



Perspective

Diagnosis and treatment of vascular graft and endograft infections: a structured clinical approach



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ABSTRACT

A vascular graft or endograft infection (VGEI) is a severe complication that can occur after vascular graft or endograft surgery and is associated with high morbidity and mortality rates. A multidisciplinary approach, consisting of a team of vascular surgeons, infectious diseases specialists, medical microbiologists, radiologists, nuclear medicine specialists, and hospital pharmacists, is needed to adequately diagnose and treat VGEI. A structured diagnostic, antibiotic, and surgical treatment algorithm helps clinical decision making and ultimately aims to improve the clinical outcome of patients with a VGEI.

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Introduction

A vascular graft or endograft infection (VGEI) is a severe infectious disease and is accompanied by high morbidity and mortality rates. Diagnosis can be challenging due to the often difficult-to-reach anatomical sites for microbiologic diagnosis and the possibility of false-positive imaging. In addition, antimicrobial and surgical treatment is challenging due to the polymicrobial nature of the infection, the presence of biofilm, and the extensiveness of surgery to achieve cure. To handle these infections, a dedicated and experienced multidisciplinary team is key. In this viewpoint article, we describe a clinical and structured approach from a Vascular Graft Infection Workgroup in a tertiary referral center in the Netherlands. The aim of this overview is to provide to clinicians who are involved in the care of patients with a suspected central and/or peripheral VGEI (with the exclusion of thoracic grafts) guidance for selecting the best diagnostic and management strategies

in various scenarios and to show the importance of a multidisciplinary team approach.

Definition of Vascular Graft and Endograft Infection

It is important to apply uniform diagnostic criteria to diagnose a VGEI. In 2016, the Management of Aortic Graft Infection Collaboration (MAGIC) introduced criteria to establish the diagnosis of a VGEI (Lyons *et al.*, 2016). These criteria were validated in a vascular graft cohort study and demonstrated good sensitivity and specificity for the diagnosis of VGEI (Anagnostopoulos *et al.*, 2021). Therefore, the MAGIC criteria offer practical clinical guidance to diagnose a VGEI and are useful in daily practice. The MAGIC criteria consist of clinical/surgical, radiologic, and laboratory criteria for diagnosis (Table 1). According to these criteria, a VGEI is diagnosed by the presence of a single major criterion along with any other criterion (major or minor) from another category. The MAGIC criteria can be used as practical tools in the diagnostic workup and need to be considered when a patient is evaluated for a suspected VGEI. It should be noted that the MAGIC criteria have a high diagnostic accuracy for central vascular grafts but a low specificity for peripheral grafts (Anagnostopoulos *et al.*, 2021). In addition, molec-

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Table 1
Management of Aortic Graft Infection Collaboration (MAGIC) criteria for VGEI diagnosis [Anagnostopoulos et al., 2021].

Clinical/surgical	Radiology	Laboratory
<i>Major</i>	<i>Major</i>	<i>Major</i> ^a
<ul style="list-style-type: none"> • Pus around graft or in aneurysm sac at surgery • Open wound with exposed graft or communicating sinus • Graft insertion in an infected site, e.g., fistula, mycotic aneurysm or infected pseudoaneurysm 	<ul style="list-style-type: none"> • Perigraft fluid on CT scan ≥ 3 months after insertion • Perigraft gas on CT scan ≥ 7 weeks after insertion • Increase in perigraft gas volume demonstrated on serial imaging 	<ul style="list-style-type: none"> • Organisms recovered from an explanted graft • Organisms recovered from an intra operative specimen • Organisms recovered from a percutaneous, radiologically guided aspirate or perigraft fluid
<i>Minor</i>	<i>Minor</i>	<i>Minor</i>
<ul style="list-style-type: none"> • Localized clinical features of VGEI, e.g., erythema, warmth, swelling, purulent discharge, pain • Fever $\geq 38^\circ\text{C}$ with VGEI as the most likely cause. 	<ul style="list-style-type: none"> • Other, e.g., suspicious perigraft gas/fluid/soft tissue inflammation; aneurysm expansion; pseudoaneurysm formation; focal bowel wall thickening; discitis/ osteomyelitis; suspicious metabolic activity on fluorodeoxyglucose-positron emission tomography/ CT; radiolabeled leukocyte uptake 	<ul style="list-style-type: none"> • Blood culture results positive and no apparent source except VGEI aneurysm sac at surgery^a • Abnormally elevated inflammatory markers with VGEI as most likely cause, e.g., ESR, C-reactive protein, white cell count

^a If microbiologic investigations identify organisms that are potential contaminants (e.g., coagulase-negative staphylococci, propionibacteria, corynebacteria, and other skin commensals), a minimum of (i) two intraoperative specimens; (ii) two blood cultures; or (iii) one intraoperative specimen plus one blood culture must have positive results for an indistinguishable organism in each sample (based on antibiograms or a recognized typing method).CT, computed tomography; ESR, erythrocyte sedimentation rate; VGEI, vascular graft or endograft infection.

Table 2
Possible symptoms of vascular graft or endograft infection

Symptoms
Fever
Cold shivers
Pain located to the vascular graft
Leaking surgical wound
Inflammation of the skin at the site of the vascular graft
Dehiscence of the surgical scar
Lymphocele/abscess around the surgical scar
Palpable mass at the level of the vascular graft
Sinus tract to the skin
(Acute) limb ischemia
High or low digestive tract bleeding
Ileus

ular and serologic techniques are not included in the criteria but may play important roles (as described in the following paragraphs on diagnostics).

Diagnostic Workup

Medical history and physical examination

When a patient with a suspected VGEI is encountered, a thorough medical history— including surgical procedure details—may help to establish the diagnosis. The following risk factors increase the likelihood of a VGEI and should be considered in the assessment of the *a priori* probability of infection: (i) insertion of the vascular graft or endograft during emergency surgery and/or suspected infectious aortitis; (ii) administration of inadequate perioperative antimicrobial prophylaxis during the index surgery (i.e., a deviation from local guidelines for type, dosing, and timing of antimicrobial administration); (iii) incision through the groin; (iv) the occurrence of bacteremia during admission for the index surgery; (v) multiple interventions before and/or after the insertion of the vascular graft; (vi) wound complications after surgery; (vii) a post-operative infection in the area around the vascular graft; and (viii) multiple co-morbidities (e.g., diabetes mellitus, chronic renal failure, obesity, compromised immune system/use of immunosuppressive drugs) (Anagnostopoulos et al., 2019; Munir et al., 2021).

Characteristic symptoms of a VGEI are listed in Table 2. When systemic signs of infection (e.g., fever, chills) are present, an alternative and more obvious explanation should be ruled out. Although an early postoperative VGEI often presents more prominently with fever (in addition to a complicated postsurgical course), and a late VGEI usually displays a more chronic/dormant character, many local symptoms may be similar and overlapping. Obviously, the symptoms depend on the location of the vascular graft.

Microbiologic investigation

Detection of the causative microorganism(s) is essential for successful treatment. Diagnostic efforts should be based on the surgical options and the clinical situation (Figures 1 and 2). Ideally, all cultures should be collected before antimicrobial treatment begins. If the patient is already treated with antimicrobials, the decision to continue treatment should depend on the *a priori* probability of infection and on the clinical situation.

Three sets (six bottles) of blood cultures should be obtained, regardless of the presence of fever. These blood cultures should be processed with extended incubation time (i.e., 7 days) to increase culture yield. It should be noted that the microbiologic yield of blood cultures is generally low (~30%) and does not always reflect the complete spectrum of causative microorganisms isolated from intraoperative material (Bisharat and Minuhin, 2012; Legout et al., 2012a). In cases when blood culture results are positive, we recommend follow-up blood cultures at 1-day intervals after the start of antimicrobial treatment until follow-up blood culture results are negative. In addition, if feasible and safe, an aspirate around the infected vascular graft should be obtained (by radiologic puncture) before surgery. The presence of microorganism(s) that are not covered by the empirical antibiotic treatment may thereby be detected; in addition, in cases when a patient becomes septic before surgery and antibiotic treatment is warranted, a culture at the site of infection has already been obtained. A culture of a sinus tract or superficial wound is discouraged, as the results cannot differentiate between skin colonization and infection.

In cases when surgery is feasible, the entire explanted vascular graft should be sent to the microbiology laboratory in a sterile container. If sonication methods are available at the treating center, the vascular graft can be sonicated to increase the culture yield of

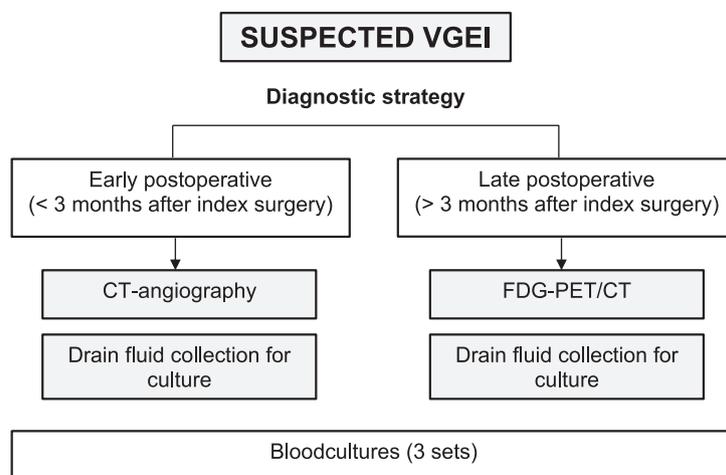


Figure 1. Diagnostic strategy. CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; VGEI, vascular graft or endograft infection.

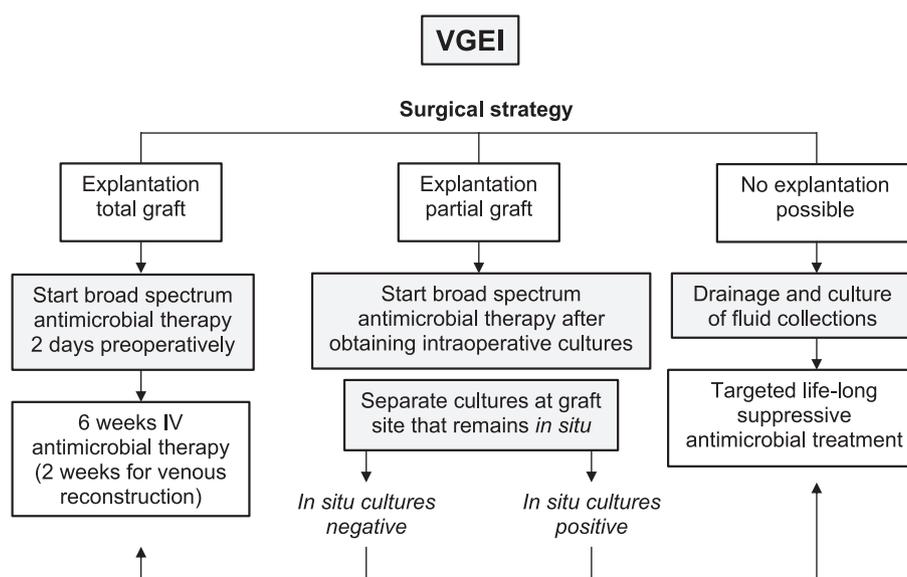


Figure 2. Surgical and antimicrobial strategy. IV, intravenous; VGEI, vascular graft or endograft infection.

biofilm-embedded bacteria (Fournier *et al.*, 1998; Kokosar Ulcar *et al.*, 2018). In addition, multiple (>3) tissue biopsy specimens near the vascular graft must be obtained (with uncontaminated surgical instruments) and immediately transferred into a sterile container (i.e., they should not be left on the sterile surgical field); these should be sent immediately to the microbiology laboratory. Pus must be aspirated in a syringe and capped with as little air as possible (to ensure the reliability of anaerobic cultures). When a part of the vascular graft cannot be removed, a separate sample/ring of the vascular graft can be collected at the site/border of the part that remains *in situ*. The culture results from this part of the vascular graft may be used to decide whether lifelong antimicrobial suppressive therapy is necessary (Figure 2).

In cases when all culture results are negative (possibly due to previous antimicrobial treatment or to the presence of fastidious—i.e., difficult-to-culture—microorganisms), molecular techniques and/or serology can be performed in patients in whom a VGEI is highly suspected. It is important to note that molecular techniques remain (in most cases) less sensitive than microbiologic cultures, and phenotypic resistance of bacteria cannot be determined. Examples of causative microorganisms diag-

nosed by serology, molecular techniques, or special culture methods are *Coxiella burnetii*, *Tropheryma whipplei*, *Bartonella henselae*, and mycobacteria; all of these have been associated with VGEI (Dehio, 1999; Seddon and Hettiarachchi, 2017; Shaikh *et al.*, 2020; Anagnostopoulos *et al.*, 2021, 2019; Bisharat and Minuhin, 2012; Bruggink *et al.*, 2022; Chafke *et al.*, 2020; Davierwala *et al.*, 2019; Dehio, 1999; Erb *et al.*, 2014; Fournier *et al.*, 1998; Gavali *et al.*, 2021; Ho *et al.*, 2022; Janko *et al.*, 2021; Keidar *et al.*, 2014; Kokosar Ulcar *et al.*, 2018; Kouijzer *et al.*, 2017; Lebeaux *et al.*, 2014; Legout *et al.*, 2012a,b; Lyons *et al.*, 2016; Munir *et al.*, 2021; Orton *et al.*, 2000; Puges *et al.*, 2021, 2018; Revest *et al.*, 2015; Rybak *et al.*, 2020; Saleem *et al.*, 2014, 2010; Seddon and Hettiarachchi, 2017; Shaikh *et al.*, 2020; Spacek *et al.*, 2009; Tokuda *et al.*, 2013; Williams and Williams, 2021; Ho *et al.*, 2022).

Imaging

Duplex ultrasound

Duplex ultrasound examination is ideal for the visualization of peripheral vascular grafts (Spacek *et al.*, 2009). In periprosthetic

collections, direct ultrasound-guided punctures can be obtained for microbiologic examination. In cases when ultrasound findings are abnormal, subsequent computed tomography (CT) angiography and/or ^{18}F -fluorodeoxyglucose (FDG)-positron emission tomography (PET) is recommended to diagnose infection and to image the extent of the infection. A normal duplex ultrasound does not rule out infection, and additional imaging is required in these cases when clinical suspicion of VGEI exists.

CT angiography (CTA)

In cases when VGEI is suspected within 3 months after vascular graft or endograft insertion, CTA is recommended (Legout et al., 2012a). The sensitivity and specificity of CTA in the detection of early postoperative VGEI are 95% and 85%, respectively (Orton et al., 2000). The sensitivity of CTA >3 months after the index surgery is low (~67%). However, CTA is considered to add value in assessment of the possibilities for vascular reconstruction with an autologous vein (if indicated) and also as a primary screening tool in emergency settings when PET-CT is not available. Radiologic signs of VGEI on CTA are periprosthetic infiltration, fluid collections, perigraft gas, false aneurysms, and local intestinal wall thickening. However, some of these signs are physiologic and may persist for several weeks after surgery. For example, it has been described that fluid around the vascular graft can be present for >2 months after the operation (Orton et al., 2000). Perigraft gas generally resolves within 1 week after the operation but may persist for up to 7 weeks after open surgery (Bruggink et al., 2022; Tokuda et al., 2013). If the diagnosis of a VGEI is uncertain, CTA can be repeated to monitor the progression of disease.

^{18}F -FDG-PET

In patients with a suspected VGEI in the late postoperative period (>3 months after the index surgery), a combination of ^{18}F -FDG-PET and low-dose CT is advised. The sensitivity and specificity of ^{18}F -FDG-PET combined with CT to detect VGEI in the late postoperative period are 95% and 85%, respectively (Chafke et al., 2020; Keidar et al., 2014; Saleem et al., 2014; Spacek et al., 2009). Focal and/or heterogeneous uptake of FDG along the graft or native vessel, especially when combined with enlarged lymph nodes, is highly suggestive of infection. An additional advantage of ^{18}F -FDG-PET/CT is that possible sources of a disseminated infection and/or alternative foci of infection can be evaluated (Kouijzer et al., 2017). However, a homogeneous pattern with a high maximum standardized uptake value along the vascular graft may remain present many years after index surgery and often represents physiologic FDG uptake.

Treatment

The management of VGEI consists of a combination of surgical intervention and antimicrobial treatment.

Surgical treatment

Surgery is the cornerstone in the treatment of VGEI. The infected vascular graft must be fully extracted to achieve infection eradication. If the infection occurs in the early postsurgical period, an attempt can be made to leave the graft *in situ* by performing extensive surgical debridement. This surgical approach is feasible for peripheral grafts but is not always possible for central grafts. In addition, the rapid formation of biofilm often mandates complete graft removal. Although an extra-anatomic reconstruction outside the infected field is an approach often preferred by surgeons, extra-anatomic reconstruction is associated with a

Table 3
Empirical antimicrobial treatment.

Abdominal vascular grafts or grafts localized in the groin area

- Piperacillin/tazobactam IV (dosed as piperacillin): loading dose 4000 mg, immediately followed by continuous infusion of 16,000 mg/24 h^a plus
- Vancomycin IV: loading dose 20 mg/kg, immediately followed by continuous infusion of 30 mg/kg/24 h^{a,b} plus
- Caspofungin IV: 150 mg QD

In case of allergy to penicillin:

- Ceftazidime IV: loading dose 2000 mg, immediately followed by continuous infusion of 6000 mg/24 h^a plus
- Metronidazole PO: 500 mg TID plus
- Vancomycin IV: loading dose 20 mg/kg, immediately followed by continuous infusion of 30 mg/kg/24 h^{a,b} plus
- Caspofungin IV: 150 mg QD

Peripheral grafts not localized in the groin area

- Cefuroxime IV: loading dose 1500 mg, immediately followed by continuous infusion of 6000 mg/24 h^a plus
- Vancomycin IV: loading dose 20 mg/kg, immediately followed by continuous infusion 30 mg/kg/24 h^{a,b}

Note: Begin treatment 48 hours before surgery if complete replacement of the infected vascular graft is possible. If only partial replacement is possible, begin treatment after deep intraoperative cultures are obtained. Narrow the antibiotic spectrum after intraoperative culture results are known.

^a Dosages based on adequate renal function (creatinine clearance >50 ml/min) and normal weight/body mass index. In other cases, contact the hospital pharmacist for dosing advice.

^b Dose adjustment based on therapeutic drug monitoring (target steady state serum concentration: 20–25 mg/l).IV, intravenous; PO, by mouth; QD, once a day; TID, three times a day.

high risk of complications and recurrence of infection. Therefore, the removal of the infected graft material and aggressive debridement of the infected bed, combined with an *in situ* reconstruction, is recommended by the European Society for Vascular Surgery (Gavali et al., 2021; Saleem et al., 2010). Various types of material can be used for vascular reconstruction. If available, autologous venous material is considered the first-line option for reconstruction (Gavali et al., 2021). If removal of the vascular graft is not feasible due to co-morbidity and/or lack of revascularization possibility, surgical debridement and/or drainage of fluid collections, followed by lifelong antimicrobial suppression therapy, is an alternative treatment choice. However, it is important to recognize that infected vascular grafts that are left in place are associated with higher mortality and morbidity rates (Janko et al., 2021; Legout et al., 2012b; Erb et al., 2014). A tailored treatment plan will be required for each patient and should be discussed within a multidisciplinary team.

Antimicrobial treatment

Choice of antimicrobial treatment

The type(s) of microorganism involved in VGEI depend on the location of the vascular graft, and the empirical antimicrobial regimen should be chosen accordingly (Table 3). A polymicrobial infection with bacteria from the gut is often seen in abdominal and/or groin grafts and includes the presence of yeasts in ~30% of cases (Puges et al., 2021; Revest et al., 2015). We consider this relatively high incidence of yeast a reason to cover yeast in the empirical treatment—especially when an infected central graft is replaced with a new prosthetic graft. The presence of polymicrobial intestinal flora suggests the presence of a connection between the prosthesis and the gut or groin; indeed, a macroscopic fistula can be found intraoperatively in many cases (in our experience). In contrast, skin bacteria are relatively more common in peripheral grafts; therefore, the choice of antimicrobial agents is targeted toward these microorganisms. Empirical therapy should be adjusted based on the intraoperative culture results.

Timing of antimicrobial treatment

Before the initiation of antimicrobial administration, the aim of treatment (i.e., salvage or curation) and potential surgical strategies should be clear, as they dictate the timing and choice of antimicrobial agents (Figure 2). In all cases, blood cultures and (in the case of a fluid collection) aspiration of fluid should be performed before the initiation of antimicrobial treatment. If complete removal of the vascular graft is considered possible, broad-spectrum antimicrobial treatment is initiated 48 hours before surgery (Table 2). The purpose of this approach is to achieve a certain degree of microbial load reduction (to place the new vascular graft in a less-contaminated area) without having a major impact on culture yield (Legout et al., 2012a). To avoid the selection of resistant strains—particularly in the case of a fistula between the graft and the intestine—initiation of antimicrobial treatment >48 hours before surgery should be avoided. If part of the vascular graft cannot be removed (and therefore curation cannot be achieved), antimicrobial treatment ideally should be initiated after perioperative cultures are obtained. The only exception is for sepsis, in which immediate initiation of treatment with antimicrobial agents before surgery is indicated. Antimicrobial treatment in this case is aimed at treating sepsis and preventing death, rather than at treating VGEI. Consequently, antimicrobial treatment in sepsis is targeted toward only the most virulent pathogens; empirical coverage for enterococci, coagulase-negative staphylococci, anaerobes, and yeasts may not be required.

Duration of antimicrobial treatment

If the infected vascular graft has been completely removed and replaced, 6 weeks of intravenous therapy is considered sufficient to achieve curation (Rybak et al., 2020). In previous studies, no distinctions were made among the treatment durations for artificial, biologic, and autologous graft materials. However, if the vascular graft has been removed and replaced with an autologous vein, a shorter treatment duration may be chosen (in the absence of foreign material), with a minimum duration of 2 weeks of intravenous therapy. In general, depending on the postoperative course and the evolution in C-reactive protein during follow-up, antimicrobial therapy can be prolonged. It should be noted that normalization of C-reactive protein and/or FDG/PET-CT does not guarantee complete infection eradication. In biofilm-associated infections in particular, persister bacterial cells can remain dormant in the biofilm and may reactivate after antibiotic treatment is discontinued (Lebeaux et al., 2014).

Multidisciplinary Team

Considering the complexity of the disease and the accompanying morbidity and mortality, a multidisciplinary approach—consisting of a team of vascular surgeons, infectious diseases specialists, medical microbiologists, radiologists, nuclear medicine specialists, and hospital pharmacists—is mandatory. A weekly meeting in which diagnostic and therapeutic dilemmas are discussed is essential to tailor the optimal individual treatment plan. Preferably, a standard diagnostic, surgical, and antibiotic algorithm is followed; however, it should be individualized based on the frailty of the patient, drug interactions, allergies, and intolerances. In addition, the toxicity of antimicrobial treatment should be monitored after patient discharge, and the patient should be followed closely for the occurrence of relapse or persistent infection that requires further intervention. These factors exemplify the necessity of a multidisciplinary team. The importance of an experienced and dedicated team has been extensively described for endocarditis (Davierwala

et al., 2019). Preferably, the team should also be involved in education, improve communication between hospitals and facilitate referrals to specialized surgical centers, and promote research to address important cavities that currently exist in the diagnosis and treatment of VGEI.

Conclusion

VGEI is a severe and difficult-to-treat infection that requires a dedicated multidisciplinary team to ensure an adequate diagnostic pathway and a tailored antimicrobial and surgical treatment plan. The described structured clinical approach, applied by a Vascular Graft Infection Workgroup of a Dutch tertiary referral center, may guide physicians who encounter patients with suspected VGEI.

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Author Contributions

MW composed the original draft of the manuscript. All other authors reviewed and edited the manuscript.

Declaration of Competing Interest

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