Clinical Infectious Diseases

STATE-OF-THE-ART REVIEW

Fostering Collaborative Teamwork—A Comprehensive Approach to Vascular Graft Infection Following Arterial Reconstructive Surgery

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Vascular graft infection (VGI) is one of the most serious complications following arterial reconstructive surgery. VGI has received increasing attention over the past decade, but many questions remain regarding its diagnosis and management. In this review, we describe our approach to VGI through multidisciplinary collaboration and discuss decision making for challenging presentations. This review will concentrate on VGI that impacts both aneurysms and pseudoaneurysms excluding the ascending thoracic aorta.

Keywords. aneurysm repair; epidemiology; comprehensive approach; vascular graft infections.

Vascular graft infection (VGI) is one of the most serious complications following arterial reconstructive surgery. Although infrequent, with an overall 5-year incidence of 1.6% [1], VGI is associated with poor outcomes [2, 3], with an all-cause, 1-year mortality rate of 21–28% [1, 4]. Vascular graft infection is also characterized by its significant financial burden among afflicted patients.

This review explores the optimal approach to VGI management through multidisciplinary collaboration. We examine the clinical presentation and diagnosis of VGI, and then provide clinical vignettes to illustrate important principles in the prevention and management of VGI. Herein, the term "graft" refers to synthetic or biological vascular grafts placed during open surgical repair (OSR) or stent grafts placed during endovascular repair (EVAR), unless specified otherwise. The review focuses on the infection of grafts used to repair arterial aneurysms and pseudoaneurysms. It delves into intracavitary and extracavitary VGI as 2 separate entities due to differences in both diagnostics and management. Intracavitary VGI occurs within the thoracic or abdominal cavity, while extracavitary VGI occurs in upper or lower extremities. For intracavitary VGI, our discussion relates to the descending thoracic aorta, abdominal aorta, and iliac arterial tree. In contrast, the ascending thoracic aorta is not addressed as its pathogenesis and management are unique and beyond the scope of this review. For extracavitary VGI, those often involve grafts in the groin and less commonly in distal parts of the lower extremities [3]. While femoral and popliteal aneurysms may occur spontaneously in patients with associated risk factors such as atherosclerotic disease, dilations in these vessels more commonly represent pseudoaneurysms [5], which may be iatrogenic due to procedures like cardiac catheterization or a result of aortitis or trauma. This review does not apply to infections of arteriovenous grafts such as those used for hemodialysis.

The current work represents a collaborative effort involving experts from vascular surgery (VS), infectious diseases (ID), and clinical pharmacy (PharmD) who practice in the United States. Our approach is in line with both a Scientific Statement from the American Heart Association (AHA) and the European Society of Vascular Surgery (ESVS) guidelines [3, 6].

CLINICAL PRESENTATION OF VASCULAR GRAFT INFECTION

The clinical presentation of VGI varies depending on pathogen virulence, route of infection, and graft location [3]. Early VGI (≤4 months from aneurysm repair [6]) is typically a result of intraoperative contamination with virulent pathogens [2], leading to an acute presentation with systemic symptoms [3]. Late VGI (>4 months from repair [6]) may also be a result of intraoperative contamination but with less virulent pathogens that lead to an indolent and chronic presentation [2]. Occasionally, late VGI may present acutely due to

Received 10 October 2023; editorial decision 24 February 2024; published online 24 April 2024

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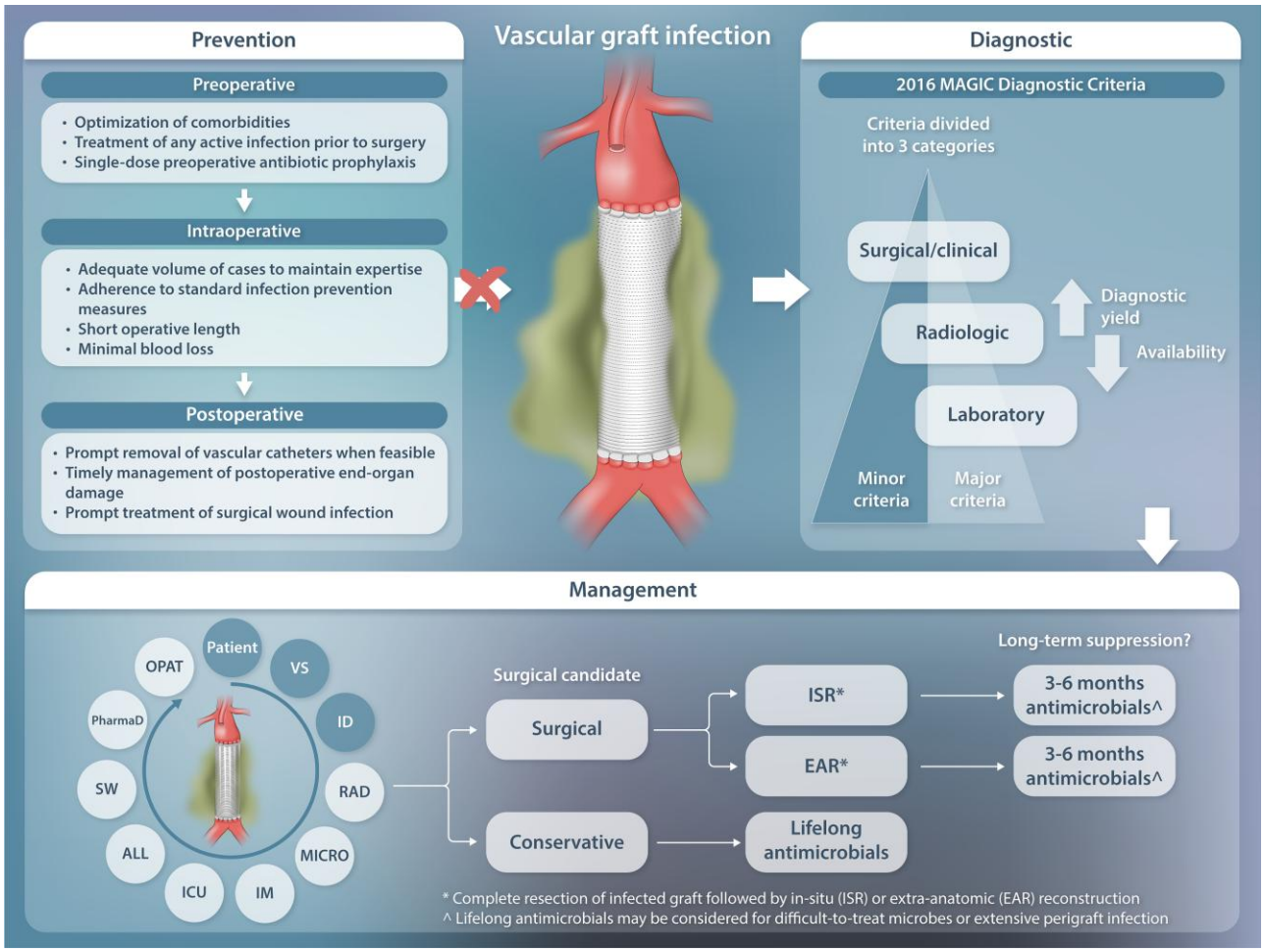
Clinical Infectious Diseases® 2024;78(6):e69–e80

https://doi.org/10.1093/cid/ciae150



hematogenous seeding from a septic focus elsewhere, graft-enteric erosion, or iatrogenic contamination during catheterization or interventional procedure [6]. In theory, the hematogenous seeding of grafts decreases over time due to partial endothelialization of the graft [3]. Figure 1 lists some of the presenting signs/symptoms for extracavitary and intracavitary VGI.

DIAGNOSING VASCULAR GRAFT INFECTION

The 2016 Management of Aortic Graft Infection Collaboration (MAGIC) criteria are the only standardized VGI definition (Table 1 [7]) and are recommended by the ESVS as the diagnostic standard [6]. The definition lists major and minor criteria in each of 3 categories—clinical/surgical, radiological, and laboratory—and categorizes VGI diagnosis into suspected or confirmed. The diagnostic accuracy of MAGIC may have low specificity with suspected VGI [8]. However, most definitive major criteria are based on radiography or surgical exploration. Hence, when radiography is equivocal and surgical management is not an option, many VGI cases will remain suspected rather than confirmed. By including a suspected category, VGI may be overdiagnosed [8]; nevertheless, this may be thought to be justifiable given the potential risk associated with failure to capture a VGI.

When VGI is considered, clinicians must first distinguish the graft as intracavitary or extracavitary with regard to location [3]. The diagnostic and therapeutic approaches for both types differ. The extent of infection can also be described using classification systems such as Szilagyi, Samson, or Bunt (Supplementary Table 1) [6]. Those may be useful tools when planning surgical interventions for VGI.

Clinical/Surgical Criteria

Surgical exploration allows for direct inspection of the graft site and sampling for cultures, which provides the best means for confirming VGI. However, surgical intervention is invasive and may be delayed until compelling evidence for VGI is available through clinical signs and/or cross-sectional imaging

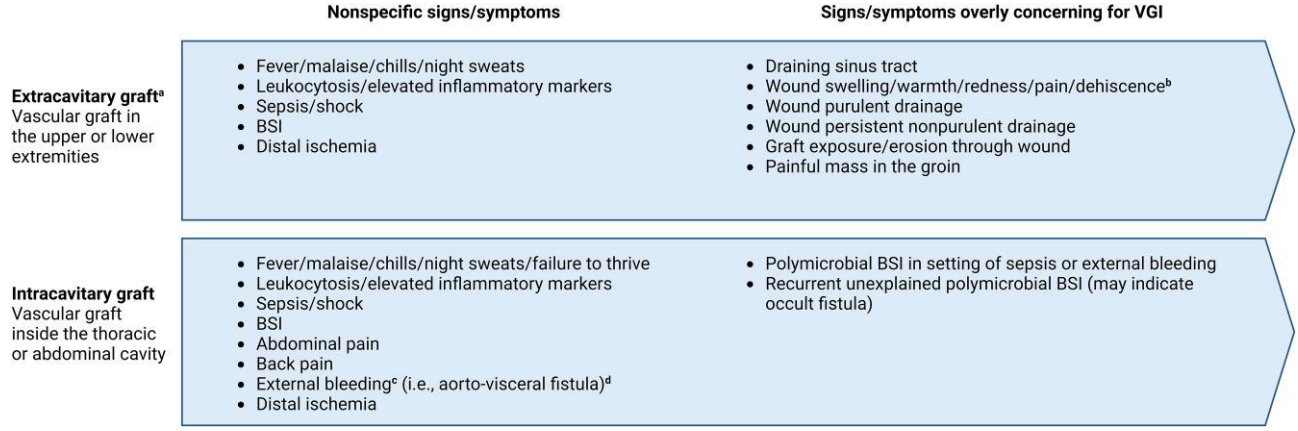


Figure 1. Clinical signs and symptoms that may indicate VGI. Abbreviations: BSI, bloodstream infection; VGI, vascular graft infection. [a]Often involves grafts in the groin and less commonly in distal parts of the lower extremities [3]. [b]Localized inflammatory signs may represent superficial infection rather than graft involvement [7] but should raise concern and prompt workup for VGI. [c]May range from minimal bleed to massive and life-threatening bleed [3]. [d]Included aortoesophageal, aortoenteric, and aorto-ureteral fistulae. Figure created by Biorender.com.

Table 1. A Case Definition for Vascular Graft Infection of the Management of Aortic Graft Infection Collaboration (MAGIC)

	Clinical/Surgical	Radiography	Laboratory[a]
Major criteria	1. Purulence (confirmed by microscopy) around graft or in aneurysm sac during surgery[b] 2. Open wound with exposed graft or communicating sinus tract 3. Fistula development (eg, aortoenteric) 4. Graft insertion in an infected site (eg, fistula, mycotic aneurysm, or infected pseudoaneurysm)	1. Perigraft fluid on CT scan ≥3 mo after insertion 2. Perigraft gas on CT scan ≥7 wk after insertion 3. An increase in perigraft gas volume demonstrated on serial imaging	1. Organisms recovered from an explanted graft 2. Organisms recovered from an intraoperative specimen 3. Organism recovered from a percutaneous aspirate of perigraft fluid
Minor criteria	1. Localized clinical features of VGI (eg, erythema, warmth, swelling, purulent discharge, and pain) 2. Fever ≥38°C with VGI as most likely cause	1. Other (eg, suspicious perigraft gas/fluid/soft tissue inflammation; aneurysm expansion; pseudo-aneurysm formation; focal bowel wall thickening; discitis/osteomyelitis; suspicious metabolic activity on FDG PET/CT; radiolabeled leucocyte uptake)	1. Blood culture(s) positive and no apparent source except for VGI 2. Abnormally elevated inflammatory markers with VGI as the most likely cause (eg, ESR, CRP, and white blood cell count)

Data from reference [7]. Suspected VGI: 1 isolated major criterion, or minor criteria from any 2 of the 3 categories. Confirmed VGI: 1 major criterion plus any other criterion (major or minor) from another category.

Abbreviations: CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography; VGI, vascular graft infection.

[a]If a skin commensal is recovered (ie, possible contaminant), then isolation of the same indistinguishable organism from at least 2 separate sterile specimen is required. The specimen can include 2 intraoperative samples, 2 blood culture sets, or 1 intraoperative sample and 1 blood culture set. The organisms are indistinguishable if they have the exact same antibiograms or type using recognizable typing methods such as pulsed-field electrophoresis.

[b]The MAGIC proposed that "cloudy" fluid on gross intraoperative inspection may be due to noninfectious reasons; hence, the major criterion requires demonstrating pus/inflammatory cells by direct microscopy.

studies. The shortcoming of the clinical criteria is the nonspecific nature of signs and symptoms in patients who present with VGI. Detecting a direct communication between the graft and a nonsterile site provides the only definitive evidence of VGI on physical examination. Such definitive signs are infrequent but are more common with extracavitary compared to intracavitary VGI [3]. If the original graft was implanted in an infected site, then it is presumed to be infected according to MAGIC criteria, although it could be argued that, for patients receiving appropriate antibiotics around the time of implantation, the new graft may be protected from infection.

Radiological Criteria

Diagnostic and interventional radiology are the most effective methods after surgical exploration for confirming VGI. The

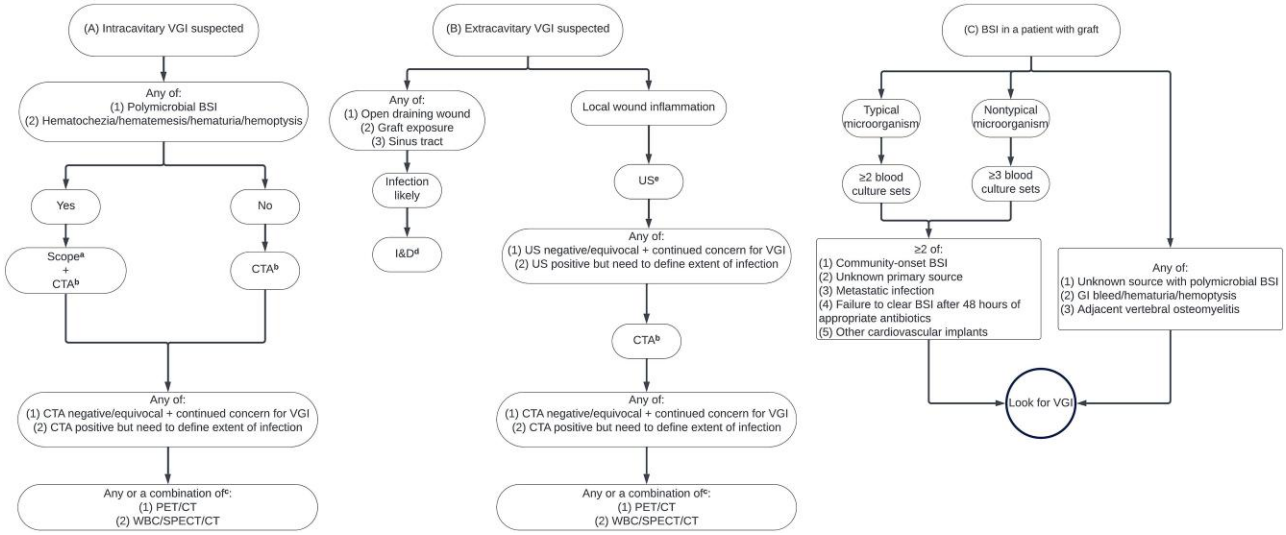


Figure 2. *A* and *B*, Radiographic workup for suspected VGI [3, 6, 7]. *C*, Red flags that should prompt VGI workup in the setting of BSI. Blood culture set consists of at least 1 aerobic and 1 anaerobic bottle. Typical and nontypical microorganisms are defined in the 2023 Duke-International Society of Cardiovascular Infectious Diseases (ISCVID) criteria for IE [13]. Abbreviations: BSI, bloodstream infection; CTA, computed tomography angiography; I&D, irrigation and debridement; IE, infective endocarditis; MRA, magnetic resonance angiography; PET/CT, 18F-fluorodeoxyglucose positron emission tomography with computed tomography; US, ultrasound; VGI, vascular graft infection; WBC/SPECT/CT, white blood cell/single photon emission computed tomography with computed tomography. [a]A scope procedure can be performed when suspecting aortic erosion or fistula. For example, patients with upper gastrointestinal bleeding can undergo esophagogastroduodenoscopy. An aortic erosion or fistula detected during examination via scope confirms the presence of VGI. [b]If CTA is contraindicated, such as with contrast allergy, MRA can be attempted [6]. Alternatively, one may proceed directly to PET/CT or WBC/SPECT/CT. [c]WBC/SPECT/CT may have the best diagnostic accuracy. However, there is a lack of adequate comparative data to recommend 1 modality over the other. The choice between both nuclear scans will depend on availability. [d]I&D is required in this setting and VGI diagnosis can be made intraoperatively. Imaging is not necessary for diagnosis but may be needed for surgical planning. [e]If US shows perigraft fluid, consider US-guided aspiration for microbiologic evaluation.

choice of imaging is best determined through consultation with experts in radiology and nuclear medicine [9].

Computed tomographic angiography (CTA) remains the reference standard for diagnosing VGI [3, 6, 7, 10]. This method can detect perigraft gas and fluid. The MAGIC criteria propose that CTA findings of perigraft gas at 7 or more weeks and perigraft fluid at 3 or more months from graft insertion are highly suggestive of VGI. However, it remains unclear at what point postoperatively do these findings become specific for VGI. When in doubt, a computed tomography (CT)–guided aspiration for microbiologic confirmation should be pursued with input from ID and VS [7]. In case of aortoenteric fistula, CTA may show contrast in the gastrointestinal tract. Additionally, complicating vertebral osteomyelitis may be seen on CTA in case of contiguous spread of infection [6].

Ultrasound (US) can detect pseudoaneurysms, graft thrombosis, and perigraft gas and fluid and allows instant percutaneous sampling for microbiologic evaluation [6]. It is more reliable for extracavitary than intracavitary VGI [10]. A positive US could be helpful, but a normal US should be followed by CTA when there is increased suspicion for VGI [6, 10]. Even when a US is positive for perigraft fluid/gas, a CTA may still be obtained for better spatial evaluation and surgical planning.

If the diagnosis is not made by US or CTA, other imaging modalities may be considered and discussed with radiology. Data are emerging regarding the use of magnetic resonance angiography, white blood cell (WBC)–labeled imaging (technetium-99m or indium-111), and ^{18}F-fluorodeoxyglucose positron emission tomography with CT (FDG PET/CT) to identify VGI [3, 6]. Due to high cost, restricted availability, and limited clinical expertise, the routine use of these studies in VGI diagnosis is not yet established. Nuclear scans are extremely sensitive for detecting VGI, yet false-positive results remain a concern [9]. Their specificity may be enhanced when combined with CT for spatial evaluation. They can identify metastatic foci of infection [10], although the survival benefit has not been proven [11, 12]. Advancements in nuclear medicine techniques will likely enhance their role in diagnostic radiography of VGI. Figure 2*A* and 2*B* highlight our proposed radiographic evaluation for VGI, which follows ESVS and AHA recommendations [3, 6].

Laboratory Criteria

The minor laboratory criteria are nonspecific and rely mainly on inflammatory markers and positive blood cultures with no apparent alternative source other than VGI. Modern automated blood culture systems have the power to identify most organisms within 5 days of incubation. However, if negative after 5 days, we advise extending incubation for 14 days, especially if infection due to *Cutibacterium* species is possible [14].

Table 2. Summary Points of the Clinical Vignettes

Vignette Number	Vignette Description	Summary Points
1	Mitigating risks for VGI	• Risk factor mitigation should start preoperatively in the outpatient setting. • In referral centers with high volume of aneurysm repairs, we encourage fostering a collegial and collaborative relationship among specialists in VS, ID, internal medicine, vascular medicine, and allergy to enable timely evaluation.
2	BSI in a patient with intracavitary vascular graft diagnosed with VGI	• BSI may be the only clue to an underlying VGI. o Existing infrastructures such as microbiology reporting practices and ASP activities may be leveraged to aid in identifying patients with BSI requiring further evaluation. o Suspicion for VGI should be gauged by (1) burden of BSI and (2) type of pathogen. o The decision to pursue workup for VGI and the type of testing should ultimately be directed by ID and VS working in coordination. o Clinicians should be cognizant of other implants and look for metastatic sites of infection accordingly. • Management of intracavitary VGI can be broadly classified as (1) curative or (2) suppressive. o Surgical explantation of graft is the only means for infection cure. o Reconstruction after explantation can be done through either (1) ISR or (2) EAR. o Graft preservation is not durable for intracavitary VGI. • Antimicrobial regimen can be divided into (1) therapy or (2) suppression. o The duration of antimicrobial suppression can be guided by (1) extent of perigraft infection and (2) type of pathogen. o Graft preservation mandates life-long suppression. o Antimicrobial therapy and suppression in outpatient settings should be managed and monitored by an OPAT program.
3	Management of extracavitary VGI	• The Samson classification can help determine surgical approach for extracavitary VGI. o Samson I–II are managed as SSTIs not involving the graft. o Samson III–V are managed as VGI. • Management of extracavitary VGI can be broadly classified as (1) curative or (2) suppressive. o Unlike intracavitary VGI, graft preservation for extracavitary VGI (Samson III and IV) may be suitable in select patients without sepsis and who have patent grafts, intact anastomosis, and easy-to-treat pathogens. o Multiple debridement with adequate wound closure is key for a successful outcome in extracavitary VGI. o Samson V mandates graft explantation. • Antimicrobial therapy and suppression for extracavitary VGI follows the same principles as those of intracavitary VGI.

Abbreviations: ASP, antimicrobial stewardship program; BSI, bloodstream infection; EAR, extra-anatomic reconstruction; ID, infectious diseases; ISR, in situ reconstruction; OPAT, outpatient parenteral antimicrobial therapy; SSTI, skin and soft tissue infection; VGI, vascular graft infection; VS, vascular surgery.

Swab cultures from a draining wound or sinus tract should be avoided because microbiology results may represent skin flora rather than the true infecting pathogen.

The major laboratory criteria require recovery of microorganisms from an intraoperative or percutaneously aspirated specimen. When aspiration is pursued, clinicians should refrain from placing a therapeutic drain until infection is confirmed, to avoid introducing infection into a possibly sterile collection [7]. Once infection is confirmed, a decision for placing a drain or surgical intervention can be determined.

Gram-positive pathogens are isolated in two-thirds of VGI cases, with coagulase-negative staphylococci, *Staphylococcus aureus*, and enterococci being most common [6]. Gram-negative pathogens are seen in one-third of cases and anaerobes in approximately 8% [6]. Atypical organisms include *Coxiella burnetii*, *Bartonella henselae* or *Bartonella quintana*, *Brucella* species, *Tropheryma whippelei*, endemic mycoses, *Mycobacterium bovis*, *Mycobacterium tuberculosis* complex other than *bovis*, and non-tuberculous mycobacteria [10]. Pathogen recovery is essential for targeted antimicrobial therapy. Liaison between the proceduralist/surgeon, ID specialist, and microbiologists can guarantee efficient acquisition and transport of clinical samples. If surgery is performed, at least 3–5 deep specimens should be sent, including perigraft tissue/fluid and the graft [6, 10]. The microbiology laboratory can provide directions for proper specimen collection and handling to help avoid contamination. Culturing infected tissue, fluid, or prosthetic material is superior to culturing intraoperative swabs, which should be avoided [6]. Sonication utilizes ultrasonic waves to disturb surface biofilm on foreign materials, releasing microorganisms and enhancing their recovery in cultures [6, 15–19]. Clinicians should contact their local laboratory to determine if a graft sonication technique is available.

Most patients with VGI receive antibiotics prior to specimen collection, which results in a high proportion of cultures being negative [20]. Involving ID early in admission can ensure proper timing of antimicrobial initiation and proper microbiologic workup. In hemodynamically stable patients without bloodstream infection (BSI), antimicrobials should start after surgical or percutaneous sampling [20]. Akin to infective endocarditis (IE) [13, 14], molecular tests may have a promising role in

VGI, but data are currently scarce. Adding 16S ribosomal RNA (rRNA) polymerase chain reaction (PCR), also known as broad-range bacterial-PCR (BRB-PCR), to conventional cultures on perigraft/graft specimen improved bacterial identification in a small prospective VGI cohort pretreated with antibiotics [20]. Broad-range bacterial–PCR uses primers that target regions of the 16S rRNA, which are highly conserved and present in all bacterial ribosomal genes [21]. It first screens for the presence of bacteria and this can then be followed by DNA sequencing for genera and species identification [21]. In our practice, we commonly send "extra" specimens to the laboratory to be held for additional testing, such as BRB-PCR, when cultures are negative. Metagenomic next-generation sequencing of microbial cell-free DNA (cfDNA) in tissue or plasma is another molecular technology that has gained recent attention in various infectious syndromes, including IE [22–26]. Microbial cfDNA circulating in plasma during infection can be detected and sequenced using a novel diagnostic tool (Karius 2017; Redwood City, CA) [27, 28]. This test can identify over 1000 pathogens including bacteria and fungi [28, 29], but studies are needed to confirm its role in VGI. Where available, clinicians may consider plasma microbial cfDNA testing when all other methods have failed to identify a pathogen [24, 25]. However, in cases of polymicrobial infection, the results of cfDNA should be interpreted cautiously, as it may not reliably capture all pathogens involved. Polymicrobial infection is common in abdominal and groin VGI [10].

CLINICAL VIGNETTES

In this section, 3 clinical vignettes are used to highlight key principles in the prevention and management of VGI. Take-home messages for each case are summarized in Table 2.

Vignette 1: Mitigating Risks for Vascular Graft Infection

A 60-year-old man with a 6-cm abdominal aortic aneurysm (AAA) is evaluated by VS for elective EVAR. The patient is a tobacco smoker and has diabetes mellitus, hypertension, and stage II chronic kidney disease. He reports childhood allergy to penicillin. What preoperative consultations/evaluations are needed to mitigate the patient's risk of surgical site infection (SSI) or VGI?

Factors Associated With Surgical Site Infection/Vascular Graft Infection

This case highlights the frequent occurrence of multimorbidity in patients scheduled for elective aneurysm repair [1]. Understanding risk factors associated with SSI/VGI following aneurysm repair can help design methods to mitigate them. Supplementary Figure 1 lists patient-related, preoperative, intraoperative, and postoperative factors associated with SSI/VGI following aneurysm repair and mitigation measures [6, 30, 31].

Preventative Measures

In elective cases, preventive measures should commence preoperatively in the outpatient setting, allowing ample time for medical optimization through multidisciplinary consultations. Important factors to address in our case include tobacco use, medical comorbidities, and antibiotic allergies. The patient should be referred to the appropriate providers to ensure comorbidities are optimized prior to surgery.

Administration of antibiotic prophylaxis at the time of vascular graft placement to prevent VGI is mandatory [31, 32]. The timing, dosing, and re-dosing of antibiotics relative to surgery are crucial and should follow practice guidelines [31, 33]. In patients who are already receiving antibiotics for other indications, special care should be taken to administer a different antibiotic at the appropriate time interval from surgery [31]. Extending antibiotic prophylaxis beyond 24 hours from arterial reconstruction adds no benefit and leads to unnecessary antibiotic exposure [32–34]. Beta-lactams are more protective than alternatives for SSI following various surgeries [34–37]. A history of beta-lactam allergy may result in the avoidance of beta-lactam prophylaxis despite inaccurate reporting by a high proportion of patients [38]. Strategies for penicillin allergy "de-labeling" should be undertaken in patients preparing for aneurysm repair to allow the use of optimal prophylaxis.

Postoperatively, prompt detection and management of incisional complications, like poor wound healing or infection or end-organ damage, will help prevent VGI [31]. Postoperative follow-up with VS and other specialties should be protocolized. Last, a topic worth discussing is the controversial use of antimicrobial prophylaxis during invasive dental procedures in patients with grafts [3, 6]. The ESVS recommends considering prophylaxis in these situations as they view grafts as analogous to valvular prosthesis, but this is solely based on expert opinion [6]. In contrast, the AHA does not suggest using prophylaxis due to lack of efficacy and safety data and the rare occurrence of VGI [3, 39].

Vignette 2: Bloodstream Infection in a Patient With Vascular Graft

A 67-year-old woman was admitted with fever and septic shock due to methicillin-sensitive S. aureus (MSSA) bacteremia (SAB) of unclear source. The patient has a history of OSR of AAA with a Dacron graft 5 months prior to admission as well as a 5-year-old permanent pacemaker. She was initiated on cefazolin, stabilized, and weaned off pressors. SAB persisted for 3 days. As an ID consultant, you are asked to determine whether the source of SAB could be a VGI.

Early Recognition and Evaluation of Bloodstream Infection in Patients With Vascular Grafts

The microbiology laboratory and antimicrobial stewardship program (ASP) are 2 entities that can enhance the early recognition of BSI in patients with grafts. The microbiology

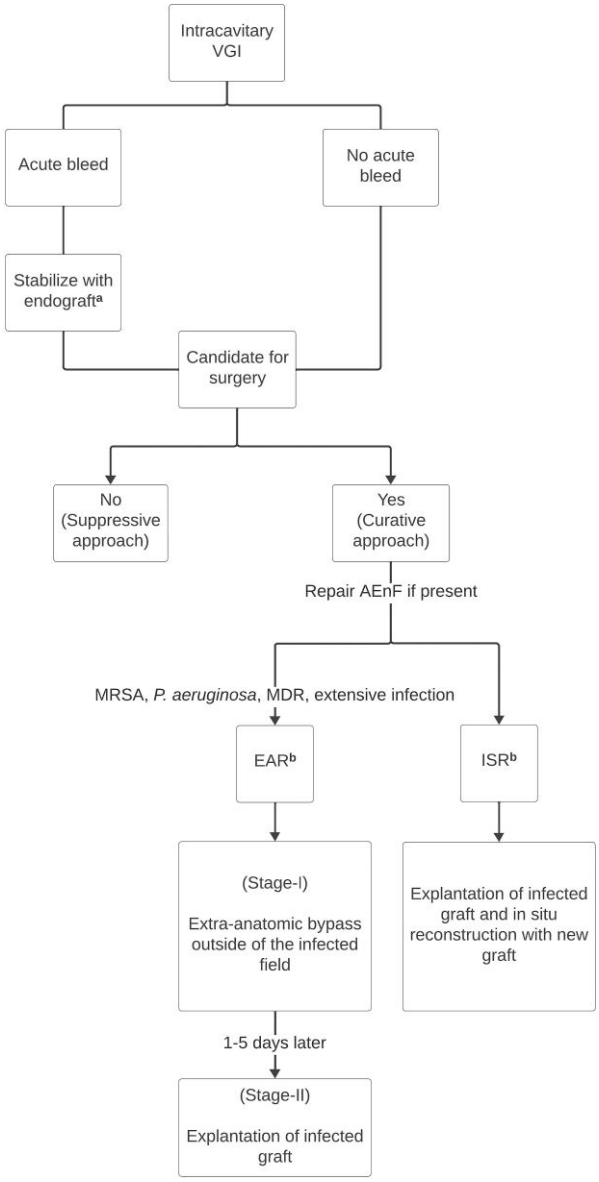


Figure 3. Surgical management of intracavitary VGI. Disadvantages of EAR: (1) Preferably done in 2 stages to minimize limb ischemia, which leads to higher operative time; (2) extra-anatomic route can be difficult to establish; (3) low patency rate of bypass graft; (4) limb ischemia during EAR may lead to amputation in 20–30%; (5) aortic stump may blow out in 10–20%. Abbreviations: AEnF, aortoenteric fistula; EAR, extra-anatomic reconstruction; ISR, in situ reconstruction; MDR, multidrug resistance; MRSA, methicillin-resistant *Staphylococcus aureus*; *P. aeruginosa*, *Pseudomonas aeruginosa;* VGI, vascular graft infection. [a]If an aortoenteric fistula exists, an arterial endograft can be placed to temporarily seal off the fistula and stop bleeding. Subsequent definitive fistula treatment will be needed for cure. [b]The dead space should be eliminated by wrapping the new graft with omentum, muscle flap, fascia, or retroperitoneal tissue. This practice lowers the rate of reinfection. Antibiotic beads may also be placed in the surgical field, although the benefit of this practice remains controversial [6].

laboratory can promptly alert care teams when blood cultures are positive and encourage early ID consultation for specific high-risk pathogens (eg, *S. aureus*) through "nudging" strategies [40–43]. Antimicrobial stewardship programs commonly include prospective audit with clinician feedback as a primary strategy of programmatic antimicrobial optimization [44]. Such strategies increase ID involvement and quality of care [45]. Historical interventions pertaining to BSI involving both microbiology and ASPs have demonstrated superior outcomes as compared with either of these tools alone [46]. Thus, designing interventions that involve both programs and leverage existing infrastructure will benefit all patients with high-risk BSI, including those with vascular grafts.

Approaching Bloodstream Infection in Patients With Vascular Grafts

The high burden of BSI, type of pathogen, and presence of other cardiovascular implants classifies the patient in this stem as being at elevated risk for VGI. The occurrence of BSI only a few months after index aneurysm repair is another reason for concern. Therefore, the patient should undergo a thorough investigation for VGI, as well as transesophageal echocardiogram (TEE) to evaluate for IE.

The exhaustive investigation to rule out VGI in every BSI case is impractical. Understanding risk factors associated with VGI in patients with BSI could assist clinicians, but there are no pertinent studies that address this scenario. Perhaps findings from prior investigations related to IE and other types of cardiovascular device–related infections could be cautiously extrapolated to identify potential red flags for VGI in patients with BSI [13, 47]. The decision to pursue workup for VGI and the type of screening should be directed by ID and VS working in coordination.

The 2 primary factors that should gauge suspicion for VGI during a BSI event include the following: (1) type of pathogen and (2) burden of BSI. The rate of concomitant VGI is higher with monomicrobial BSI due to gram-positive as compared with that of gram-negative bacteremia [48]. However, the risk varies based on the specific species involved [1, 13, 49]. Until more data specific for VGI prevalence in patients with BSI are available, pathogens considered to commonly cause IE should be considered high risk for VGI [13]. Figure 2*C* outlines our approach to BSI in patients with vascular grafts.

After determining that the patient is high risk for VGI, you recommend a CTA which shows perigraft gas and organized fluid. TEE shows IE. VGI is confirmed and VS consulted for graft explantation with consultation of cardiac electrophysiology (EP) for permanent pacemaker removal. The patient is considered fit for surgical intervention. What is the standard surgical approach for cure?

Surgical Management of Intracavitary Vascular Graft Infection

Vascular graft infection management is designated under 2 umbrellas, depending on whether the graft is explanted or preserved, and includes either a curative or suppressive approach. The curative approach requires a patient fit for surgery with explantation of the entire infected graft and careful irrigation and

debridement (I&D) of infected tissue followed by vascular reconstruction and antimicrobial therapy. Graft explantation may be associated with mortality rates of up to 18–30% [3, 7]. Nonetheless, the mortality rate may reach 100% after 2 years if the infected graft is not removed [7]; hence, a curative approach should be pursued when feasible [6]. The suppressive approach constitutes conservative treatment defined as graft preservation and lifelong antimicrobial therapy [50]. In our opinion, limited interventions like percutaneous drainage of perigraft abscesses or partial graft debridement without complete resection should also be regarded as conservative treatment.

Figure 3 describes the surgical approach recommended by the AHA and ESVS [3, 6]. Graft explantation during hemodynamic instability increases the risk of ischemic complications. Therefore, when feasible, graft explantation should be delayed until the patient is hemodynamically stabilized [6]. Our patient presented with septic shock, but this has now resolved and she is ready for surgical intervention. Other patients with VGI may present with hemodynamic instability from internal or external bleeding. This may occur with anastomotic rupture or with aortic erosion or fistulas, which require emergent intervention by a cadre of surgeons and interventionists. In case of fistulas, this historically meant open fistula takedown and graft revision. However, in contemporary practice, when feasible, an endograft offers a fast and temporizing approach to stabilize physiology for later definitive repair [6]. If not resolved, a fistula will lead to the persistence or recurrence of infection. When patients with fistulas are not fit for graft explantation, they may undergo endograft placement as definitive palliative therapy [6].

Curative Approach for Intracavitary Vascular Graft Infection

There is no standard surgical approach for VGI [3]. The choice of procedure will depend on the complexity of the case, patient's physiology, and the surgeon's expertise [3]. Surgeons may elect to perform graft explantation with either extra-anatomic reconstruction (EAR) or in situ reconstruction (ISR), as shown in Figure 3 [6]. In situ reconstruction is now the preferred technique and is associated with reduced early mortality, amputations, graft occlusion, and overall reinfection compared with EAR [51]. In theory, ISR may be less suitable compared with EAR for VGI caused by difficult-to-treat pathogens or presence of extensive perigraft infection to avoid reconstruction in a heavily contaminated field [3].

Suppressive Approach for Intracavitary Vascular Graft Infection

Graft preservation is not considered a durable option for intracavitary VGI [3, 6]. This is especially true for confirmed VGI with anastomotic aneurysm, fistula, perigraft abscess, virulent microorganisms, and multidrug-resistant organisms (MDROs) [50]. The lack of safe and effective oral antibiotics as lifelong treatment will also preclude a suppressive approach. Conservative management in our patient with high-burden SAB and VGI will lead to a poor outcome. Elevated mortality rates have been documented with graft preservation in small series due to septic complications and rupture [6]. Conservative management in this setting is usually either a preparatory step for explantation at later date, or a palliative strategy [6]. Surgical debridement of perigraft infection followed by continuous perigraft space irrigation with targeted antimicrobials through indwelling catheters until perigraft space cultures are negative have been attempted to allow graft preservation but there are scant data to support this approach [3, 6, 50].

VS performed graft explantation and ISR. EP exchanged the pacemaker. What recommendations should you provide for antimicrobial therapy?

Antimicrobial Treatment for Intracavitary Vascular Graft Infection

Recognizing the broad array of pathogens that could be involved, an empiric combination regimen with activity against methicillin-resistant staphylococci, enterococci, Enterobacterales, and *Pseudomonas aeruginosa* is often used. If there is an aortoenteric fistula, the addition of empiric anaerobic and fungal coverage (against *Candida* species) is reasonable. Once blood and tissue culture results are known, therapy can be adjusted accordingly. The pathogen in the current stem was identified as MSSA and the empiric therapy was de-escalated to cefazolin. Some follow the pathogen-specific therapy recommendations for IE [52]. However, given a lack of VGI-specific data and risk of toxicity, we avoid the use of gentamicin for synergy against *S. aureus* or enterococci. Furthermore, we use dual beta-lactam therapy against enterococci for monomicrobial but not polymicrobial VGI. The optimal route and duration of antimicrobials are not defined. Figure 4 describes our approach, which follows recommendations from the AHA [3].

Choosing and executing a prolonged antimicrobial regimen for VGI is complex and often involves ID specialists, allergists, ID pharmacists, and an outpatient antimicrobial therapy (OPAT) team. Both empiric and targeted therapy should be directed by an ID specialist [6]. Two antibiotic classes that deserve special attention are rifampicin and fluoroquinolones. Systemic rifampin is commonly used as an adjunctive to primary antimicrobials for staphylococcal prosthetic infections due to its biofilm activity. Small retrospective reports showed higher treatment success with rifampin-based regimens for staphylococcal VGI, but high-quality studies are lacking [53, 54]. We encourage the use of rifampin due to its potential therapeutic benefit. However, due to a scarcity of data, the addition of rifampin typically does not alter our antimicrobial duration and we would still consider lifelong suppression for *S. aureus* (Figure 4). Of note, adding rifampin to a high bacterial inoculum will select for its resistance. Similarly, using rifampin as primary monotherapy will lead to the selection of rifampin-resistant strains. Hence, for the current vignette, we would

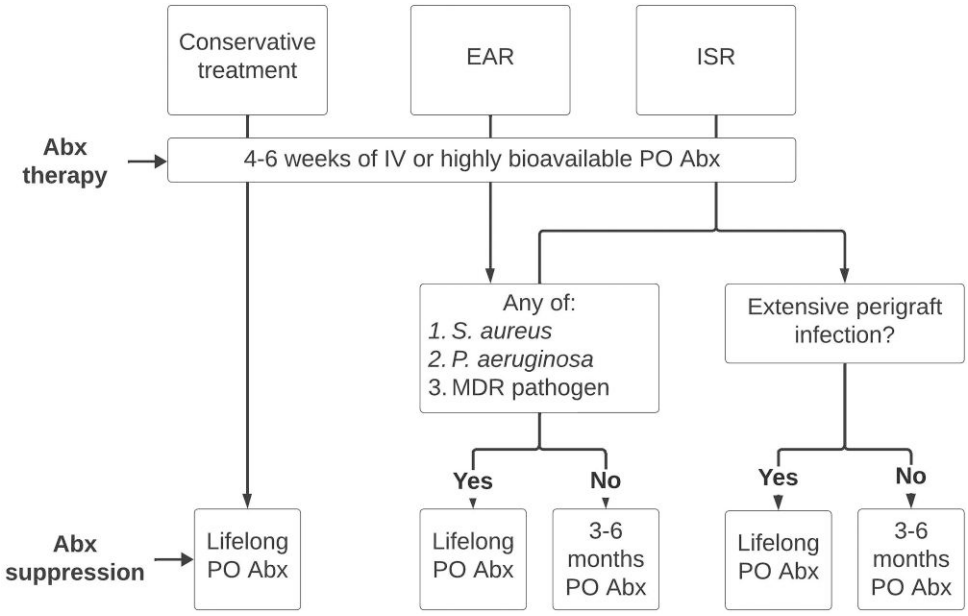


Figure 4. Antimicrobial course for VGI. The course can be divided into therapy and suppression phases. For therapy (4–6 weeks), patients will typically receive parenteral antimicrobials at first. They may then continue the entire phase with parenteral therapy or switch to PO to finish the phase. The ability to switch to PO depends on (1) the patient's immune status, (2) presence of BSI or metastatic infection (such as IE), (3) pathogen susceptibility to highly bioavailable PO antibiotics, and (4) the ability of the patient to take PO. A few examples of commonly used highly bioavailable PO antimicrobials include fluoroquinolones, trimethoprim-sulfamethoxazole, linezolid, metronidazole, and azoles. The duration of PO suppression is based on expert opinion. If a biologic graft was used for reconstruction following EAR or ISR (eg, cryopreserved graft), then shorter periods of suppression can be considered even for difficult-to-treat pathogens. Abbreviations: Abx, antimicrobials; BSI, bloodstream infection; EAR, extra-anatomic reconstruction; IE, infective endocarditis; ISR, in situ reconstruction; IV, intravenous; MDR, multidrug-resistant; PO, per os; *P. aeruginosa*, *Pseudomonas aeruginosa; S. aureus*, *Staphylococcus aureus*; VGI, vascular graft infection.

add rifampin as adjunctive to primary antimicrobial therapy after definitive surgical management and blood culture clearance [55]. In case of graft preservation, some clinicians add rifampin after BSI clearance only if there has been thorough I&D of perigraft infection, although this practice varies widely. If the graft is salvaged without adequate I&D, the bacterial inoculum will remain high and so rifampin should not be added. When prescribed, we typically use a 6-week rifampin course alongside primary therapy. Rifampin should not be used for long-term suppression. Rifampin is associated with many drug–drug interactions (DDIs) due to its induction of cytochrome P450 and P-glycoprotein transporter systems [56, 57]. Its full potential of enzyme induction does not peak until 1–2 weeks following its initiation. Resolution of enzyme induction also occurs over a similar period following rifampin discontinuation [56]. Thus, for patients on multiple medications and started on rifampin, we consult with a clinical pharmacist at the time of rifampin initiation and discontinuation to facilitate screening for potential DDIs and the subsequent need for therapy augmentation.

Fluoroquinolones have been linked to causing serious adverse drug events (ADEs), among which the risk of aortic aneurysm or dissection is particularly concerning in patients with VGI. The Food and Drug Administration added a fluoroquinolone class warning to that effect in 2018 [58]. This considered, the long-term risks of fluoroquinolone use in VGI are poorly understood. The spectrum of activity and excellent bioavailability make this class attractive and commonly used in gram-negative VGI. Fluoroquinolones are the only available oral antibiotics for VGI due to *P. aeruginosa* and, at times, other MDRO gram-negative bacilli. When utilized, proper patient counseling and close monitoring for ADEs should be instituted, especially the risk of *Clostridioides difficile* infection and tendinopathy. Due to the risk of QT prolongation and torsade de pointes, an electrocardiogram (ECG) should be obtained at baseline and following therapy initiation. The frequency of ECG monitoring should be individualized. For patients receiving other QT-prolonging medications, we generally monitor with ECG biweekly during the first 4–8 weeks of therapy. For others, ECG can be done monthly. Beyond an initial 4–8-week period, monitoring can be spaced out at the discretion of the managing provider.

Transition of Antimicrobial Therapy to an Outpatient Setting

Given the length of antimicrobial therapy indicated for VGI (Figure 4), antimicrobial planning at transitions of care should be carefully considered well before patient discharge. Involvement of case management, nursing, and pharmacy will help to assure that therapy is not interrupted, or discharge delayed,

due to issues pertaining to case coordination. For proper delivery and monitoring of therapy, patients with VGI should ideally be followed by an OPAT program. OPAT programs are directed by a team of social workers, ID pharmacists, ID physicians, nurse coordinators, and advanced practice providers. They are designed to aid with outpatient parenteral antimicrobial or complex oral antimicrobial administration, coordinate and follow-up on laboratory and ADE monitoring as per guidelines [59], and facilitate planned or unplanned therapy changes mid-course [59, 60]. OPAT programs are critical for the provision of safe and effective antimicrobial therapy beyond the inpatient setting, and our institution relies heavily upon their careful purview to assure VGI management progresses as planned after hospital discharge.

Vignette 3: Management of Extracavitary Vascular Graft Infection

A 65-year-old woman was hospitalized due to pain and swelling in her right thigh. She had percutaneous coronary intervention 8 months ago complicated by a large common femoral pseudoaneurysm requiring repair with polyester graft. US of the thigh demonstrated an organized fluid collection communicating with the graft. The patient is hemodynamically stable and so antibiotics were held. A percutaneous aspiration was performed showing purulent fluid, which yielded polymicrobial growth in cultures. VS is consulted for surgical management. What is the best approach?

Surgical Management of Extracavitary Vascular Graft Infection

Like intracavitary VGI, treatment of extracavitary VGI can be either curative or suppressive. The Samson classification (Supplementary Table 1) can be used to guide management of extracavitary VGI [3, 6]. In Samson I and II, infection is limited to the skin and soft tissue and does not involve the graft. Patients with these categories of infection can be treated with 2–4 weeks of antibiotics [3]. Samson II is deeper and has a higher risk for progressing to VGI. Hence, it often needs thorough debridement and proper wound closure. Wound closure may require negative-pressure wound therapy (NPWT) and/or myocutaneous flap [3, 6]. Care should be taken with the use of NPWT as it may lead to serious bleeding in up to 7–10% of patients [6, 61]. Samson classes III–V are managed as VGI.

Curative Approach for Extracavitary Vascular Graft Infection

Like intracavitary VGI, ISR and EAR are the 2 main reconstruction techniques available for extracavitary VGI (Figure 3). Ideally, reconstruction is done through new, noninfected, tissue planes, if feasible. Multiple debridement with proper wound closure is necessary for success [3].

Suppressive Approach for Extracavitary Vascular Graft Infection

Graft preservation for extracavitary VGI in patients without sepsis and who have patent grafts, intact anastomosis (ie, Samson III–IV), and easy-to-treat pathogens has been advocated by some [61–65]. Multiple debridement with adequate wound closure using muscle flaps was associated with long-term success and low amputation rates in those patients [3, 64]. The use of antibiotic beads is anecdotal; however, there seems to be selective success in their use [3, 66–69]. One author suggested repeat debridement coupled by povidone-iodine irrigation until the bacterial load becomes less than 10^5 colony forming unit (CFU) [61]. If target CFU was not achieved, then explantation was necessary [61]. However, there are no good-quality data supporting this practice. Difficult-to-treat pathogens with high failure rates where graft preservation should be avoided are methicillin-resistant *S. aureus*, *P. aeruginosa,* and MDROs [64]. Samson V mandates graft explantation due to graft anastomosis compromise [6].

Antimicrobial Therapy for Extracavitary Vascular Graft Infection

The principles of antimicrobial therapy are similar for intracavitary and extracavitary VGI and were previously discussed (Figure 4).

HEALTHCARE DISPARITIES IN VASCULAR GRAFT INFECTION

The resources required for optimal VGI care are substantial and place a high burden on both afflicted patients and healthcare organizations. Such resources are not readily available to vulnerable groups with low socioeconomic status due to inequities in social determinants of health, placing them at higher risk for poor outcomes. For VGI, access to specialized care is paramount given the complexity of disease and the level of expertise required in its treatment. Hence, the uneven geographic distribution of specialized clinicians and surgeons may be a major disparity in this setting. Centers caring for patients with VGI should, at a minimum, have the capability to provide intensive care for unstable vascular patients, have timely access to nuclear medicine imaging when needed, and have inhouse vascular surgeons and ID physicians experienced with treating VGI. Furthermore, they should have access to an OPAT team to ensure safe administration of long antimicrobial therapy. Consulting with experts in other specialties may be needed based on the case. When patients with VGI present to a center unable to provide the level of care described in this review, the receiving center should stabilize the patient and then promptly transfer the patient to a large tertiary care center with access to necessary resources.

CONCLUSIONS

Vascular graft infection is a rare occurrence but with severe manifestations and complications. Optimal management requires a sophisticated collaborative model that involves multiple specialties working together in a collegial fashion and is best done in a high-volume center. With scarce background literature, management is based on expert opinion, but the field is gaining more contemporary and promising attention. Advancing VGI care in the future should focus on assuring timely access to specialized care for all affected patients.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. H. T.: conceptualization, writing—original draft, writing—review and editing, visualization. S. C., A. S. S., R. W. S., R. R. D., Y. M. E., and W. R. W.: writing—original draft, writing—review and editing. L. M. B. and D. C. D.: conceptualization, supervision, resources, writing—original draft, writing—review and editing.

Financial support. This work was supported by the philanthropic support provided by a gift from Eva and Gene Lane (L. M. B.) and a Mayo Named Professorship, the Edward C. Rosenow III, M.D. Professorship in the Art of Medicine (W. R. W.), which were paramount in their work to advance the science of cardiovascular infections, an ongoing focus of investigation at Mayo Clinic for over 60 years. L. M. B also reported royalty payments for authorship duties from UpToDate, Inc (Wolters Kluwer Health).

Potential conflicts of interest. L. M. B. reports royalty payments (authorship duties) from UpToDate, Inc. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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