

Vascular Graft Infections

An update



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KEYWORDS

- Vascular graft infection
- Vascular reconstructive surgery
- Biofilm
- Bacteremia
- Staphylococci

KEY POINTS

- Vascular graft infections can be divided into intracavitary, located within the abdomen and thorax, and extracavitary grafts, located in the groin.
- Vascular graft infections occur either in the immediate postoperative period, mainly because of contamination during the procedure, or later, due to graft seeding following bacteremia.
- The most common Gram-positive organisms implicated in vascular graft infections are coagulase-negative staphylococci, followed by methicillin-sensitive *Staphylococcus aureus*. The most common Gram-negative organism is *Pseudomonas aeruginosa*.
- Patient-specific risk factors include periodontal disease, nasal colonization with *S aureus*, postoperative bacteremia and graft characteristics, and diabetes mellitus and postoperative hyperglycemia. Procedure-specific risk factors include incision in the groin area, wound infection, and emergency procedure.
- Initial antibiotic therapy requires broad Gram-positive and Gram-negative coverage. Rifampin-based combinations are preferable, owing to its anti-biofilm activity. Antibiotic therapy, combined with surgical intervention, is associated with better outcomes compared to antibiotic therapy alone.

INTRODUCTION

The early 1950s witnessed the introduction of vascular reconstruction surgery using prosthetic vascular grafts.¹ These grafts are important in the management of peripheral artery disease, arterial aneurysms, and in the establishment of an arteriovenous access for hemodialysis.² The use of vascular grafts has led to a significant improvement in the quality of life in patients with vascular disease.³ The increase in the use of

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vascular reconstructive surgery has been accompanied with a concomitant increase in the incidence of vascular graft infections (VGIs). VGI is a rare, yet grave complication of vascular surgery.¹ Infections are associated with a high mortality rate, a high amputation rate of affected extremities, and a possibility of reinfection.^{4–6} Vascular grafts can be divided into 2 categories: extracavitary, located in the groin, and intracavitary, located in the abdomen and thorax.¹ The incidence of intracavitary aortic graft infections is 0.2% to 5.0%^{1,7–9} and the incidence of extracavitary graft infections can be as high as 6%.^{1,10} Intracavitary aortic graft infections have a higher mortality (24%–75%) compared with extracavitary graft infections (17%). However, extracavitary graft infections are associated with high morbidity, with an amputation rate of up to 40%.³

In this review, we provide a summary of the available data regarding the pathogenesis, microbiology, and mechanisms of invasiveness in VGI. We also address the risk factors that predispose to such infections as well as the clinical manifestations and the available diagnostic techniques. Finally, we comment on the treatment strategies and prevention of VGI.

PATHOGENESIS

Studies have demonstrated 2 peaks in the incidence of VGIs after graft implantation. The first peak occurs in the early postoperative period and is largely due to contamination at the time of surgery or by direct extension from a superficial infection to the graft. The second peak occurs after a long time from the index surgery and is thought to be due to seeding of the graft by a new bacteremia or activation of a dormant infection.^{3,11} Graft infections are, therefore, thought to arise as a result of either contamination at the time of graft insertion or a hematogenous infection.^{12,13} Contamination during surgery may occur owing to the use of a nonsterile graft, inadequate sterile techniques, contact with the patient's skin or intraabdominal organs, or deposition of airborne particles into the surgical bed. Contamination from the skin of the groin is the most frequent cause of graft infection. The groin incision may cut through infected lymphatic channels or glands, owing to distal infected tissues or ulcers, resulting in direct graft contamination. In addition, the groin incision cuts through skin creases and has a tendency to gape. In obese patients, the surgical wound lies within moist skin folds.^{13,14} The vascular graft remains susceptible to infection up to 1 year after implantation, as long as the pseudointimal lining is not yet well-developed. Thereafter, bacteremia can secondarily contaminate the vascular graft.¹⁵ When vascular grafts are infected, the infection will likely spread to native vessels, resulting in inflammation and subsequent disruption of the graft–artery anastomosis and erosion, leading to hemorrhage or the formation of a false aneurysm.¹³

MICROBIOLOGY

Staphylococcus aureus used to be the most frequently isolated organism in infected vascular grafts. More recently, coagulase-negative staphylococci have been recognized as the most common cause of VGI.^{1,16} In a retrospective cohort study involving 478 patients undergoing prosthetic bypass grafts of the femoral artery, *Staphylococcus epidermidis* was recovered from 37% of infected grafts, followed by methicillin-sensitive *S aureus* (26%), enterococci (10%), methicillin-resistant *S aureus* (MRSA), *Pseudomonas* species, and others.¹⁰ *Pseudomonas* species are the most common gram-negative bacilli responsible for VGI.¹ In general, gram-negative pathogens are recovered in the setting of an aortoenteric fistula.³ Other organisms implicated in VGI include anaerobes, fungi,¹⁷ *Cutibacterium* (formerly *Propionibacterium*) species,¹⁸ and other gram-negative organisms such as *Klebsiella pneumoniae*,¹⁰ *Prevotella* species, and

Salmonella species.⁷ *Pasteurella multocida* has also been reported and should be suspected as the cause of VGI in patients with or animal scratches or bites.^{19,20}

Many factors contribute to this microbiological epidemiology, such as the use of prophylactic antistaphylococcal antibiotics, the improvement in surgical techniques, performing surgery on patients with multiple underlying comorbidities, evolution of the hospital flora, and many others.^{1,14} The microbiology of VGIs is also influenced by the location of the graft. In one study,²¹ staphylococci were more likely to be isolated from thoracic and peripheral VGIs, whereas abdominal VGIs were polymicrobial, growing gram-negative bacteria, anaerobes, enterococci, and *Candida* species (Box 1).

MECHANISMS OF INVASIVENESS

Biofilm Production

Staphylococci are capable of establishing infection through biofilm formation.^{16,22} Staphylococcal biofilm formation can be divided into 3 phases: attachment, maturation, and detachment (Fig. 1). During the first phase, surface proteins mediate the initial attachment to host matrix proteins such as fibrinogen and fibronectin. Then in the maturation phase, intercellular aggregation, mediated by polysaccharide intercellular adhesin, and biofilm structuring take place. Finally, single cells or clusters of cells detach from the biofilm, resulting in the dissemination of infection.²²

Biofilms provide resistance to antibiotics mainly by preventing them from reaching the bacterial cells in the biofilm matrix and by limiting their efficacy.^{22–24} In addition to their antibiotic resistance, biofilms protect the bacteria against the innate immune system. By shielding the cells within the matrix, neutrophils are prevented from reaching them for phagocytosis.^{22,25,26}

Virulence Factors

α -Toxin of *S aureus*

α -Toxin, also called α -hemolysin, is a common virulence factor of *S aureus* pathogenic strains. It is initially secreted as a water-soluble monomer, capable of oligomerization on the host cell membrane, resulting in pore formation and cellular lysis.^{27,28} Caiazza and O'Toole²⁹ proposed that α -hemolysin plays a role in biofilm formation, by mediating cell–cell interaction. They showed that mutant strains, carrying a mutant α -hemolysin gene, are capable of colonizing a surface, but would not fulfill the maturation phase and form colonies. ADAM10, a zinc-dependent metalloprotease, has been shown to function as a cellular receptor for α -toxin. Inoshima and colleagues³⁰ showed that mice lacking the ADAM10 receptor in the respiratory epithelium had a marked improvement in the outcome of pneumonia caused by both methicillin-sensitive *S aureus* and MRSA.

Box 1

Organisms commonly implicated in vascular graft infections

Coagulase-negative staphylococci (most common)

Methicillin-sensitive *S aureus*

Methicillin-resistant *S aureus*

Pseudomonas species (most common among gram-negative organisms)

Anaerobes

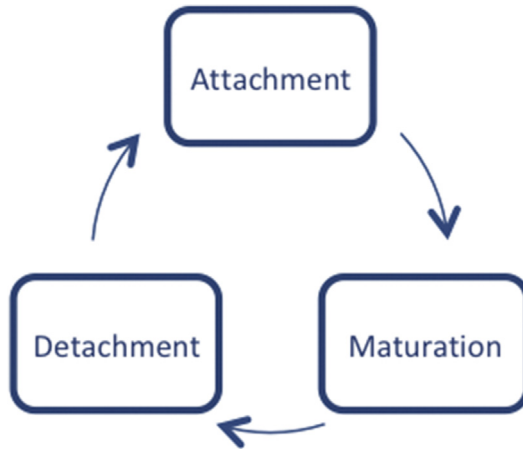


Fig. 1. Phases of biofilm development.

Cell wall-anchored proteins

S aureus expresses on its surface an abundance of cell wall-anchored (CWA) proteins that facilitate the bacteria's adhesion and invasion into host tissues. These CWA proteins include fibronectin-binding protein A, collagen-binding protein, protein A, clumping factor A, and clumping factor B, each with a specific function. For example, fibronectin-binding proteins promote the adhesion and internalization of *S aureus* into host cells, and protein A impairs opsonization allowing *S aureus* to escape opsonophagocytosis.^{31,32} *S epidermidis* expresses CWA proteins that mediate infection in humans, but to a lesser extent than *S aureus*.³³

RISK FACTORS

Patient-Specific Risk Factors

Periodontal disease

Thomas and colleagues³⁴ described a possible association between periodontal disease and late-onset VGIs. They reported 4 cases of VGIs, three of which had 16S ribosomal DNA gene analysis, confirming that the bacterial mixture causing the infection was oral in origin. Furthermore, all 3 cases had severe periodontal disease, confirmed postoperatively after the results of nucleic acid amplification. Therefore, the authors suggest that periodontal disease could be a risk factor for late-onset prosthetic VGIs, acknowledging the need for more studies on this matter. A systematic review of 44 studies³⁵ found that there was a general agreement on the need to screen and treat dental infections before cardiovascular procedures; however, protocols were lacking.

Nasal colonization with *S aureus*

Nasal colonization with *S aureus* has been shown in many studies to increase the risk of vascular surgical site infections.³⁶ In fact, nasal carriers of a high burden of *S aureus* are 3 to 6 times more likely to develop a health care-associated infection compared with noncarriers or carriers of a lower burden.^{37,38} Safdar and Bradley³⁹ showed that MRSA colonization poses a 4-fold increased risk of clinical infection compared with methicillin-sensitive *S aureus*. In addition, MRSA infection complicating vascular surgery results in significant morbidity, increased hospital duration of stay, and is more likely to result in amputation and graft removal.⁴⁰ The mechanism by which *S aureus*

nasal colonization is thought to result in postoperative infections is by direct transmission from the nares to the surgical site via the patient's hands.⁴¹

Postoperative bacteremia and graft characteristics

Moore and colleagues⁴² showed that the aortic grafts, before the formation of a pseudointima, are susceptible to infection in the setting of transient bacteremia. In another study, bacteremia was associated with a higher risk of developing aortic graft infections.⁶ Rosenman and colleagues⁴³ investigated the different susceptibility of commonly used grafts to *S aureus* adherence. Using indium-111 and a pulsatile perfusion system, they found that polytetrafluoroethylene (PTFE) grafts were the least likely to harbor bacteria, with umbilical vein grafts harboring 5 times more bacteria and Dacron grafts 50 times more. In addition, the presence of a suture line in PTFE grafts increased their susceptibility to bacterial adherence. This difference in bacterial adherence is attributed to the different graft characteristics, such as graft fiber surface characteristics, the material's hydrophobicity, and the surface charge of the graft. Different bacteria and different strains within the same bacterial species have different adherence capacities. Using ultrasonic oscillation, Schmitt and colleagues⁴⁴ studied the adherence capability of different bacteria (*S aureus*, non-mucin-producing *S epidermidis*, mucin-producing *S epidermidis*, and *Escherichia coli*) to expanded PTFE (ePTFE), woven Dacron, and velour knitted Dacron. All bacterial strains had the greatest affinity to velour knitted Dacron. The purpose of the addition of velour to Dacron grafts is to enhance the graft's attachment to the perigraft tissue, resulting in improved development of an intimal lining, proven previously to decrease the risk of infection after bacteremia. However, the increased bacterial adherence to velour knitted Dacron grafts is probably related to the porous nature of the graft, providing greater surface area for bacterial adherence. Another important observation in this study was that the production of mucin by mucin-producing *S epidermidis* strains significantly increased bacterial adherence to both ePTFE and velour knitted Dacron compared with *S aureus* and non-mucin-producing *S epidermidis*.

Diabetes mellitus and postoperative hyperglycemia

Vriesendorp and colleagues⁴⁵ showed that postoperative hyperglycemia was associated with a higher risk of postoperative infections in vascular surgery, although the risk was decreased in patients with diabetes. They attributed these results to the use of insulin in diabetic patients and its absence in nondiabetics but who have postoperative hyperglycemia. Insulin has been shown to have antiinflammatory effect in both humans and animal experiments whereas glucose has been shown to have a proinflammatory effect.⁴⁶ Other studies consistently reported diabetes to be a risk factor for VGIs.^{10,16,47} This finding can be attributed to the impaired immune response observed in patients with diabetes.⁴⁸

Procedure-Specific Risk Factors

Location of the incision

Groin incision has been shown in many studies to be a significant risk factor for VGIs.^{16,41,49} The groin area is particularly susceptible to infections because of its rich microbial flora,⁴⁹ the proximity of this area to the perineum, and the superficial location of vascular grafts in the groin.⁵⁰

Wound infection

This entity poses an added risk for VGI possibly by direct extension.^{10,49}

Emergency procedure

It has been shown that emergency procedures are associated with an increased risk for prosthetic VGIs.^{3,16,41} This is due to insufficient time, resulting in inadequate patient preparation before surgery and, thus, a greater risk for contamination and subsequent VGI.¹⁴

Additional risk factors for VGI include inappropriate antibiotic prophylaxis, invasive procedures before or after graft placement, poor wound healing, comorbid conditions like chronic renal insufficiency and an immunocompromised state, prolonged operation time, and prolonged duration of hospital stay before the index surgery.^{3,41}

CLINICAL CLASSIFICATION

Szilagyi and colleagues¹² classified VGIs into grades I, II, and III infections. Grade I infections are the most superficial, and they involve the dermis only; grade II infections extend beyond the dermis into the subcutaneous tissue but do not reach the vascular implant; and when the implant is affected, the infection is classified as grade III. Whereas grades I and II infections are usually easy to manage, grade III infections pose the greatest therapeutic challenge. Another classification system by Bunt⁵¹ divides infections into graft infections, graft–enteric erosions, graft–enteric fistulae, and aortic stump sepsis. Noticing different microorganisms as the cause of infection in early and late infections, Bandyk⁵² classified graft infections according to the organisms implicated. Finally, Samson and colleagues⁵³ divided VGIs into 5 groups, depending on the extent of infection and the structures involved (**Table 1**).

CLINICAL MANIFESTATIONS

Early VGIs occur within the first 4 months after graft placement surgery, whereas late VGIs occur after 4 months. However, early VGIs mostly occur within the first 2 months postoperatively.²¹ Early VGIs are usually caused by virulent bacteria, such as *S aureus*, and gram-negative bacteria, such as *E coli*, *Proteus* species, and *P aeruginosa*. Late infections are usually caused by less virulent bacteria such as *S epidermidis*.

Early infections are usually easier to diagnose, because the signs and symptoms of infection and inflammation are more apparent. Patients may present with signs of sepsis such as fever, chills, and leukocytosis. Other findings include sinus tract drainage, abscess, limb ischemia as a result of thrombotic occlusion of the infected graft, and local signs such as erythema and tenderness of the skin overlying the graft. Late-onset infections are usually indolent, with signs of systemic sepsis often lacking.^{1,16} Patients with abdominal VGIs can present with an aortoenteric fistula, whereas patients with thoracic VGIs can present with an aortobronchial fistula.²¹

Group	Areas of Involvement
I	Dermis only
II	Subcutaneous tissue but not the graft
III	Body of the graft without the anastomosis
IV	Graft and anastomosis, without bacteremia or anastomotic bleeding
V	Graft and anastomosis, with bacteremia and/or anastomotic bleeding

DIAGNOSIS

The approach to the patient presenting with a suspected VGI starts with obtaining an accurate medical history and performing a thorough physical examination. Leukocytosis and increased inflammatory markers, such as C-reactive protein, are seen commonly. A Gram stain and culture should be taken for blood and any wound before antibiotic administration.⁵

Extracavitary Infections

According to the American Heart Association, the initial imaging modality of choice when suspecting a VGI is ultrasound examination.¹ It is widely available, inexpensive, quick, and poses no risk of kidney injury, because it does not need contrast material for visualization. Ultrasound examination allows evaluation for pseudoaneurysm formation or any fluid collection. When ultrasound examination findings are indeterminate, computed tomography (CT) angiography or MRI can be considered. When these 2 modalities also prove to be unhelpful in confirming a diagnosis of VGI, a PET/CT scan or indium-labeled white blood cell study scan can be done. PET/CT is useful in the setting of late infections, where the symptoms are nonspecific and non-localizing, and where all other diagnostic modalities have provided no evidence of a focus of infection.⁵⁴ In a prospective cohort study involving 34 patients suspected to have a VGI, Sah and colleagues⁵⁵ aimed at investigating the diagnostic accuracy of PET/CT with fludeoxyglucose F 18 in VGIs. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of FDG-PET/CT were 100%, 86%, 96%, 100%, and 97%, respectively. Therefore, PET/CT scanning is an effective diagnostic tool in VGIs.

Intracavitary Infections

It is recommended to perform a CT angiography scan as the initial imaging modality. If the CT angiography scan does not provide a diagnosis and the suspicion of a VGI is high, an MRI, PET/CT, or indium white blood cell study scan can be considered. In the setting of an aortoenteric fistula and gastrointestinal bleeding, patients should undergo esophagogastroduodenoscopy to look for erosions, ulcers, or thrombi. When the infected vascular graft is intrathoracic, imaging findings should be combined with blood culture results and echocardiography.¹

MANAGEMENT

Determining the best management plan for an infected vascular graft depends on the location of the graft, the extent of the infection, and the organism(s) implicated.¹⁴ The optimal management of prosthetic VGIs involves excision of the graft, complete debridement of the infected surrounding tissues, restoration of blood flow distal to the infected graft, and, finally, appropriate antibiotic therapy.³

Antibiotic Therapy

Empiric antibiotic therapy should be parenterally administered, with targeted activity against the organisms expected to grow in culture. In addition, the antibiotic should have an antibiofilm activity enabling it to penetrate into the biofilm and kill slow-growing bacteria. Once the antibiotic susceptibilities become available, antibiotic therapy can be adjusted or deescalated to cover the implicated organism(s). Initial therapy involves broad gram-positive coverage (accounting for MRSA), and broad gram-negative coverage (accounting for *Pseudomonas*). Daptomycin, vancomycin, or linezolid can be used for gram-positive coverage and the antipseudomonal

β -lactams can be used for initial gram-negative coverage.² In patients with penicillin allergy, fluoroquinolones can substitute for β -lactams.⁵⁶

Daptomycin is the preferred antibiotic. Vancomycin and linezolid are active against MRSA; however, unlike daptomycin, they demonstrate time-dependent slowly bactericidal or bacteriostatic activity and lack antibiofilm activity.⁵⁶ Daptomycin is a cyclic lipopeptide exhibiting rapid concentration-dependent bactericidal activity against staphylococci, enterococci, and streptococci. It has been approved for the treatment of complicated skin and soft tissue infections, right-sided endocarditis, and MRSA bacteremia.⁵⁷ In an in vitro study using a guinea pig foreign body infection model, the use of a combination of high-dose daptomycin (>6 mg/kg) and rifampin was associated with greater killing of planktonic and adherent MRSA.⁵⁸ In addition, Legout and colleagues⁵⁹ showed in a retrospective study of 26 patients treated for prosthetic VGI that the use of high-dose daptomycin (>8 mg/kg) is a potentially successful approach with acceptable side effects in the severely ill patient population.

Conservative treatment with antibiotic therapy alone, without surgical intervention, is associated with high mortality.⁶⁰ However, in a study conducted by Erb and colleagues,²¹ among 17.6% of the patients who were treated conservatively, the cure rate exceeded 90%. The management should be highly individualized, with the choice of conservative treatment reserved for a limited carefully selected group.⁶⁰ In the same study by Erb and colleagues,²¹ treatment with a rifampicin-based regimen was associated with a higher cure rate. Similarly, another study showed that the nonuse of rifampin in the treatment of prosthetic VGIs was associated with poor outcome.⁶¹ It was, therefore, suggested that rifampin-based combinations be used as definite therapy to achieve a better response. The use of combination therapy aims at preventing the emergence of bacterial resistance. In an in vitro study conducted by Cirioni and colleagues,⁶² the use of both daptomycin and rifampin had a greater efficacy against *S aureus* infections compared with the use of either antibiotic alone. In addition, the use of rifampin alone resulted in the emergence of 4 resistant isolates, although no resistance was observed when daptomycin was administered concomitantly with rifampin.

There are no clinical trials that have evaluated the optimal duration of antibiotic therapy after a VGI. However, there is general consensus that at least 4 to 6 weeks of parenteral antibiotic therapy is necessary. In cases of partial graft excision or graft preservation, patients may be placed on lifelong suppressive therapy.^{2,63}

Surgical Management

Surgical excision with extraanatomic bypass

Aggressive management of prosthetic VGIs, including excision of the graft, debridement of infected tissues, and extraanatomic bypass if collateral circulation is inadequate, has been the standard of care.⁶⁴ To avoid prolonged tissue ischemia distally, it is essential to construct the extraanatomic bypass first through noninfected tissue and then remove the infected graft.^{63,65} O'Hara and colleagues⁶⁶ reported that patients undergoing a staged procedure experienced a significantly lower amputation rate (7%) compared with the group of patients in which graft excision and the extraanatomic bypass were performed in a combined procedure (41%; $P = .04$). Also, in a retrospective review of aortic graft infection cases, the best results were seen when the standard approach is taken.⁶⁵ After a follow-up period of 34 months, none of the patients undergoing total excision with extraanatomic bypass experienced complications of recurrent infection or amputation. Finally, in a case series of 36 patients treated for aortic graft infection with extraanatomic bypass and graft removal, the postoperative mortality rate was 11% and the overall treatment-related mortality

was 19.4%.⁴ Four patients (11%) eventually required amputations in the postoperative period. The 5-year survival was 56%, and recurrent infection occurred in only 1 patient with bilateral axillofemoral bypass graft infection.

The high morbidity and mortality associated with the aforementioned approach has led to the consideration of alternative options, such as excision and in situ replacement of the infected graft.⁶⁴ The study conducted by Erb and colleagues²¹ showed that graft retention or graft replacement were not associated with treatment failure. The in situ replacement can be done using either prosthetic grafts impregnated with silver or rifampin, to decrease the risk of reinfection, or tissue grafts such as arterial allografts, venous allografts, and venous autografts. Patients with low-grade infections in whom blood and perigraft fluid cultures are negative can benefit from graft resection and in situ replacement, whereas patients with more severe infections in whom blood and perigraft fluid cultures are positive would not, owing to the high mortality rate.⁶⁷ There are specific conditions that eliminate any possibility of graft replacement or preservation and necessitate an aggressive management and these include sepsis, anastomotic disruption, aortoenteric fistula, and the presence of virulent organisms like MRSA or *Pseudomonas*. Despite this finding, some patients who are severely ill with many comorbidities are considered high risk and may not qualify for extensive procedures with total graft excision.⁶³

In situ reconstruction using antibiotic-impregnated prosthetic grafts

The use of rifampin-soaked grafts has proven appealing owing to its potential in both prevention and treatment of VGIs. Rifampin has activity against staphylococci and a variety of gram-negative pathogens. Torsello and colleagues⁶⁸ reported 5 cases in which the gold standard of management was not feasible. Therefore, they resorted to the use of rifampin-soaked grafts. There was no recurrence of infection or any other complication at a follow-up period of 6 months to 1 year. Another study showed that total graft excision followed by the in situ placement of a rifampin-soaked grafts is a feasible option with favorable long-term results⁶⁹; however, it can be limited in the setting of an MRSA infection. Bandyk and colleagues⁶⁴ recommended the use of rifampin-soaked prosthetic grafts for in situ treatment of VGIs in a selective patient population. They showed that it can be safely used in patients with low-grade gram-positive infections and that failure of this technique was due to infections caused by virulent and resistant strains. Having in mind that the use of rifampin as a single agent can result in the emergence of resistance, Aboshady and colleagues⁷⁰ investigated the effectiveness of Dacron grafts bonded with rifampin, minocycline, and chlorhexidine in resisting colonization and infection during the first 8 weeks postoperatively in a pig model. Before implantation, the triple antibiotic-bonded grafts were immersed into an *S aureus* solution. Eight weeks after implantation, there was no bacterial growth detected on the grafts.

Some patients with VGI present in such a debilitated condition that they do not qualify for open repair. These patients are managed with endografts. Escobar and colleagues⁷¹ reported the case of a 66-year-old patient with a history of aortic patch angioplasty presenting with hemorrhagic shock owing to an aortoduodenal fistula. The patient was managed with a rifampin-soaked endograft without removing the infected graft or repairing the duodenum. This process allowed the immediate management of her life-threatening condition, delaying the definitive procedure so it could be done electively at a later stage when the patient would be in a stable condition. Until now, there are no clinical trials to evaluate the use of rifampin-soaked grafts in the treatment of VGIs compared with non-antibiotic-impregnated grafts in terms of

reinfection rates and other outcomes. It is worth mentioning that Schneider and colleagues⁷² previously showed in a dog model areas of necrosis at the anastomotic sites of the rifampin-soaked graft, with no evidence of bacterial colonization and suggested that this finding might be due to rifampin toxicity. In light of the potential for toxicity, the use of rifampin-soaked grafts should be reassessed and studied carefully.

In contrast, endolysins, which are bacteriophage-based enzymes aiming at destroying the peptidoglycan layer of bacteria, have become interesting candidates in lieu of traditional antimicrobial agents.⁷³ In addition, in light of their low toxicity,⁷² their potential use for impregnating grafts before their placement in the human body should be explored.

In situ reconstruction using cryopreserved arterial allografts

The use of biological grafts such as autologous veins and human allografts may provide increased resistance to infection compared with prosthetic grafts. They can be implanted inside an infected surgical field after resection of the infected graft.⁷⁴ This increased resistance has not been affirmed, but it could be related to the better antibiotic diffusion and attraction of immune cells into the allograft wall.⁷⁵ Excellent results had been obtained previously with the treatment of endocarditis with cryopreserved allograft valves.⁷⁶ This finding has led to the use of allografts in the settings of VGIs. The use of fresh allografts has been abandoned owing to the high associated complication rate.⁷⁷ Vogt and colleagues⁷⁸ compared the use of cryopreserved arterial allograft with prosthetic material in the management of mycotic aneurysms or prosthetic VGIs. The use of cryopreserved arterial allografts was associated with better disease-related survival, disease-related survival free of reoperation, duration of intensive care, duration of postoperative antibiotic therapy, incidence of complications, elimination of infection, and costs. In a large published case series evaluating the use of 220 cryopreserved allografts in patients with aortic graft infections,⁷⁹ the authors recommended the use of arterial allografts as a first-line treatment for aortic graft infections. Despite the effectiveness of cryopreserved arterial allografts in the management of prosthetic VGIs, the complications reported in the literature include allograft thrombosis, anastomotic pseudoaneurysm, aneurysmal degeneration, and allograft disruption.^{80,81} A high 5-year reintervention rate has been reported for patients with prosthetic VGIs treated with cryopreserved allografts, reaching 55% when the intervention is at the aortoiliac level and 33% at the peripheral level.⁸¹ Lowampa and colleagues⁸⁰ proposed several interventions to minimize allograft-related complications. The authors proposed avoiding size mismatch when using several allografts for aortic reconstruction and using through-and-through transfixing polypropylene stitches in ligating the collateral side branches of the allograft. Finally, in the setting of an aortoenteric fistula, the authors recommend wide resection of the bowel harboring the fistula followed by intestinal reanastomosis away from the area of vascular repair. A recent study has evaluated the use of cryopreserved arterial allografts for in situ reconstruction of an abdominal aortic native graft or secondary graft infection.⁸² The reintervention rate was 12.7% (9 of 71) for the following complications: proximal anastomotic rupture (n = 1), stenosis/thrombosis (n = 5), ureteral-graft fistula (n = 1), and distal anastomosis false aneurysm (n = 2). Primary patency after 5 years was 93%.

Graft sparing

The treatment of prosthetic thoracic aortic graft infections is associated with significant morbidity and mortality in the range of 25% to 27%.^{83,84} Therefore, an aggressive surgical management is not always possible. In a selected patient population, and when the VGI occurs less than 1 month after the index procedure, graft preservation

might be an option. Graft-sparing therapy involves aggressive debridement with antibiotic irrigation and systemic antibiotic therapy for at least 2 weeks.⁸⁴ However, when the patient presents with signs of graft infection 3 to 6 months after the index surgery, graft replacement is always preferred. This phenomenon is probably related to the life-cycle of a biofilm. Early in the postoperative period, biofilms are still immature and thus easier to eradicate, whereas in the late postoperative period, biofilms have become mature, making graft preservation an unviable option.^{85,86}

Management of complications

Aortoenteric fistula is a serious complication of aortic graft infections.⁸⁷ Standard treatment of abdominal VGIs complicated by aortoenteric fistula is a staged procedure that consists of an axillofemoral bypass through a noninfected field, graft removal, and closure of the aortic stump.⁸⁸ Oderich and colleagues⁸⁷ investigated the in situ replacement of the infected grafts complicated with aortoenteric fistula with rifampin-soaked grafts. Their surgical technique consists of excising the infected graft, repairing the intestinal defect, placement of the in situ rifampin-soaked graft, and finally covering the graft with omentum. The patients are then treated with long-term oral antibiotic suppression. This technique could be used in patients with limited infection, but not in those patients with large abscesses and excessive purulence.

Another complication of aortic graft infections is the formation of an aorto-esophageal fistula, with patients typically presenting with gastrointestinal bleeding. If the patient is hemodynamically unstable on presentation, thoracic endovascular aortic repair can be done as an emergent procedure to stabilize the patient.⁸⁹ However, thoracic endovascular aortic repair will not repair the esophageal defect nor control the infection and, therefore, the risk of graft infection and fistula recurrence remains.⁹⁰ Before the final surgical management, the patient's general medical condition should be stabilized and broad-spectrum antibiotics should be administered. Radical surgery then follows, with debridement and excision of the infected tissue, extraanatomic bypass or in situ repair, and repair of the esophageal defect.^{89,90} The optimal duration from thoracic endovascular aortic repair to definitive surgical therapy is usually no longer than 1 week to avoid progression of the infection.⁹¹

Management of peripheral grafts

As indicated, the incidence of extracavitary graft infections can be as high as 6%.¹ The gravity of peripheral graft infections as compared with aortic graft infections is related to the high rate of morbidity and mortality associated with this complication. The risk of limb loss and amputation can reach 41%.⁹² The surgical management of peripheral graft infections is similar to aortic graft infections and it consists of one of the following: complete graft excision with extraanatomic bypass or in situ reconstruction, partial graft excision, or complete retention of the graft.⁹²⁻⁹⁴ Caution should be exercised while selecting patients to undergo partial graft excision or graft preservation as the rate of reinfection and subsequent need for reoperation could be high. Mertens and colleagues⁹² reported that 82% of the peripheral graft infection cases managed with partial graft excision required reoperations for sepsis control, compared with only 13% of the cases managed with total graft excision. Therefore, total graft removal is the preferred management strategy for patients presenting with peripheral graft infections.⁹⁵

Management of infected arteriovenous grafts

In the setting of anastomotic involvement, presence of virulent organisms, or sepsis, complete or total graft excision is advocated. In the absence of any of the former

conditions, subtotal graft excision can be considered. In subtotal graft excision, a small part of the prosthetic graft is retained, maintaining the arterial lumen patent.^{2,96} The incidence of recurrent infection as a complication of subtotal graft excision is conflicting in the literature, with some studies reporting increased incidence of recurrence and others reporting no increased risk of recurrent infection.^{96–98} Other surgical approaches involve partial graft excision with bypass in the setting of a localized infection. The advantage of this technique lies in the possibility of immediate cannulation postoperatively for dialysis, thereby eliminating the need to establish a temporary dialysis access. However, similar to subtotal graft excision, partial graft excision carries the risk of a recurrent infection.⁹⁶

In summary, the optimal surgical intervention for prosthetic VGIs remains controversial. The treatment should be highly individualized and depends on the availability of autologous veins, cryopreserved allografts, or prosthetic grafts, as well as the surgeon's experience.⁸⁰ Fig. 2 is a simplified flowchart to aid in the management of VGIs.

PREVENTION

Given the often devastating effects of VGIs, significant efforts have been directed at various preventive strategies. Table 2 lists some of the risk factors of VGIs and potential preventive methods.

Decolonization

Bode and colleagues³⁸ conducted a randomized, double-blind, placebo-controlled trial to assess the efficacy of screening for *S aureus* and subsequent decolonization

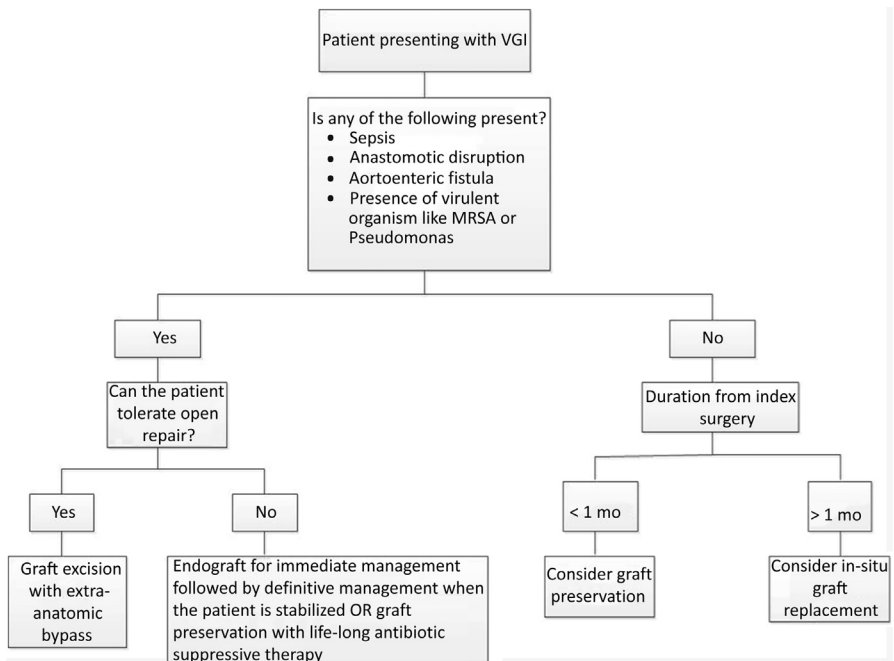


Fig. 2. General management of vascular graft infections (VGIs). MRSA, methicillin-resistant *Staphylococcus aureus*.

Risk Factors	Prevention	Comments
Colonization with <i>S aureus</i>	<ul style="list-style-type: none"> • Use of mupirocin for nasal decolonization and chlorhexidine for extranasal carriage • Use of vaccines that target <i>S aureus</i> 	<ul style="list-style-type: none"> • Mupirocin decolonization carries with it the risk of emergence of resistance, so its use should be reserved for high-risk patients. • Vaccines targeting <i>S aureus</i> should be further explored as they eliminate the need for decolonization and the subsequent dilemma of antibiotic resistance.
Extensive dental disease	Screen for and treat dental infections before vascular procedures	<ul style="list-style-type: none"> • There are no randomized clinical trials to confirm the effectiveness of treating dental infections before vascular procedures. • There are no protocols that make this a preventive strategy and standard practice.
Use of prosthetic grafts (eg, Dacron)	Use of autologous grafts, cryopreserved human allografts, or tissue-engineered vascular grafts	<ul style="list-style-type: none"> • Tissue-engineered allografts offer the possibility of a nonimmunogenic, nonthrombogenic graft; however, they are still under development.
Intraoperative and postoperative contamination	<ul style="list-style-type: none"> • Antibiotic prophylaxis within 60 min of the incision • Collagen-implant impregnated with gentamicin sulfate • Negative pressure wound therapy • Use of antibiotic- or endolysin-impregnated vascular grafts 	<ul style="list-style-type: none"> • More research is needed to prove the superiority of negative pressure wound therapy to standard occlusive dressings. • The toxicity of antibiotics in antibiotic-impregnated grafts might limit their future use, and the use of endolysin-impregnated grafts should be further studied.
Diabetes mellitus and postoperative hyperglycemia	Tight sugar control in patients undergoing vascular procedures	<ul style="list-style-type: none"> • Diabetes results in an impaired immune response. • Insulin has been shown to have antiinflammatory effects.

in the prevention of surgical site infections. A total of 917 patients with positive nasal swabs for *S aureus* on admission were divided into treatment group (504 patients), receiving mupirocin and chlorhexidine, and into placebo group (413 patients). In the treatment group, 3.4% of patients developed *S aureus* infections compared with 7.7% in the placebo group. This trial proved that the use of both mupirocin (for nasal carriage) and chlorhexidine (for extranasal carriage) resulted in a significant decrease in surgical site infections. However, caution should be exercised if hospitals decide to implement this preventive strategy. The use of mupirocin can lead to the development of resistance among *S aureus* strains. Therefore, the use of mupirocin should be limited to carriers who are at high risk

for infection. Second, to avoid unnecessary use of mupirocin, tests that detect *S aureus* should be highly specific. A similar trial is needed to assess whether such an intervention could decrease prosthetic VGIs after vascular surgery in particular. In addition to these antimicrobial strategies, nonantimicrobial strategies for the decolonization of *S aureus* and prevention of *S aureus* infections have also been investigated. Vaccines that target clumping factor B⁹⁹ and alpha-hemolysin¹⁰⁰ are still under experimentation and may prove to be effective for *S aureus* decolonization and prevention of *S aureus* infections.

Tissue-Engineered Vascular Grafts

Birinyi and colleagues¹¹ showed that the presence of an endothelial lining on the surface of vascular grafts is associated with increased resistance to bacterial adherence in dogs. ePTFE grafts are one of the most commonly used grafts in vascular reconstructive surgery. However, these grafts do not undergo endothelialization. Chen and colleagues¹⁰¹ presented a method to allow for the endothelialization of ePTFE grafts, via coating the graft with extracellular matrix and CD34 monoclonal antibodies. CD34 monoclonal antibodies serve as a capturing tool for CD34⁺ endothelial progenitor cells that can differentiate into mature endothelial cells. The addition of extracellular matrix aims at supporting endothelial growth on the surface of the graft. Tissue-engineered vascular grafts could be a promising tool and a better alternative to the currently used synthetic grafts because of their potential nonthrombogenicity and nonimmunogenicity; however, they are still under development.^{96,102}

Antibiotic Prophylaxis

The aim of antibiotic prophylaxis is to achieve serum and tissue concentrations of the antibiotic at a level above the minimum inhibitory concentration for organisms likely to have colonized the surgical site to prevent surgical site infections.¹⁰³ For vascular procedures, the recommended prophylactic antibiotics are cefazolin and cefuroxime. Antibiotics should be administered within 60 minutes of the incision, and additional dosing is warranted if the surgical procedure persists for more than 2 half-lives of the antibiotic administered (2–5 hours for cefazolin and 3–4 hours for cefuroxime). Antibiotic prophylaxis should be discontinued within 24 hours of the end of surgery, because prolonged prophylaxis duration does not decrease the risk of postoperative infections and has been associated with increased resistance should a surgical site infection occur.¹⁰⁴ In patients allergic to β -lactams, it is recommended to give either vancomycin or clindamycin.¹⁰³ With vancomycin use, the infusion should begin 120 minutes before the incision and an additional dose is recommended after 6 to 12 hours for prolonged surgery. With clindamycin, a second dose is needed after 3 to 6 hours.

Some guidelines and observational studies recommend the administration of antibiotic prophylaxis closer to the incision time, within 30 minutes.^{105,106} To settle the debate about the optimal timing for administering prophylactic antimicrobial agents, Weber and colleagues¹⁰⁷ conducted a phase III clinical trial that included patients undergoing general, trauma, and vascular surgery. They compared the early administration of antibiotic prophylaxis (within 60 minutes of incision) with late administration (inside the operating room) and did not find any significant difference in the surgical site infection rates between the 2 groups. Therefore, the findings of this trial do not support late administration of antibiotic prophylaxis, and that the dosing within 60 minutes of the incision remains adequate.

Collagen Implant Impregnated with Gentamicin Sulfate (Collatamp)

This implant has been shown to decrease the incidence of surgical site infections in general, cardiac, and orthopedic surgery.^{108,109} Almeida and colleagues¹¹⁰ investigated the usefulness of this implant in the prevention of VGIs. They recruited 60 patients with lower limb ischemia to undergo femoropopliteal PTFE prosthetic bypass and divided them into a control group and an implant group. The control group, in which Collatamp was not used, had a surgical site infection rate of 20% (6 of 30), whereas the implant group, which had Collatamp applied next to the prosthesis, had a surgical site infection rate of 0% (0 of 30). The infections in the control group were grades I and II according to the Szilagyi classification. Because VGIs can develop by direct extension,^{10,111} the prevention of a grade I or II infection will likely prevent the occurrence of VGI.¹¹⁰ A randomized, controlled trial is needed to confirm the validity of these results.

Postoperative Wound Care

As indicated, it is hypothesized that one way by which graft infections develop is by direct extension from a nearby infection, such as a superficial wound infection. Hence, by preventing postoperative wound infection, subsequent graft infection could be prevented as well. Efforts are therefore tailored at creating an optimal sterile environment to promote wound healing. One means by which this can be achieved is via the use of negative pressure wound therapy. Matatov and colleagues¹¹² investigated the use of Prevena, a new negative pressure incision management system, in the prevention of wound infections in patients undergoing vascular surgery. In the non-Prevena group, the infection rate was 30% (19 of 63) with 10 patients having Szilagyi grade I infections, 7 patients with Szilagyi grade II infections, and 2 patients with Szilagyi grade III infections. In contrast, the infection rate in the Prevena group was significantly lower (6% [3 of 52]; $P = .0011$), with all infections being grade I. In addition, a single-center, randomized, clinical trial was conducted to evaluate the use of negative pressure wound therapy compared with standard dressing in the prevention of postoperative infections after lower extremity vascular surgery in a high-risk population.¹¹³ The postoperative 30-day surgical site infection rate was numerically lower in the negative pressure wound therapy group (11%) compared with the group that received standard dressing (19%); however, the difference was not statistically significant ($P = .24$).

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