bridging to a more complete treatment if general condition of the patient has to be stabilized.

Keywords Aortic graft infection · TEVAR · Homografts · Xeno-pericardial aortic tubes

Introduction

Infection of a vascular prosthesis is the most serious complication following surgical or endovascular implantation that

dramatically affects the prognosis of the patient. Removal of the infected graft or stent-graft is almost always required but even though surgery has been successful, morbidity may still be significant. Incidence of a vascular graft infection has been reported between 0.5 and 5% [1, 2]. It is influenced by implant site, indication for the prior intervention, underlying diseases and host defense. In the current literature, prosthetic graft infection following thoracic aortic procedures is significantly lower than after abdominal aortic surgery or peripheral vascular interventions. The incidence of infections following percutaneous insertion of endovascular stent-grafts is even lower (around 1% or below) in some series [3–5].

An appropriate perioperative prophylactic strategy and expedient surgery are important factors to avoid graft infection. Prophylactic antibiotic administration is recommended before vascular and endovascular prosthetic implantation and has been shown to decrease the risk of wound infection that may be a risk factor for subsequent graft infection [6]. Systemic antibiotics (usually cephalosporins, exceptionally vancomycin) should be administered before skin incision and at regular intervals during the procedure, particularly in case of prolonged operative time (> 4 h).

Three different mechanisms may lead to infection of a vascular graft or stent-graft with bacteria or fungi: (1) perioperative contamination, (2) bacteremia with consecutive seeding of the implant material and (3) mechanical erosion of the graft/stent-graft into the esophagus or the bronchial system. Potential causes for graft contamination include breaks in aseptic operative technique, prolonged procedures, a diseased aortic wall (with contaminated thrombus material), as well as injury to lung tissue or esophagus when dissecting adhesions.

While skin is probably the major source of bacteria, graft surface can directly contact microorganisms during the procedure, later during follow-up in case of a wound

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complication or by hematogenous spread from remote sites of infection (the most frequent ones being urinary tract infection, pneumonia, and central-venous catheter infection). Mechanical erosion of an aortic prosthesis into an adjacent structure (esophagus, bronchial system and duodenum) is a very rare but specially challenging complication.

Depending on the timing of clinical presentation, prosthetic graft infection can be classified into early versus late, the threshold for late infection being 4–6 months after the primary surgery or endovascular intervention. Prompt diagnosis and adequate treatment are essential to avoid more dramatic outcome (uncontrolled septicemia, massive bleeding through erosion of neighbor tissues and/or anastomotic dehiscence). Initial clinical presentation may be subtle, particularly in those patients with intracavitary graft infection (e.g., thoracic and abdominal location). Patients with a thoracic aortic graft infection may present with signs of subcutaneous, sternal or retrosternal infection, recurrent pericardial effusion as well as single or recurrent episodes of hematemesis or hemoptoe in case a descending aortic graft is involved [7].

Late infections typically results from colonization through low-virulence organisms, such as staphylococcus epidermidis and candida species. The nature of late infection is more indolent without signs of septicemia; one of the most suggesting sign is the absence of graft incorporation with surrounding tissue and the presence of perigraft fluid (\pm gas particles) containing large amounts of leucocytes.

In patients with unspecific symptoms but clinical suspicion, extensive imaging techniques (echocardiography, CT-scan, MRI, PET-CT-scan, other nuclear examination) should be performed. The following signs should be considered as indicative of a prosthetic infection:

- Perigraft abscess and anastomotic aneurysm
- Perigraft air or fluid
- Contrast-enhancement as well as border contour, and perigraft seroma
- Lymph node enlargement (more than 3 nodes $>$ 6 mm on the short axis)
- Fat-stranding
- Osteomyelitis of the sternum or thoracic vertebrae

In any case, the patient should be asked for recent illnesses that may have resulted in hematogenous or lymphatic seeding of the graft. In the lab exams, elevated white blood cell count associated to a left-shift is common, but not obligatory neither specific. In unclear cases, assessment of pro-calcitonin may be helpful. Functional radionuclide imaging (PET-scan) may confirm the presence of a clinically suspected graft infection when signs of perigraft abscess are equivocal. The presence of fluid and air surrounding the aortic graft is a normal finding in the early postoperative

period and should resolve with time; however, any gas in the periprosthetic tissue on CT-scan should be judged as abnormal beyond 6–8 weeks after primary surgery. The most useful feature of MRI is its ability to distinguish between perigraft fluid and perigraft fibrosis, thanks to signal intensity differences between T1 and T2 weighted images. This type of examination is not useful in the early postoperative period because of non-specific uptake in the vicinity of the perigraft but the accuracy of functional imaging increases to approximately 90–95% after 3–4 months.

Addressing the lack of diagnostic criteria, Lyons et al. recently proposed a case definition of aortic graft infection including clinical/surgical, radiological and laboratory criteria [8]. Intraoperative collection of tissue and graft samples for microbiological and histopathological analyses is of utmost importance, not only to find causing microorganisms, but to differ between infection-specific and foreign body inflammatory reaction.

Fortunately, most cases of graft infection are discovered in time to allow adequate preoperative planning, determination of the extent of the graft infection and perhaps also identification of the responsible pathogen. This is important because additional surgical procedures may be needed at the level of the esophagus, the bronchial system and/or the lung tissue. Since persistent infection of a non-excised prosthetic graft segment is the major reason for treatment failure, surgical exploration remains the most reliable method to resect the prosthetic material as completely as possible and to clean the surrounding tissues: this is still the best option to definitely cure the patients [9–13].

However, attempts of graft preservation with antibiotic therapy and local vacuum treatment have been reported in singular cases, especially in cases of early graft infection [14, 15]. In a recently published study by the group of Hannover, 25 patients were reported [16]. They all were treated for early graft infection after thoracic aortic surgery via sternotomy. In 11 patients, the infected prosthesis was replaced by a cryopreserved homograft or a biological valved pericardial xenograft. In 14 patients, an attempt to salvage the graft was made by resternotomy, aggressive debridement and subsequent continuous mediastinal antibiotic irrigation over a course of 2 weeks, accompanied by systemic antibiotic therapy. In-hospital mortality was comparable (replacement group: 2/11 = 18%, graft-sparing group: 2/14 = 14%, $P = ns$). The time interval from the initial surgery was significantly shorter in the graft-sparing group: 24 days (range 15–93 days) versus 165 days (range 95–300 days) in the replacement group ($P = 0.004$). Two patients treated with the graft-sparing approach more than 100 days after the initial surgery, required additional treatment because of infection, and one patient was not amenable to external irrigation because of an infection of an aortic arch hybrid stent graft. The authors concluded that in-situ graft-sparing surgical

therapy may be safe and effective if diagnosis and treatment of aortic graft infection is initiated promptly and aggressively (ideally < 1 month post-surgery). This method produced good mid-term results up to 3 years. For aortic graft infections that become clinically apparent > 3–6 months after surgery, the authors recommended replacement of the infected grafts with biological conduits (homografts or pericardial xenografts) as the best treatment option.

After graft and endovascular graft excision, débridement of all inflammatory tissues and appropriate drainage of the prior graft bed are important principles for preventing persistence of the infection process. Since the aortic wall adjacent to the infected graft is a potential reservoir of bacteria, the wall itself and perigraft tissues should be debrided. In some instances, coverage of the new graft and its anastomoses with viable non-infected tissue (omentum, intercostal muscle flaps) may favor healing and separate the new graft from adjacent structures.

The principle of graft excision and extra-anatomic bypass useful for peripheral reconstruction is not applicable for the majority of patient with a thoracic aortic graft infection and/or a prosthetic aortic valve endocarditis in a composite graft prosthesis. In these cases, in-situ maintenance of the circulation is the only viable option.

To replace the resected prosthetic graft or endovascular stent-graft, different materials have been described: antibiotics- and silver-coated prosthetic grafts, xenografts (for instance the porcine mini-root and xeno-pericardial industrial conduits). Homografts have been generally considered more resistant against reinfection. Unfortunately, their availability is limited.

Coated vascular graft

The idea to coat vascular prosthetic graft material with antibiotics or silver as an anti-infective agent goes back to the late eighties. In a study published in 1991, the efficacy of bonding rifampin to double-velour small caliber Dacron grafts with collagen to prevent graft sepsis was tested in a canine model [17]. Fifty 6.0 mm Dacron grafts impregnated with either collagen (control) or collagen plus rifampin (experimental) were implanted into the infrarenal aorta. The dogs were divided into four groups as a function of time between grafting and bacterial challenge. The groups were challenged with 1.2×10^8 (8) colony forming units of *Staphylococcus aureus* (clinical isolate) intravenously suspended in 250 ml normal saline at day 2, 7, 10 and 12. Three weeks after hematogenous seeding, the grafts were harvested. In the 2- and 7-day group, 4/6, respectively 5/6 control grafts were infected compared with zero of 12 experimental grafts (P less than 0.030). In the 10-, respectively 12-day group, 1/6, resp. 2/6 experimental grafts were infected, but the control

group had only 2/6 and 1/6 graft infections. These results indicated that rifampin bonded with collagen to knitted Dacron grafts may effectively protect the graft from bacteremic infection during 7 days after implantation. Additional literature is available on this topic [18–20].

In a clinical setting, a postmarket surveillance registry was performed to document the efficacy of a vascular prosthesis coated with metallic-silver in high-risk patients undergoing vascular reconstructions [21]. Patency and freedom from graft infection data were assessed at a minimum of 12 months in patients with significant co-morbidity and/or confirmed graft infections or infected native vessels. 230 patients with high-risk factors underwent aortic, peripheral and/or extra-anatomic reconstructions with Silver Graft®. Ten of these 230 patients had graft infections at baseline whereas the remaining 220 subjects had significant risk factors vascular access in scar tissue (27.3%), chronic renal insufficiency (26.8%) and diabetes (21.0%). There was a freedom from de novo graft infection rate of 95.9% (211/220) in the high-risk group without graft infections at baseline. This registry revealed favorable patency and freedom from de novo infections rates in a ‘high-risk’ population with significant co-morbidities. However, the experience is too scarce to draw some valuable conclusions. One of the main advantages of course is the immediate availability of such grafts but some significant issues remain unsolved or unanswered: so the rate of definitive cure, the need for additional long-term antibiotic treatment and the rate of recurrent infection. In addition, the outcome in the thoracic aortic segments is unknown since in the published series, the majority of patients underwent peripheral or abdominal aortic surgery.

Experience with a xeno-pericardial conduit (the former Shelhigh conduit: now bio-integral)

We have used—as other—the Shelhigh™ stentless aortic valve conduit in the setting of aortic root infection and in cases of complex redo-procedures [22, 23]. This was a totally biologic conduit, available in size between 21 and 31 mm. The conduit and the valve were glutaraldehyde cross-linked, detoxified and heparin-treated with No-react®. It was expected that this proprietary detoxification process eliminates residual glutaraldehyde and ensures stable tissue cross-linking with less calcification and tissue deterioration in the long-term. The 15 cm long pericardial tube can be trimmed for each case (Fig. 1).

Initial clinical experience was very satisfying regarding the technical handling of the graft, the postoperative hemodynamics and the short-term clinical results. Excellent short-term outcome data were demonstrated as well by several teams in UK and Germany when the Shelhigh valves

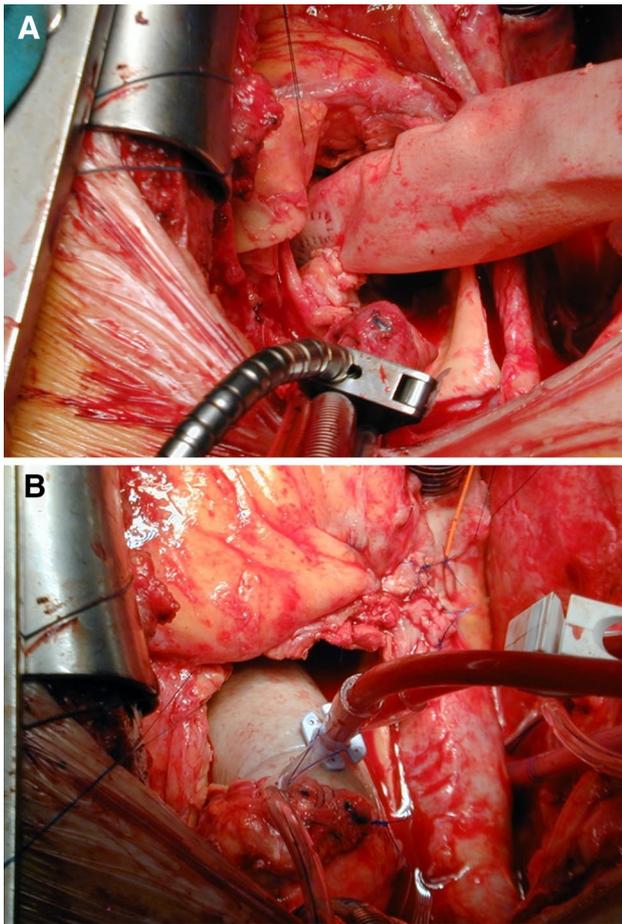


Fig. 1 **a** Implantation of a Shelhigh porcine xeno-pericardial composite graft in a patient with prosthetic valve endocarditis and destruction of the aortic root. The anastomosis with the left coronary ostium has been performed. **b** Intraoperative situs after completion of the distal anastomosis. Very satisfying hemostasis

or valved conduits were used in infective valve endocarditis. We optimistically implanted this graft in patients scheduled for a biological aortic root replacement, especially in complex situations (acute type A aortic dissection, endocarditis and complex redo-procedures). After a short positive experience, our expectations were increasingly conflicted since several patients presented with unclear findings, looking like a disintegration of the graft along with rupture of the aortic root requiring extensive re-operation [23]. At that time, exchange with other institutions that implanted this conduit revealed that our observations were not singular. In a retrospective study in 2 institutions, we reported the experience in 291 consecutive patients. In 26 patients, the conduit was implanted in an infective situation re-operation was required after a mean interval of 5 ± 3.8 years in 25 (8.6%) patients due to infection of the conduit ($n=9$), aorto-ventricular disconnection ($n=4$), pseudo-aneurysm formation ($n=4$) and structural valve degeneration ($n=8$) [24].

Similar findings were described by Calderon who presented a series of 51 consecutive patients with a re-operation rate of 13% (7/51) [25]. We have stopped the implantation of Shelhigh conduits years ago and recommend close follow-up of patients with this aortic valved conduit.

Other have started with a similar implant (the Bio-Integral© conduit) from the same company and have reported satisfying early and mid-term results [26].

Freestyle mini-root porcine graft

This xenograft implant is a promising material for the treatment of aortic valve endocarditis with aortic root involvement (abscess, aorto-ventricular disconnection) [27, 28]. However, the implant is usually too short when a longer segment of the ascending aorta has to be replaced. In these cases, it has to be combined with a new prosthetic graft or better with a xeno-pericardial aortic tube (see below). Our experience is limited to 4 cases with promising outcome, however, the results cannot be generalized due to the small number of patients.

Aortic homograft

Initial enthusiasm for use of cryopreserved arterial allografts was subsequently tempered by suboptimal long-term outcome [29–32]. Severe calcification, anastomotic pseudo-aneurysm, allograft disruption, aneurysmal degeneration, and more rarely persistent infection have been reported in series with long-term follow-up. In a recent series including quite a lot of patients operated because of an infected vascular prosthesis, the authors reviewed their experience over the past 15 years with the use of cryopreserved arterial allografts as a vascular substitute for vascular prosthetic infection or for primary arterial infection and investigated allograft-related complications [33]. 103 cryopreserved arterial allografts were inserted in 96 patients. There were 78 patients with infected vascular prosthesis (IVP), nine patients with an aorto-enteric fistula (AEF), and nine patients with primary arterial infection (PAI).

The in-hospital mortality was 9% in patients with an infected vascular prosthesis, and 30% in those with an aorto-enteric fistula, while there was no mortality in patients with primary vascular infection. Median follow-up was 49 months. Allograft-related re-interventions were necessary in 29% of the patients with IVP and four of the patients with AEF, but none of the patients with PAI. Five-year survival for the IVP, AEF, and PAI patients was 53, 44, and 90%, respectively.

This series highlighted some shortcomings of cryopreserved arterial allografts in the long-term, including suboptimal outcome-results and shortage of material.

In contrast to these relatively modest results, homografts have been considered as optimal substitutes for the infected aortic root with intra- or peri-aortic abscess, subvalvular aneurysm and for all types of ventriculo-aortic desinsertion (Fig. 2). Several series with very satisfying early and long-term outcome have been published. Of course, valvular degeneration is an important issue (like any biological valve) and the main problem during re-operation is usually the calcification of the vascular part of the homograft, making the access to the aortic valve difficult. In cases of circular calcification of the homograft, either complete replacement of

the aortic root is necessary. In cases in which a less aggressive procedure would be a wise option, aortotomy may be performed distally to the suture between the homograft and the native aorta and the implantation of a sutureless valve may be a valuable and much easier option after resection of the calcified valve.

Self-made bovine pericardial tube grafts

Our clinical experience towards these different strategies has evolved over the last 20 years. While we started with pre-fabricated xeno-pericardial implants and homografts, the use of self-fabricated xeno-pericardial aortic tubes is now the

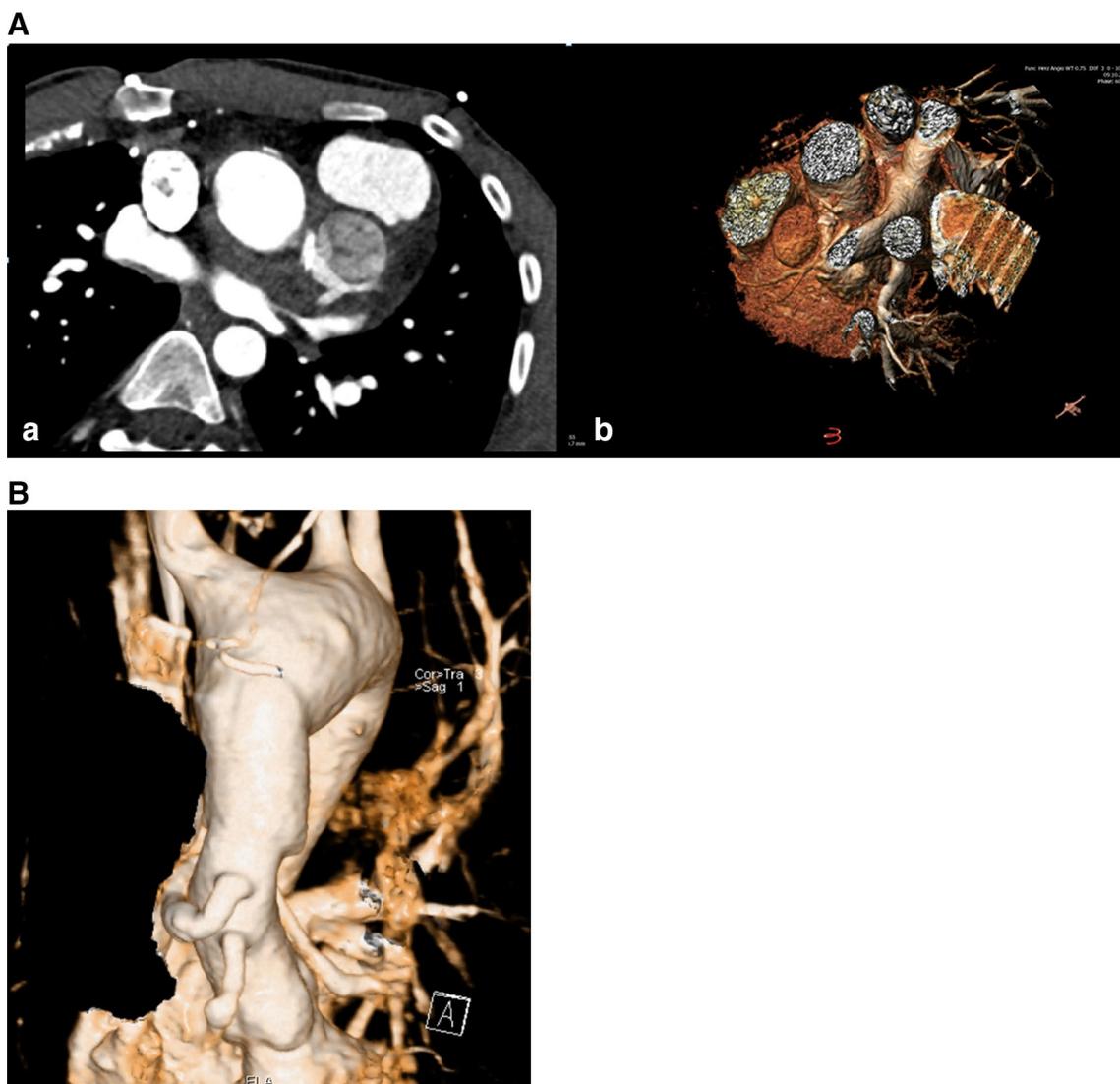


Fig. 2 **a** Younger Loey–Dietz patient with an infected pseudoaneurysm of the left main coronary following multiple surgeries on the aortic root (repeated composite graft procedures). **b** Postoperative

imaging following homograft replacement of the aortic root using short saphenous vein grafts to re-attach the coronary arteries

preferred method beside homografts that remains the gold standard in cases in which the aortic root has to be replaced.

Preoperative positron emission computed tomography as well as radiologically guided aspiration of peri-aortic fluid was used in selected cases in the most recent period. Postoperative follow-up include regular visits in the dedicated aortic outpatient clinic with imaging by computed tomography and/or magnetic resonance performed at least between 3 and 6 months postoperatively and thereafter according to the patient's condition and laboratory parameters. The imaging studies are reviewed on a regular basis for signs of reinfection, graft calcification, thrombosis, anastomotic stenosis and aneurysm.

We started with self-made aortic tube grafts of xeno-pericardial tissue in 2008. Our experience has been published previously [7, 34]. The pericardial tube graft is prepared simultaneously by a second surgeon using a 14 × 8 cm Supple Peri-Guard® (Synovis Surgical Innovations, St. Paul, MN, USA) or 15 × 10 cm SJM Biocor™ (St. Jude Medical, St. Paul, MN, USA) bovine pericardial patch. The patch is tailored according to the diameter and length of the aortic segment using a bougie-like caliper (Fig. 3). The patch is sewn to form a tube using a non-absorbable (polypropylene) 4-0 running suture (Prolene®, Ethicon, Somerville, NJ/Cincinnati, OH, USA) that is interrupted every 5 cm.

Patients requiring surgery because of an infected graft in the ascending and/or aortic arch ($n=7$) location were operated on using cardiopulmonary bypass and hypothermic circulatory arrest using selective antegrade cerebral perfusion if the distal anastomosis or reconstruction involved the aortic arch. Patients with a pathology involving the descending or thoraco-abdominal aorta ($n=14$) were operated on using a left-heart bypass (Figs. 4, 5).

Endovascular aortic repair was used in one patient with aortic rupture due to primary infection as a bridge to open reconstruction with a pericardial tube graft. In one patient with infection of an ascending and thoracoabdominal aortic polyester graft, a two-stage reconstruction was performed with replacement of the ascending aorta and aortic arch first and thoracoabdominal reconstruction 4 weeks later.

In addition to the pericardial tube grafts for aortic reconstruction, an Omniflow® II graft (LeMaitre Vascular, Burlington, MA, USA) was used in one patient with reconstruction of the aortic arch, to facilitate reimplantation of the left common carotid artery.

Thirty-day mortality was 30% in this group ($n=7$). The majority of the patients who did not survive had undergone emergency repair. The most common cause of death was postoperative sepsis with multiple organ failure. Freedom from reinfection was 100% and no graft related complications or re-operations have been documented so far. Median radiological follow-up was 12 months (range 1–67), performed by computed tomography angiography

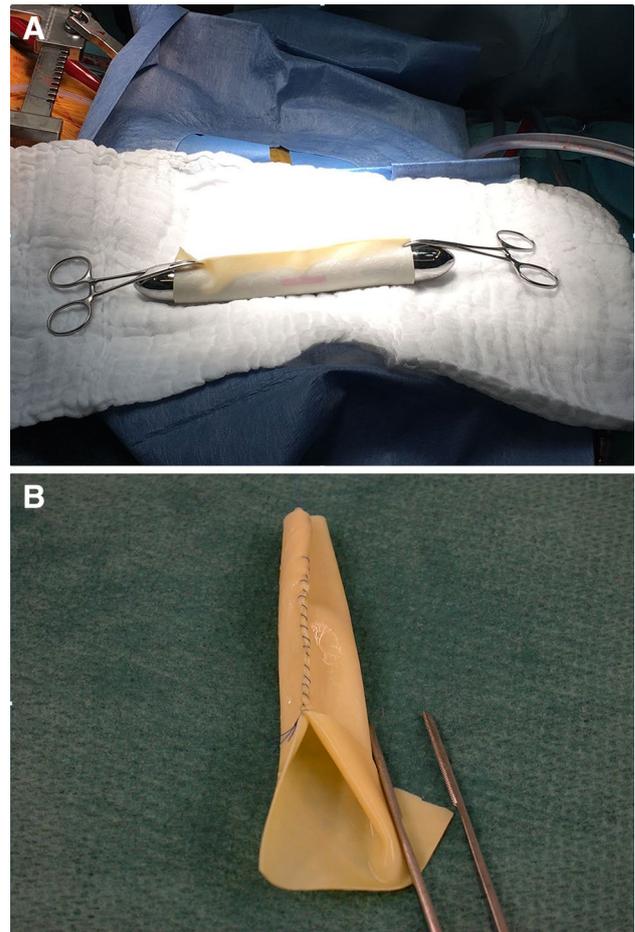
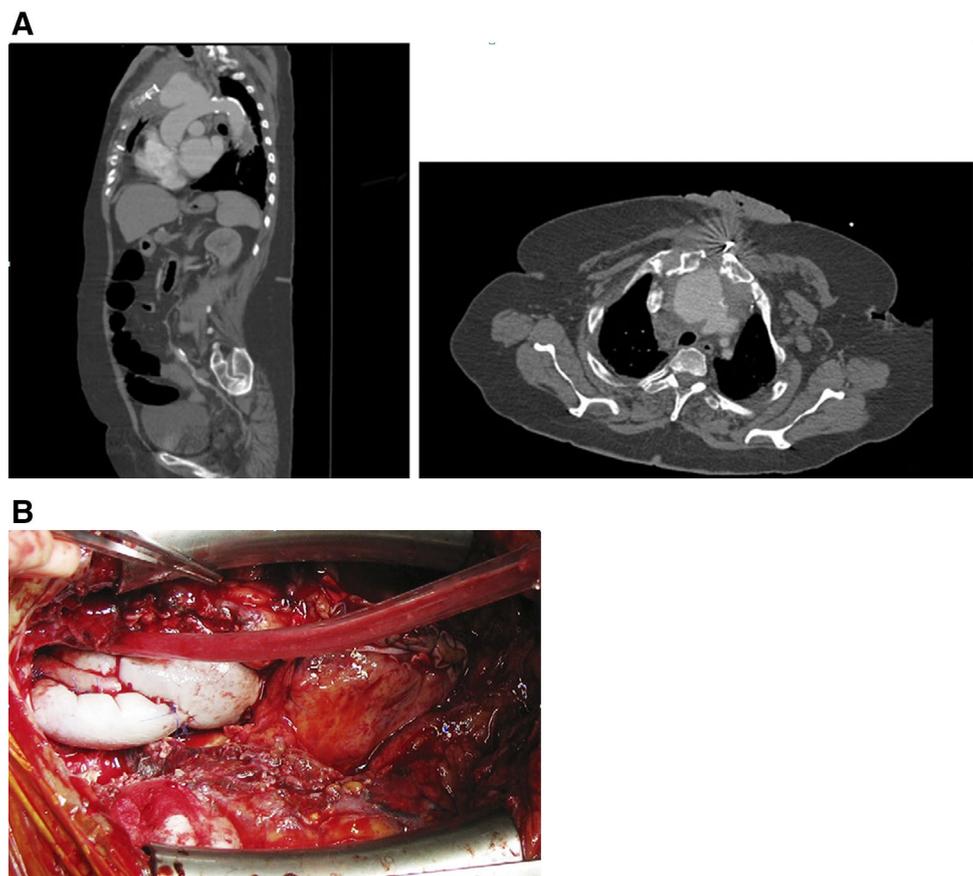


Fig. 3 **a** Construction of a pericardial aortic tube graft from a xeno-pericardial patch using a dilator. **b** The suture is interrupted several times to adapt for the optimal length

in 21 and magnetic resonance angiography in four patients. In one patient with infrarenal aortic reconstruction long-term follow-up was performed by duplex ultrasound. No follow-up imaging was available in four patients. Imaging did not demonstrate reinfection, nor graft calcification, thrombosis, stenosis or aneurysmatic degeneration in any of the patients.

Type and duration of antibiotic therapy was determined individually after consultation of the infectiologist. In case of poor patient condition or sepsis empirical preoperative antibiotic therapy was administered after blood cultures. If antibiotic treatment had been initiated before referral, antibiotics were continued and adapted postoperatively according to the results of the microbiological cultures. If a fistula (bronchial, oesophageal) was present or suspected, pre- or intraoperatively, antifungal treatment was initiated immediately. Postoperative antibiotic therapy depended on the type of pathogen, intraoperative findings and clinical evolution, but was usually continued for 6 weeks or longer.

Fig. 4 **a** Patient presenting with a ruptured infected aneurysm of the ascending aorta following multiple previous interventions, the last one being a prosthetic patch closure of an infected aortic cannulation site. The aneurysm performed the sternum. **b** Complete replacement of the ascending aorta and the aortic arch using a xeno-pericardium aortic tube with separate reconstruction of the innominate artery with a second pericardial tube and of the left common carotid artery using a Omniflow graft



Comment

Several options exist to replace an infected aortic graft following previous aortic surgery or endovascular insertion of a stent-graft. Our technique has evolved over the time and more recently we have used mainly when not exclusively xeno-pericardial tissue to construct a biological aortic tube. This biological aortic tube can be used in every thoracic aortic location and in the aortic root as well. For this purpose, a biological valve (Perimount Magna Ease, Edwards Lifesciences, California, USA) can be sewn in the proximal tube portion. Alternatively, homografts have been used in the aortic position when available.

Previous studies have shown variable outcomes in such patient collectives, depending on the material used for in-situ reconstruction. Following prosthetic graft implantation, reinfection rates of 4 to 10% have been reported.

Compared to the literature, our results show that the use of self-made bovine pericardial tube grafts is a very promising alternative to all other strategies, especially regarding reinfection and graft durability. The main advantage is the simple, easy and quick graft construction from pericardial patches. Storage and availability of xeno-pericardium is unproblematic and the commercially available patches

may be tailored to construct any graft size and length desired for the individual patient.

Thirty-day mortality remains high in the majority of reported series. This can be explained by the severity of aortic infections with the frequent need for emergency surgery. Our series includes patients undergoing reconstruction of all aortic segments as well as complex aortic arch and thoraco-abdominal repair with more than one xeno-pericardial aortic tube. Previous surgery in the affected area may additionally complicate open reconstruction, especially in emergency situations. Some patients with a delayed diagnosis of aortic graft infection were already in poor nutritional condition at the time of surgery: this may have contributed to increase the perioperative risk.

In a retrospective review, Oda analyzed the records of 68 patients treated for postoperative prosthetic vascular graft infection (mean age 62.3 ± 15.1 , male 51) from January 2000 to December 2013 [35]. The number of patients and the locations of the treated infections were as follows: 13 for aortic root, 16 for ascending aorta, 35 for aortic arch and four for aortic root to arch. In-hospital infection occurred in 43 patients and after discharge in 25.

The mean follow-up time was 2.0 ± 2.3 years. The follow-up rate was 94.1%. The most commonly isolated

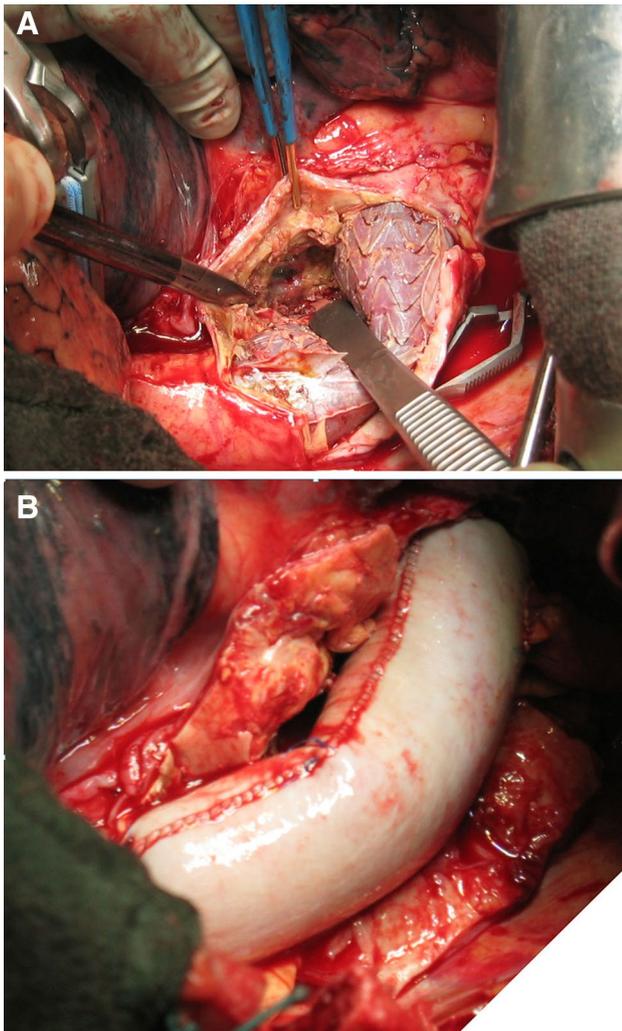


Fig. 5 **a** Patient presenting with infected aortic stent-graft following endovascular procedure in the descending aorta. Intraoperative site showed communication between the infected prosthesis with the left bronchial system. **b** Intraoperative view at the end of the procedure, showing the xeno-pericardial aortic tube in orthotopic position

micro-organism was *Staphylococcus aureus* (72.1%). Re-replacement of infectious graft was performed in 18 patients (Dacron graft in 12, homograft in 4 and rifampicin-bonded Dacron graft in 2). The overall hospital mortality rate was 35.3% (24/68). The mortality rate among the patients with graft re-replacement was 33.3% (6/18), with pedicled muscle flaps or pedicled omental flaps to cover the graft 25.9% (7/27), with irrigation 55.0% (11/20) and on antibiotic therapy only 0% (0/3). The multivariate analysis demonstrated that the risk factors of hospital death increased in the absence of pedicled flaps (muscle or omentum) to cover the graft ($P=0.001$), age over 55 ($P=0.003$), time from onset of initial operation < 1 week ($P=0.031$) and period before 2008 ($P=0.001$). The overall 1-year survival rate was 58.6%.

The authors concluded that the treatment outcomes of thoracic prosthetic vascular graft infection were not satisfactory but that the use of pedicled muscle or omental flaps to cover the graft could improve the outcomes. This has been reported years ago [36–38].

Fujii and Watanabe concluded that a multi-disciplinary approach is mandatory to increase the understanding of aortic graft infection improve the results [39]. In conclusion, our experience confirms that open surgical treatment including radical debridement and in-situ reconstruction with bovine pericardial tube grafts is a valuable option. Patients with primary aortic infection who are fit enough for open surgery should undergo open in-situ reconstruction while endovascular management should be reserved for high-risk patients denied from surgery as well as for those in very bad condition as a bridging until open reconstruction [40–42].

Compliance with ethical standards

Conflict of interest All authors have declared that no conflict of interest exists.

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