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Review Article

Management of abdominal aortic prosthetic graft and endograft infections. A multidisciplinary update☆

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ABSTRACT

Abdominal aortic graft infections (AGIs) occur in 1–5% of aortic prosthetic placements. It can result in limb amputation, pseudo-aneurysm formation, septic emboli, aorto-enteric fistulae, septic shock and death. The most frequently involved pathogens are methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci, followed by Enterobacteriaceae and uncommon bacteria. In case of gut involvement the presence of fungi has to be considered. Computed tomography angiography is actually the gold standard diagnostic imaging but magnetic resonance is a valid alternative. Nuclear medicine imaging is commonly used to improve sensitivity and specificity. Signs and symptoms are often aspecific and blood cultures can be negative, requiring alternative ways to detect the microorganism responsible for infection, such as 16S rRNA gene sequencing and molecular rapid diagnostic tests. Curative surgical intervention is the first choice approach, with in-situ reconstruction providing by far the best outcome and xenopericardial bovine patch as a promising option. For patients unable to undergo major surgery, the outcome of conservative approach remains uncertain but usually provides for life-long suppressive therapy. However, in selected cases an attempt of stopping antibiotic treatment after 3–6 months can be done. Given the difficulty in their management, we performed a review of AGIs, in order to raise awareness on clinical presentation, current available diagnostic tools, prophylaxis, surgical and anti-infective treatment of AGIs.

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1. Introduction: epidemiology, risk factors, microbiology

Progress in surgical techniques and advances in interventional radiology alongside with the ageing of general population and the growing number of people living with multiple comorbidities led to an increase in the number of vascular graft procedures [1]. For several decades the risk of abdominal aortic graft infections (AGIs) was reported to be low (<1%). However, in the last decade the overall approach to aorto-iliac disease has shifted from open to endovascular (often addressing sicker and/or older patients), with some study reporting a cumulative rate of AGIs of 5% despite materials amelioration. A nearly double infection incidence has been reported in case of re-operation [1,2].

Risk factors for abdominal AGIs include both risk factors in common with several other infections (such as chronic kidney disease, diabetes, immunosuppression), and risk factors specifically regarding AGIs (such as congenital aortic coarctation, emergent operation, simultaneous gastrointestinal procedures during the insertion of an aortic graft) (Table 1).

Among intrinsic risk factors, the biofilm formation plays a major role. Biofilms are made of microorganisms attached to a living or abiotic surface plus an extracellular matrix. They can make embedded pathogens up to 600 times more resistant to antibiotics than planktonic bacteria [8], limiting therapeutic options to surgical removal of the infected device or suppressive long-term therapy.

Pathogens can infect vascular grafts in several ways. Most cases are determined by contamination at the time of implantation or in the immediate postoperative period, but there is also the possibility of colonization of a thrombus, spreading of an infection from a contiguous site, reintervention and transient bacteremia (e.g. intestinal translocation, dental procedures).

The most frequently involved pathogens are Gram positive bacteria, with methicillin-susceptible *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA) and coagulase-negative staphylococci (CoNS) accounting approximately for more than 50% of AGIs, followed by Enterobacteriaceae and polymicrobial infections. A small percentage is caused by other bacteria, often difficult to detect, and fungi (Fig. 1) [3]. Among less frequent pathogens accountable for AGIs, *Corynebacterium* spp., *Propionibacterium acnes* and *Candida* spp. must be considered. Usually *S. aureus* is responsible for early AGIs, while *CoNS* are more often involved in late AGIs. A strong connection between *S. aureus* bacteremia and endovascular device infection has long been known, so special care must be taken also to those patients who have both an aortic graft and a pacemaker [9].

In case of infections concerning prosthetic materials, the first-choice treatment is usually represented by the removal of the

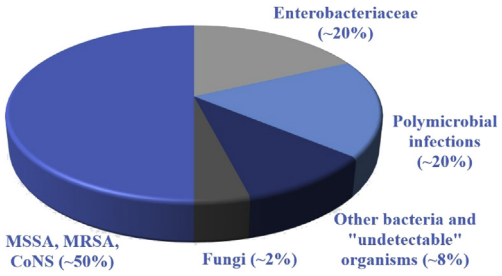


Fig. 1. Pathogens most frequently responsible for AGIs and relative percentages.

Table 1
Common risk factors for abdominal AGIs.

	Ref
Comorbidities (diabetes mellitus, chronic renal insufficiency, congenital aortic coarctation, obesity, immunocompromised state, malnutrition)	[3–6]
Prior surgery for cancer, history of malignancy or active malignancy	[3]
Prolonged preoperative hospital stay	[6]
Nasal carriage of *S. aureus*	[6]
Emergent surgery	[3,6]
Hair removal at the surgical site with a razor	[7]
Lack of appropriate antimicrobial prophylaxis	[6]
Simultaneous gastrointestinal procedures during the insertion of an aortic graft	[3]
History of multiple invasive interventions before or after graft placement	[4]
Groin incision	[3]
Surgical site infection	[1,3]
Chronic skin disorder or skin ulcers at time of surgery	[3]
Intraoperative/immediate postoperative bacterial contamination of the vascular graft	[6]
Spread of infection from a contiguous site	[1]
Bacteremia during hospitalization: the risk is highest in the first 2 months postoperative	[1,3]
Bacterial colonization of a thrombus	[6]
Erosion of the vascular graft: fistulous communication with the duodenum or colon	[6]
Transient bacteremia from a gastrointestinal, genitourinary, or dental procedure	[1]
Re-intervention	[6]
Treatment of early-stage bladder cancer with bacillus Calmette-Guérin instillation	[5]

infected device, and antibiotic therapy plays an ancillary role. Despite this, comorbidities and re-intervention in case of AGIs are associated with high mortality rate (up to 50%) and limb loss rate (up to 25%), therefore outlining a laborious clinical picture and the necessity of reassessing the role of chemical and surgical therapeutic options [10].

Management of AGIs is a challenge and no standardized practices exist: clinical trials and universally accepted clinical guidelines are lacking, as well as precise case definition and diagnostic criteria classification.

2. History of aortic devices and prosthetic materials

The aorta represents a challenging environment for life-long implantation of vascular and endovascular devices. Haemodynamics is significantly altered at the site of vascular anastomoses, where the native endothelium might be exposed to abnormal shear forces due to the physical stress of cyclical loading. This may also determine a fatigue in the structure of endovascular devices.

Despite the design of vascular and endovascular devices has evolved and improved over the past decades, failures still occur and a general loss of thickness in the explanted devices is usually reported, especially in the setting of infection [11]. Examination of explanted endografts has revealed that a layer of pseudo-intima covers the internal wall of the device, but in some areas of kinking the covering can be very thin or broken up, revealing bare stent wire and the outside textile [12]. It is reasonable to assume that these uncovered areas represent a vulnerable point for the development of graft infections.

Seventy years of experience in aortic replacement with prosthetic grafts have led to the selection of the following materials: polyester textile, polyethylene terephthalate, and expanded polytetrafluoroethylene (ePTFE). Endovascular stent-grafts, after their introduction in the early 1990s, have evolved and now differ in the combination of cover material (polyester textile or ePTFE) and stent material (Nitinol, Elgiloy, or stainless steel).

3. Clinical presentation

AGIs may differ in clinical presentation and timing of onset according to the location and the pathogen responsible for the infection.

Patients with AGIs are more frequently elderly, often with a medical history of atherosclerosis or diabetes [3]. There are no pathognomonic signs and symptoms, but fever, abdominal pain, leukocytosis, tachycardia, tachypnea, hypotension and findings of sepsis (also altered mental status) are usually present [1].

The timing of infections have been proposed to be divided in “early” graft infections (<3 months), involving virulent organisms (*S. aureus*) introduced at the time of surgery and generally producing an abrupt-onset and an increased risk of embolic complications, and “late” graft infections (>3 months), typically running a more mild, subtle, and chronic course reflecting the more indolent nature of the pathogens involved (CoNS, *Streptococcus viridans* or enterococci) [1]. When gram negative organisms are involved, it is reasonable to suspect a polymicrobial infection, sustained by *E. coli*, enterococci and anaerobic microorganisms including *Bacteroides* spp., *Fusobacteria* spp., anaerobic cocci, and occasionally *Candida* spp. In this case it is advisable to exclude the possibility of an aorto-enteric fistula (AEF), resulting from the graft erosion of the duodenum or colon (according to the location, associated with haematemesis, haematochezia or melena) [13]. AEFs are defined as an abnormal connection between the aorta and the gastrointestinal tract. The majority of AEFs are secondary to aortic interventions after the erosion of an aortic prosthetic graft and occur between the aortic graft and the duodenum, typically several years after the primary repair. The prevalence of secondary AEFs is reported at 0.5%–1% after previous aortic surgery, and occurs at equal frequency after both open and endovascular repair, carrying a worse prognosis [14].

As signs and symptoms are not pathognomonic of AGIs, it is fundamental to get the patient's history accurately, taking into consideration the awaited time for the onset of symptoms. If the aortic graft contamination happens intraoperatively or suddenly after, it is reasonable to expect the first symptoms within 1–3 months after the graft implantation, although abdominal graft infections may occur several years after surgery [1,15]. Approximately one third of patients with an AGI will present with a chronic infectious process, one third with severe acute sepsis, and one third with an AEF [16].

The possibility of septic embolic dissemination as first clinical manifestation of AGI should always be kept in mind. In case a patient with an abdominal aortic graft or endovascular stent-graft develops fever, septic emboli should be investigated. They may result more frequently in renal, splenic, colic or encephalic embolism with related symptoms and signs. In such cases the diagnosis can be made starting from symptoms that do not refer to the cardiovascular system [17]. Although rare, there is also the possibility of the embolus to become responsible for the formation of a mycotic aneurysm [18]. Possible complications of AGIs are shown in Table 2.

The differential diagnosis of AGI should consider post-implantation syndrome (PIS). PIS consists of a systemic inflammatory response that can occur in up to 30% of patients who have undergone endovascular aneurysm repair (EVAR) according to some series. PIS can resemble an AGI because it fulfills at least two of the SIRS criteria (fever and leukocytosis are usually present). The impact of PIS on the patient's outcome is still unknown and still remains a poorly understood phenomenon. Different history and time of onset, negative blood cultures and imaging investigation non consistent with AGI suggest PIS as a more likely diagnosis [19].

4. Diagnosis

Signs and symptoms consistent with infection (fever, abdominal pain, tachycardia, tachypnea, hypotension, altered mental status) in a patient who underwent an aortic graft placement should always raise suspicion for AGI. Laboratory tests in case of AGI usually reveal elevated peripheral white blood cells (WBC) count and increased inflammatory markers (e.g. erythrocyte sedimentation rate, C-reactive protein, [procalcitonin]) [1]. They are not pathognomonic, especially if the patient has multiple underlying comorbidities, but their measurement is useful to monitor the evolution of the infection after the start of medical and surgical therapy or to monitor chronic suppressive antimicrobial therapy.

Blood cultures are supportive in the diagnosis and treatment of AGIs: when positive cultures are available, antibiotic therapy should be guided by the antimicrobial susceptibility testing. However, the microorganism identified with blood cultures is not necessarily the same causing the graft infection and this requires careful clinical judgement [7,20].

Positive cultures of microorganisms from surgically explanted grafts or other intraoperative specimens (e.g. pus, tissue) are the gold standard to prove an AGI [21]. Similarly, as a percutaneous aspirate of perigraft fluid/pus using radiological guidance entails an aseptic technique that minimizes contamination, positive microbiology from such samples is highly suggestive of AGI. Sometimes the collection is unreachable with a percutaneous approach, therefore a surgical intervention may represent the only way of

Table 2
Complications of AGIs.

Sepsis/septic shock
Ischemia, often leading to amputation
Disruption of anastomotic suture line with rupture or pseudoaneurysm formation
Embolization of infected thrombi
Reinfection of vascular grafts
Aorto-enteric fistulae to duodenum or colon
Abscess
Spreading of infection to other sites

access to material for culture. It should be kept in mind that culturing of (peri) prosthetic vascular material, even if found in a frankly infected area, may not always yield positive results usually because of sensitivity issues or previous antibiotic exposure. Standard laboratory culture can be negative, therefore parallel use of highly sensitive molecular techniques should be considered in order to have significant diagnostic value.

Another diagnostic challenge is represented by “uncultivable” organisms. Percentages as high as 99% of bacteria usually do not grow in the environment of the laboratory [22]. At the present time the most well established technique is 16S rRNA gene sequencing. It is a PCR sequencing technique based on the fact that the 16S rRNA gene is made of both stable and hypervariable regions. The deep sequencing of the target gene, leading to taxonomic classification, permits in addition a real time analysis of genomic mutations [23–25].

Molecular rapid diagnostic tests (mRDTs) are used as a complement to ordinary tests to diagnose especially bloodstream infections [26]. The use of mRDTs (e.g. PNA-FISH, MALDI-TOF, FilmArray BCID system, Nanosphere, GeneXpert) correlates with earlier diagnoses and better patient outcomes when associated with antimicrobial stewardship programs [27,28].

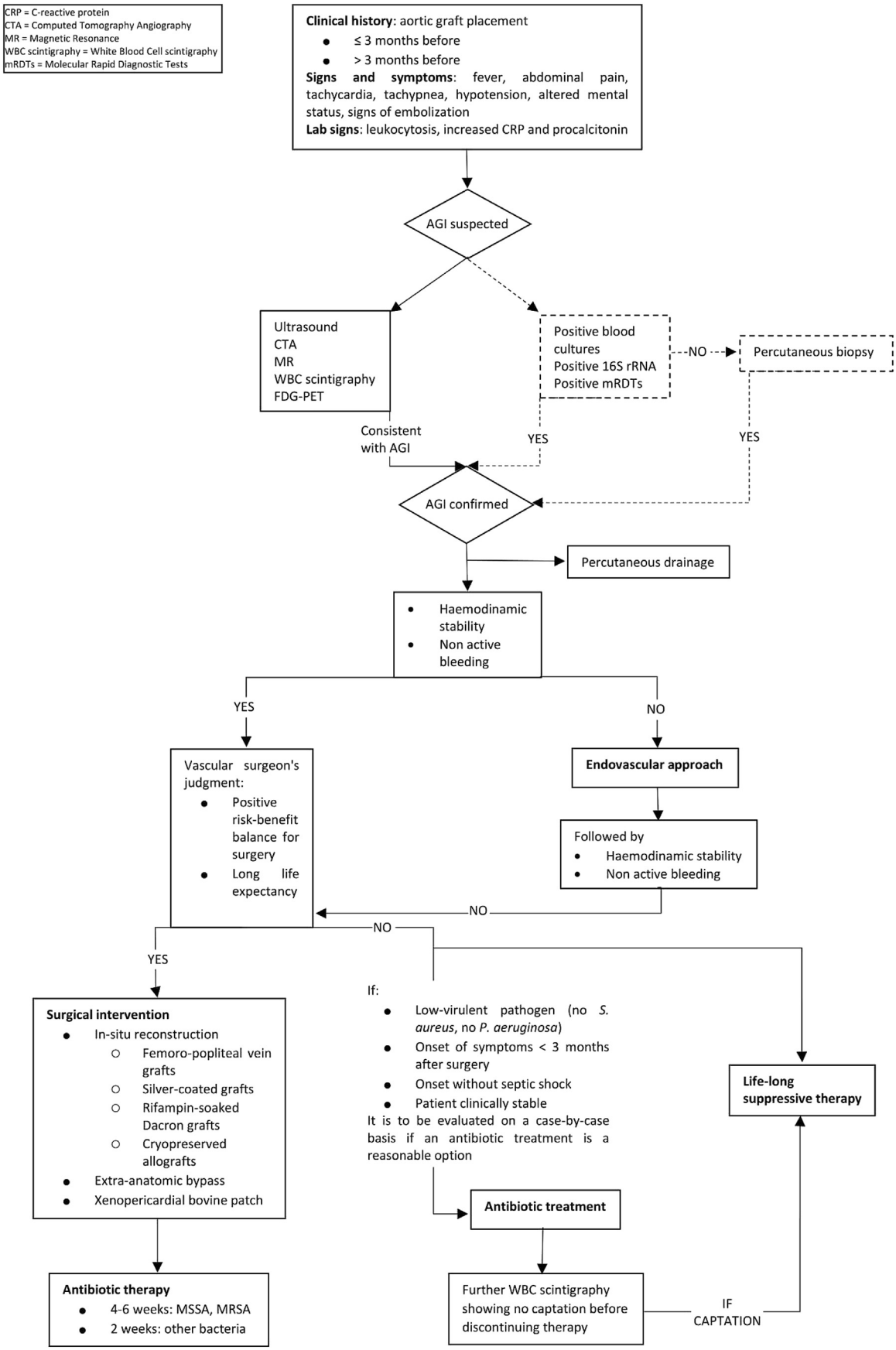
Since no pathogen is identified in a considerable percentage of cases, there are some parallels that might be extrapolated from prosthetic joint infections where multidisciplinary consensus has produced universally accepted diagnostic and management paradigms over the last decade. Standard practice in the field is to obtain at least 3, and optimally 5–6, intraoperative samples in order to estimate the possibility of contaminant organisms. In addition, sonication has been used to improve isolation of pathogens from explanted joint prosthesis by disruption of bacterial biofilm, but its benefit remains unknown for AGIs.

Imaging techniques play an even greater role. Ultrasound (US) is generally a primary imaging modality used to assess vascular diseases, thanks to its inherent advantages such as cost-effectiveness, safety profile, repeatability and availability, but it is obviously limited by overlying bowel gas and the patient's body habitus (e.g. obesity or ascites). Moreover, most surgeons would not operate only on the basis of the US appearance because a more detailed anatomic road map is essential for a correct graft bed evaluation. Ultrasound findings include anechoic fluid collection or hyperechoic areas around the graft, but diagnosis have to be confirmed with other exams. Also contrast enhanced ultrasound (CEUS), successfully tested in many vascular diseases, did not show a high diagnostic performance for the evaluation of graft infections and so it is not routinely used in this setting [29]. Computed Tomography (CT), especially computed tomography angiography (CTA), is considered the gold standard imaging modality for graft infection diagnosis. CTA shows with more accuracy than US for signs of graft infection such as peri-graft air, peri-graft fluid collection, peri-graft soft-tissue attenuation and pseudo-aneurysm formation as well as AEF findings, like focal bowel thickening and direct contrast enhancement in the bowel during arterial phase. Using these criteria CTA shows a very high sensitivity (94%) but it has lower specificity (85%) [30], since in the post-operative period the presence of fluid or air around the graft could represent normal findings difficult to differentiate from inflammatory changes [31]. As a general rule, radiological suspicion of graft infection should be considered if new CT findings appear on follow-up imaging and if peri-graft fluid persists beyond 3 months or increases over time [32]. In selected cases CT can be used to guide percutaneous aspiration of peri-graft fluid: peri-graft drainage is mandatory if conservative treatment is planned, because antimicrobial therapy has to be based properly on antibiogram results. Magnetic Resonance (MR) is a useful modality for graft infections diagnosis and, although it has not been evaluated as extensively as CTA, it probably has similar sensitivity and specificity. Thanks to its high contrast resolution MR can easily demonstrate very small peri-graft fluid collections but, similarly to CT, it is not able to distinguish normal peri-graft fluid in the early post-operative period from an infected peri-graft fluid collection; moreover MR imaging does not allow the differentiation of the signal void produced by calcifications of aortic walls from that of air [33]. In case of graft infection, MR shows eccentric fluid collection with low to medium signal intensity on T1-weighted images and high signal intensity on T2-weighted ones.

Nuclear medicine, particularly white blood cell (WBC) scan, is an important complementary test to CT in ambiguous cases such as in the early post-operative period, and may be more sensitive than CT in detection of early graft infection [34]. The co-registration of CTA with WBC scintigraphy or SPECT improves the diagnosis because the WBC study raises the suspicion for a graft infection due to abnormally radiotracer activity adjacent to the spine while CTA reveals heterogeneous soft tissue density surrounding the graft; the fusion of CTA and WBC scintigraphy matches precisely the abnormal radiotracer activity with aortic graft soft tissue stranding and thickening (Fig. 2). In recent years fluorodeoxyglucose (FDG)-PET has been successfully used to detect graft infection and, similarly to WBC scan, the combination of FDG-positron emission tomography (PET) and CT imaging is used to increase both sensitivity and specificity. It is demonstrated that if a focal intense FDG uptake and a suspected lesion on CT imaging are present, the predicted prosthetic graft infection probability is around 97% [35]. So the combination of FDG-PET results with CT data represents the current gold standard for graft infection diagnosis.

Recently, the Management of Aortic Graft Infection Collaboration (MAGIC) has proposed the first formal case definition for AGI derived by a process of multidisciplinary expert consensus [36]. Diagnostic criteria from three categories (clinical/surgical, radiology, laboratory) were classified as major or minor. It is proposed that AGI should be suspected if a single major criterion or two or more minor criteria from different categories are present. AGI should be diagnosed if there is one major plus any other criterion (major or minor) from another category (Table 3). This AGI definition offers a practical and consistent diagnostic standard, which is essential for comparing management strategies and developing evidence-based clinical guidelines.

Management of AGIs. Algorithm.



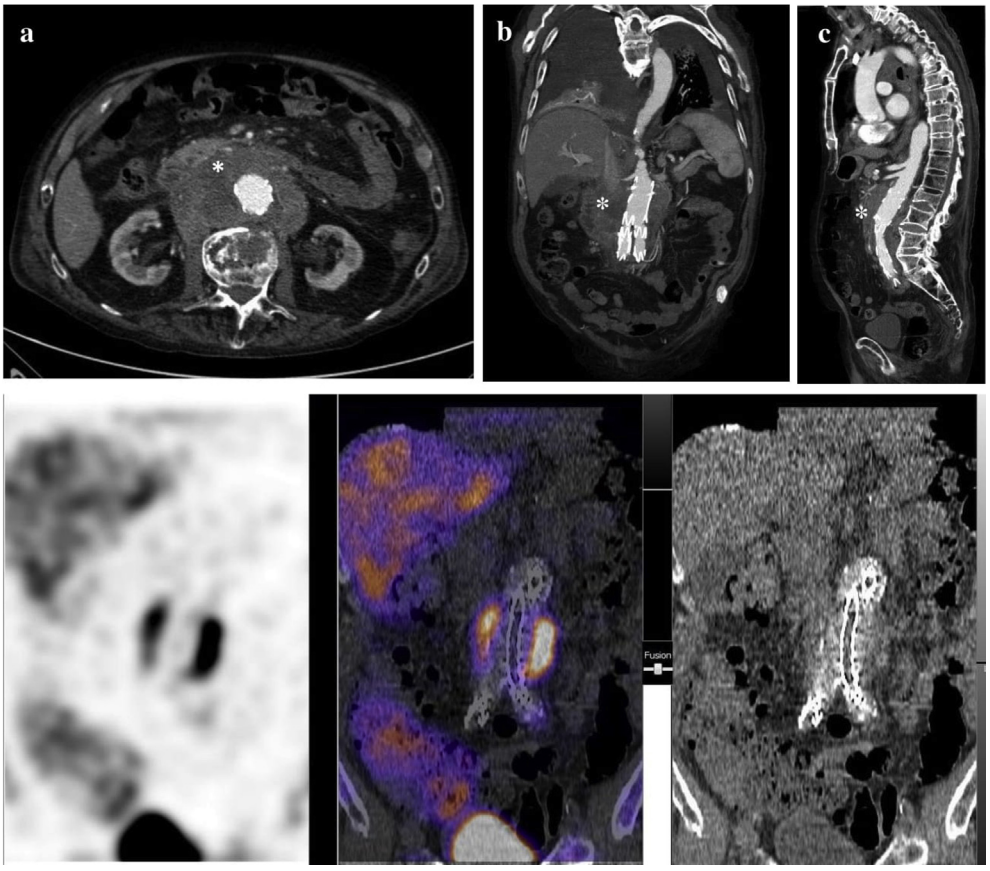


Fig. 2. Above: Graft infection in a patient with an aortoiliac graft. Axial CTA image (a) shows an area of soft tissue attenuation (asterisk) around aortic graft. Coronal (b) and sagittal (c) images show the exact cranio-caudal extention of the perigraft collection (asterisk). **Below**: Graft infection in a patient with an aortoiliac graft. SPECT taken 24 hours after administration of radiotraced WBC (left) demonstrate a focal high-level site of radiotracer activity. The exact localization is possible thanks to the co-registration of CT image (SPECT/CT middle, CT right), Confirming the diagnosis of AGI.

Table 3
Major and minor criteria according to the Management of Aortic Graft Infection Collaboration (MAGIC). Adapted from *Lyons* et al. [36].

	Clinical/Surgical	Radiology	Laboratory
Major criteria	• Pus (confirmed by microscopy) around graft or in an aneurysm sac at surgery • Open wound with exposed graft or communicating sinus • AEF • Graft insertion in an infect site (e.g. aneurysm, fistula)	• Peri-graft fluid on CT scan ≥3 months after insertion • Peri-graft gas on CT scan ≥7 weeks after insertion • Increase in peri-graft gas volume demonstrated on serial imaging	• Organisms recovered from an explanted graft • Organisms recovered from an intra-operative specimen • Organisms recovered from a percutaneous, radiologically-guided aspirate or peri-graft fluid
Minor criteria	• Localized clinical features of AGI (e.g. erythema, warmth, swelling, purulent discharge, pain) • Fever ≥38 °C with AGI as most likely cause	• Other (e.g suspicious peri-graft gas/fluid/soft tissue inflammation; aneurysm expansion; pseudo-aneurysm formation; focal bowel wall thickening; discitis/osteomyelitis; suspicious metabolic activity on FDG-PET/CT; radiolabeled leukocyte uptake)	• Blood culture(s) positive and no apparent source except AGI • Abnormally elevated inflammatory markers with AGI as most likely cause

5. Treatment

To our knowledge, no established consensus/guidelines on abdominal AGIs treatment exist. A multidisciplinary team including specialists in vascular/cardiovascular surgery, infectious diseases, vascular medicine, cardiology and imaging medicine should be ideally involved. The therapeutic strategy should balance the operative risk against the patient's life expectancy but, at the same time, the procedure more likely to achieve better results should be offered to the patient [37].

No studies have directly compared conservative treatment versus graft removal strategies, but a long-term conservative management is associated with high mortality (>75%) and a substantial risk of relapse (>50%) [38]. Therefore a non-operative management with systemic antibiotics and evacuation of infected material should be regarded as a palliative treatment and limited to patients unable or unwilling to undergo major surgery [39–41], or otherwise be used as a bridge to definitive operative management for patients with minimal graft contamination by low-grade virulent organisms [42]. There is general agreement that in patients

with a predicted short life span (<6 months), no further intervention is generally required; conversely, in patients with a predicted long life-span (>6 months), in-situ endografting should serve as a bridge to a more definitive traditional procedure [43]. When feasible, curative surgical intervention is regarded as the primary treatment modality and is essential in the presence of active bleeding, AEF, or threatening septic shock [44].

Reinfection after resection of infected abdominal aortic grafts is a life-threatening complication that portends a poor outcome with many patients requiring amputation or dying thereafter. In general, patients with AEF carry a worse prognosis if compared to those without [45]. To reduce the risk of perioperative contamination, it is suggested to postpone aortic reconstruction after the patient is hemodynamically stable, not anymore septic and with ameliorating inflammatory markers [46].

All surgical options for abdominal AGIs treatment share the same principle: to perform radical treatment by excising the infected tissues and material, and to re-establish arterial continuity. While extra-anatomic bypass (EAB) with infrarenal aortic ligation was long considered as the gold standard technique for surgical management of AGIs, contemporary clinical studies and systematic reviews have demonstrated that in-situ reconstruction (ISR) provides by far the best outcomes with better survival, better patency, and lower reinfection and amputation rates [47]. However, if there is a frank abscess with purulent and necrotic debris, EAB may be a safer initial choice, provided there is enough aortic neck for a safe suture without compromising patency of the renal arteries, therefore followed by secondary ISR according to the patient's predicted life expectancy. Currently, there are three well established options for ISR in the setting of AGIs: femoro-popliteal vein (FPV) grafts [47], silver-coated [48] or rifampin-soaked [49] Dacron grafts, and cryopreserved allografts (CPAs) [50].

Finally, the newest surgical concept for the treatment of abdominal AGIs is the use of self-made tube grafts from xenopericardial bovine patch (XBP) [51]. Advantages and disadvantages of each of these options are described in Table 4.

In addition to these techniques, a number of adjunctive measures also warrant emphasis: a thorough debridement of all infectious tissues, irrigation of the operative field using an antiseptic solution, and the placement of multiple suction drains at the end of operation, remain decisive. In addition, it should always be attempted to re-route the graft through a new tunnel or thoroughly debride the old one if a new tunnel cannot be created, and the new graft should be covered with a 360-degree viable flap (e.g. greater omentum or fascia lata) if available [74]. Finally, it is worth mentioning uretereal drainage (for safe debridement of infectious tissues) and good wound care in the groin as other important factors for a successful outcome.

Currently, the role of in-situ endovascular repair without graft excision in this setting has yet to be defined. Extension with new devices or sac drainage are useful temporizing measures but are not curative, and inevitably result in death from disease progression, usually within two years after infection. However, this technique may play an essential role to temporize or treat AGI in patients at very high physiologic risk, and in the presence of active bleeding or rupture [75]. In this clinical scenario, endografts without suprarenal fixation should be used to make future explantation technically easier. Endovascular techniques may also deserve an important role in the treatment of late graft complications, such as stenosis or dilatation, provided that no reinfection has occurred.

Aortic endograft infection is particularly high-risk due to the challenge of performing a treatment that is more complex than if the original procedure was done with an open technique and has to be carried out in patients who may be poor candidates for open surgery [75]. Endograft design also poses particular problems as none are intended to be removable and bare proximal stents may become embedded in the aortic wall, complicating the explantation procedure which requires more extensive surgical approach and more frequent supravisceral aortic clamping. Alternatively, an aortic occlusion balloon can be inflated proximally under fluoroscopic guidance and the device explanted with care taken not to break the balloon [76]. However, the same principles of complete

Table 4
Surgical options for AGIs treatment [29,52–83].

Femoro-popliteal vein (FPV)	Pros	Strongly reduces the risk of reinfections
	Cons	Need for preoperative duplex evaluation
		Longer operative time
		Deeper surgical trauma
		Possible chronic and acute venous morbidity in the donor limb
		Risk of insufficient anastomosis or relative aortic stenosis in case of diameter mismatch
Silver-coated/rifampin soaked Dacron graft	Pros	Easy to use
		Readily available for emergent procedures
		Excellent anti-staphylococcal activity of rifampin
		Silver actively inhibits bacterial colony formation on graft surfaces
	Cons	High reinfection rates, especially when used in deeply infected fields
		Rifampin is poorly effective against Gram negatives and rifampin-resistance can easily emerge
		Silver loses its antibacterial activity in few weeks
Cryopreserved allografts (CPAs)	Pros	Reduced risk of reinfection as compared with prosthetic grafts
		Shorter duration and magnitude of the intervention when harvesting deep veins
		Antimicrobial activity due to the storage in antibiotic solution
		Reduced risk of ischemic colitis and lower limb ischaemia
	Cons	Preparation of CPAs is critical and time-consuming
		Not indicated for emergent procedures and not always immediately available
		Risk of pseudo-aneurysm, rupture and thrombosis because of degeneration due to an immune response
		Need for graft-related reintervention
Xenopericardial bovine patch (XBP)	Pros	Safe and feasible
		Long duration
		Constant off-the-shelf availability
		Low risk of reinfection and reintervention
		Relatively few risks for the patient
	Cons	Given its recent introduction into clinical practice, the results must still be confirmed in long-term follow-up with larger cohorts of patients

graft explantation, thorough debridement of adjacent tissues, and anatomic vascular reconstruction still apply to infection of aortic stent-grafts [77].

When in presence of AEFs, the traditional treatment includes graft excision, bowel repair and lower extremities revascularization with long-term results remaining in favour of ISR [78]. The usefulness of extra-anatomic repair is to be evaluated but generally limited in case of large abscesses, diffuse infection, or virulent bacteria (such as P. aeruginosa or MRSA). However, the integrity of the intestinal repair is the primary determinant of outcome, rather than the type of reconstruction or conduit [79]. Indeed, current evidence suggests that multilayer closure of the duodenum with selective duodenal diversion and use of the omentum for meticulous exclusion of the duodenal repair from the vascular reconstruction are preferable to the simple closure of the fistula [80]. A new alternative to conventional open surgery has been recently

Table 5
Suggested first-choice antibiotics for AGIs treatment and life-long suppressive therapy [28,84–87,90–105].

Doses refer to normal renal function. Drugs signed with ▪ require dose adjustment according to the patient's glomerular filtration rate.
* usually after 14 days of daily therapy with other active antimicrobials.

	3-6 months or post-surgery antibiotic treatment	Life-long suppressive therapy
MSSA	Cefazolin▪ 2 g IV q8h **or** Oxacillin 2 g IV q4h + Rifampin 600 mg IV/PO q24h Dalbavancin▪ 1500 mg IV over 30 minutes once a week* + Rifampin 600 mg IV/PO q24h	Amoxicillin-clavulanate▪ 1 g PO q8h **or** Cephalexin▪ 1g PO q8h **or** Trimethoprim/Sulfamethoxazole▪ 2 tablets PO q12h **or** Clindamycin 450 mg PO q8h
MRSA	Vancomycin▪ loading dose of 25-30 mg/kg then 15-20 mg/kg IV q8-12h + Rifampin 600 mg IV/PO q24h Daptomycin▪ 6 mg/kg IV q24h + Rifampin 600 mg IV/PO q24h Dalbavancin▪ 1500 mg IV over 30 minutes once a week* + Rifampin 600 mg IV/PO q24h	Minocycline 100 mg PO q12h **or** Doxycycline 100 mg PO q12h **or** Trimethoprim/Sulfamethoxazole▪ 2 tablets PO q12h
VRE	Daptomycin▪ 8-10 mg/kg IV q24h + Ampicillin▪ 2 g IV q4h **or** Ceftaroline▪ 600 mg IV q12h	Linezolid 600 mg PO q12h [Unavoidably leading to pancytopenia. Consider surgical treatment as far as possible]
***Enterococci* penicillin-susceptible**	Penicillin G▪ 20–24 million units IV q24h continuously or in 6 divided doses **or** Ampicillin▪ 2 g IV q4h Dalbavancin▪ 1500 mg IV over 30 minutes once a week.*	Amoxicillin▪ 1 g PO q8h
P. aeruginosa	Piperacillin-Tazobactam▪ 4,5 g IV q6-8h **or** Cefepime▪ 2 g IV q8h **or** Ceftazidime▪ 2 g IV q8h **or** Ciprofloxacin▪ 400 mg IV q8-	Ciprofloxacin▪ 500-750 mg PO q12h

Table 5 (*continued*)

	12h **or** Colistin▪ loading dose 9 MU IV, then 4.5 MU IV q24h + Gentamicin▪ 5-7 mg/kg IV q24h **or** Amikacin▪ 15 mg/kg IV q24h if life-threatening infection	
CoNS	Vancomycin▪ loading dose of 25-30 mg/kg then 15-20 mg/kg IV q8-12h **or** Daptomycin▪ 6 mg/kg IV q24h **or** Oxacillin [if susceptible] 2 g IV q4h + Rifampin 600 mg IV/PO q24h Dalbavancin▪1500 mg IV over 30 minutes once a week. + Rifampin 600 mg IV/PO q24h	Flucloxacillin▪ 500 mg PO q6h if susceptible **or** Linezolid 600 mg PO q12h **or** Tedizolid 200 mg PO q24h
***Enterobacteriaceae* cephalosporins-susceptible**	Cefepime▪ 2 g IV q8h **or** Cefotaxime▪ 2 g IV q8h **or** Ceftazidime▪ 2 g IV q8h **or** Ceftriaxone 2 g IV q24h **or** Meropenem▪ 1-2 g IV q8h	Trimethoprim/Sulfamethoxazole▪ 2 tablets PO q12h
KPC-producing *K. pneumoniae*	[Therapy based on antimicrobial susceptibility] Drugs to be considered: Colistin▪ loading dose 9 MU IV, then 4.5 MU IV q12h Fosfomycin▪ 6–8 g IV q8h Ceftazidime-Avibactam▪ 2.5 g IV q8h Gentamicin▪ 5-7 mg/kg IV q24h Trimethoprim/Sulfamethoxazole▪ 20 mg/kg/day IV divided q6h Meropenem▪ 2 g IV q8h. Tigecycline 100 mg IV loading dose, then 50 mg IV q12h is not a first-choice drug for bloodstream infections but can be considered in case of antimicrobial resistance to other drugs.	[Therapy based on antimicrobial susceptibility testing]

described using an endovascular approach. If endovascular treatment is applied appropriately, early outcomes seem to be superior compared to those achieved with open surgery [81]. Endovascular stent-graft coverage of the fistula is an excellent damage control technique to treat ongoing bleeding as a bridge to open surgery in unstable patients with hemorrhagic shock [82,83] and should be followed by radical surgical treatment in feasible candidates with good life expectancy.

When performed, surgical intervention must be strengthened by antimicrobial treatment. Every effort should be made to identify the pathogen and its antibiogram, because this is crucial to determining both the choice of the antimicrobial agent and the duration of the therapy. In case MSSA or MRSA strains are involved, the estimated duration is 4–6 weeks, otherwise 2 weeks are generally sufficient to eradicate possible residual infected loci [13,84].

In patients where surgical intervention is not feasible, an attempt to treat the AGI with an antibiotic therapy can be made (3–6 months) especially in case of early infections (≤3 months after surgery), low-virulent pathogens and clinically stable patients. If these conditions are not present, life-long suppressive therapy is usually preferred. Table 5 shows first-choice antibiotics for all these scenarios according to the identified pathogen, but the final decision is to be taken according to the results of the susceptibility testing, when available. In case of AGI it is strongly suggested to consult an expert in infectious diseases and

antimicrobial therapy, to make the empirical treatment tailored for each patient on the basis of possible patient colonizations, local antimicrobial resistance patterns and recent antibiotic therapies. For 3–6 months antibiotic treatment we indicated drugs to be administered intravenously but, considering the long-term use, according to the clinical stability of the patient and the trend of inflammatory markers, a shift to oral antimicrobial agents can be evaluated after at least 2–4 weeks of parenteral therapy, especially if this results in benefits such as shorter hospitalization and improvement of the quality of life. Hydrophilic drugs should be preferred to lipophilic ones because of their better distribution in the bloodstream. Despite this, some lipophilic agents (e.g. rifampin) can be used because of their activity against biofilms [85]. We also reported dalbavancin as a therapeutic option, a novel lipoglycopeptide active against Gram-positives, which is off-label for AGIs but to be taken into consideration as it is effective against methicillin-resistant strains and its elimination half-life is of approximately 346 h, resulting in a one day a week administration [86]. When starting an empirical treatment in a patient with septic shock or in case of findings suggestive of AEF, an antifungal agent should be considered together with the antibiotic coverage, as these conditions frequently involve gut commensals including anaerobes and fungi.

The possibility of a lifelong suppressive therapy is to be individualized for each patient, but it is most commonly administered if the patient is a poor candidate for reoperation or has already undergone multiple surgical procedures for AGIs. A lifelong suppressive therapy may obviously induce antibiotic resistance, but for elderly patients with multiple comorbidities this is often the only option to extend life and the quality of remaining life. Among recently approved antimicrobial agents, Tedizolid can be an option for CoNS infection treatment, as it can be administered once a day (elimination half-life of 11 h) and is better tolerated than linezolid [87,88]. Patients assuming lifelong therapy have to be seen regularly by a specialist to evaluate if the antibiotic therapy is well tolerated and to monitor the progression of the infection [1,89].

6. Prophylaxis

Two possible prophylaxis are possible for AGIs: primary and secondary prophylaxis.

Primary prophylaxis is administered to prevent perioperative infections. The antibiotic chosen for primary prophylaxis is usually a beta-lactam (e.g cefazolin) administered 30–60 min before the procedure as in cases of clean vascular graft surgery [106]. In case the patient is allergic to beta-lactams or colonized with MRSA, vancomycin is a valid alternative.

Secondary prophylaxis, instead, is intended to prevent infection after a transient bacteremia due to an invasive procedure, such as a dental procedure [107]. The use of antibiotic therapy as secondary prophylaxis is controversial. The American Heart Association does not recommend it for prevention of vascular or endovascular graft infection in patients who undergo a dental, urologic or gastrointestinal procedure, because a clear level of evidence is lacking [108]. Otherwise, considering the hypothetical consequences of a transient bacteremia, most clinicians perform secondary prophylaxis in real life [109,110].

7. Conclusion

Abdominal AGIs are a life-threatening complication occurring after aortic graft placement whose health burden is growing due to the increasing number of vascular procedures performed each year and the presence of several potential risk factors in vascular patients. They represent a very demanding challenge both for diagnosis and treatment. Diagnosis is difficult because there are no pathognomonic signs or symptoms and the time of onset varies from few days to several months after operation. Thus, AGI should be diagnosed by a combination of clinical, radiological and laboratory findings. Treatment is demanding because of the lack of evidence-based data and guidelines. It requires a multidisciplinary approach, common sense as well as a constant updating of surgical and chemical therapeutic options in order to improve survival chances and quality of life.

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Conflicts of interest

None.

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