Management of prosthetic vascular graft infections

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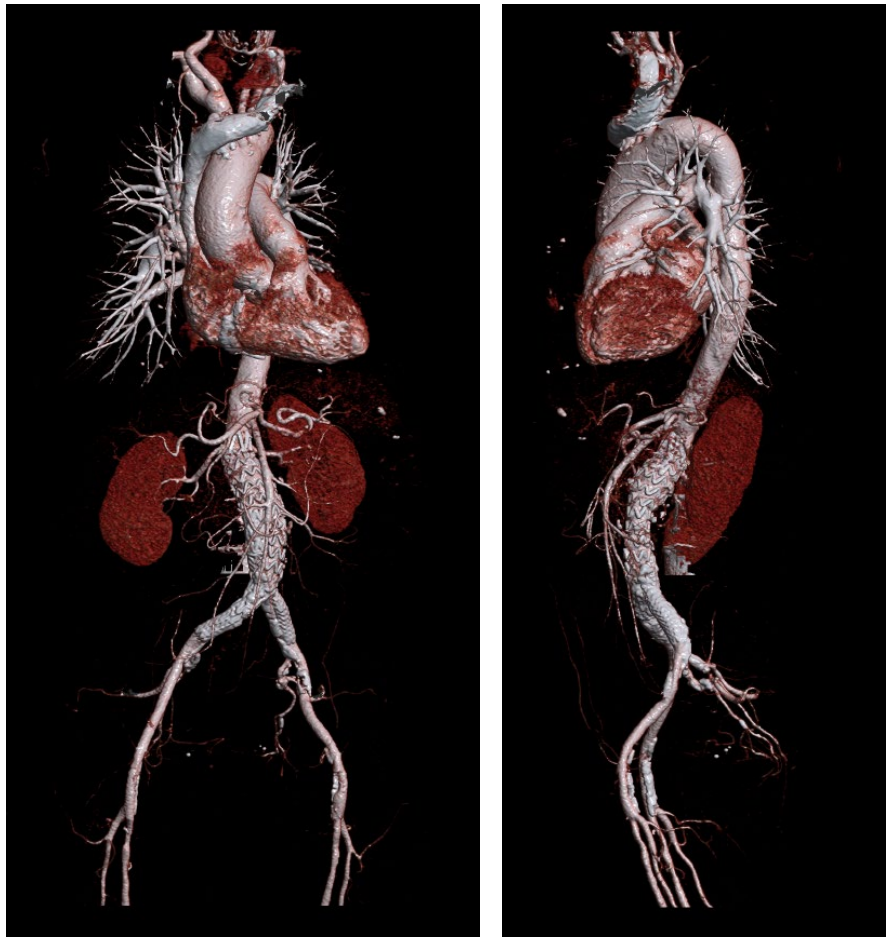
Medical history #1

70 year old lady with history of percutaneous endovascular aortic repair (EVAR) due to infrarenal aortic aneurysm



History

- Three months history of recurrent pain in the lower abdomen ascending to the epigastrium.
- Micturition/bowel movement unremarkable
- No fever/chills

Physical examination:

- Hemodynamically stable, afebrile
- Painful resistance to pressure in the lower abdomen, no let-go pain
- Gynecological examination unremarkable (former hysterectomy)

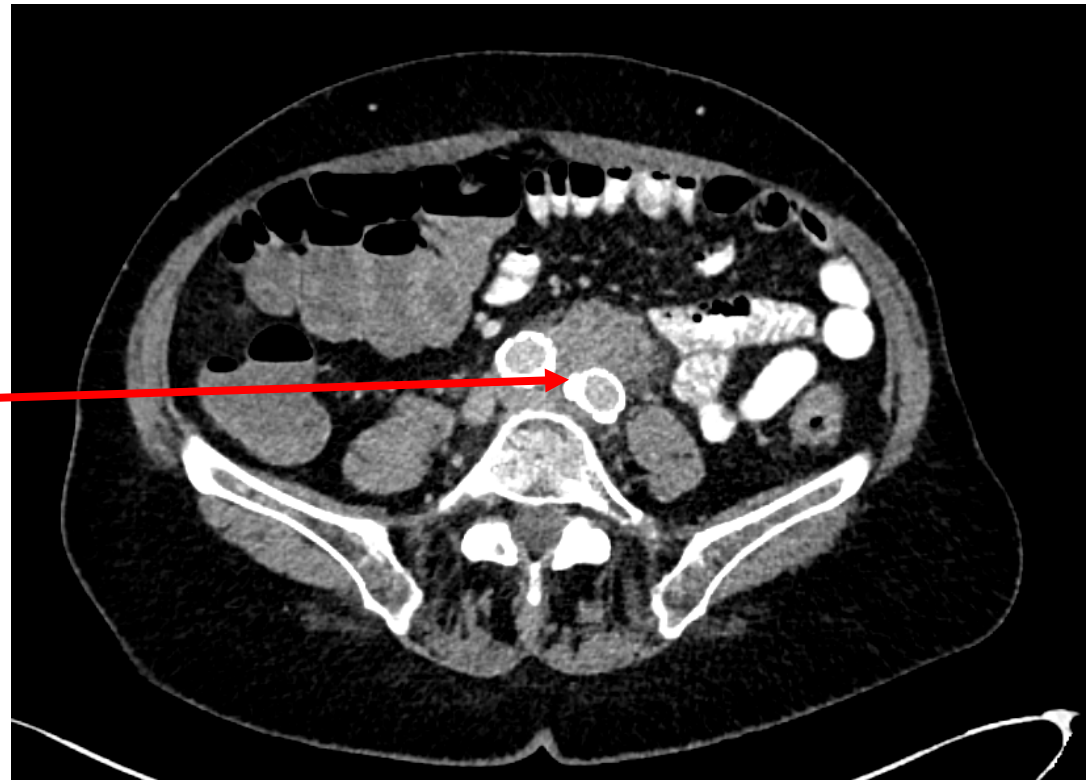
Medical history #1

Laboratory

- Leucocytes 10.4 G/L, CRP 94 mg/L

CT abdomen

- Soft tissue plus in the proximity of the aortic bifurcation
- Y-EAP with surrounding adipose tissue inhibition
- Urinary retention due to compression of the left ureter by soft tissue plus.



Question #1

You are the Infectious Diseases consultant and you suspect a vascular graft/ endograft infection (VGEI). What are your recommendations?

Test for occult blood in stool; consider endoscopy in search for aortoenteric fistula
No empirical antimicrobial therapy; CT scan sufficient for diagnosis

Perform percutaneous, radiologically guided aspirate of perigraft fluid; establish Vancomycin and Piperacillin/Tazobactam

Collection of 3 sets of blood cultures. No empirical antimicrobial therapy. Perform PET/CT

Collection of 3 sets of blood cultures; establish empirical therapy with Vancomycin and Piperacillin/Tazobactam; perform 111In or 99m Tc- white-blood-cell (WBC)-scintigraphy or MRI

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Microbiology in VGEI

Microorganism identification key issue

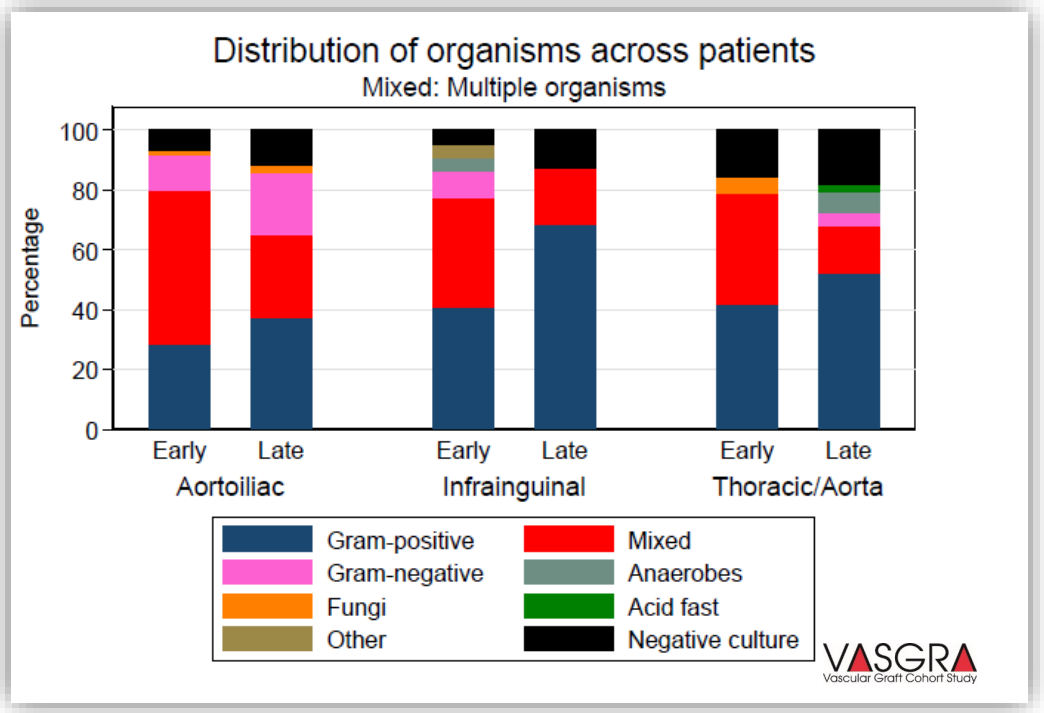
- Samples should be harvested before the start of antimicrobial therapy

Direct methods:

- **Culture specimens** obtained directly from the suspected infection site (surgically explanted prosthetic materials, intra-operatively obtained tissue and graft biopsies from the infected area, or **at least three samples** from perigraft fluid collection).
- **PCR**
- **Swabs should be avoided**.

Indirect methods

- Blood cultures (only 35% positive)
- Sonicate fluid culture, Serology



182 patients stratified by time point of infection and/or location of VGEI.

Chafke et al. European Society of Vascular Surgery (ESVS) Guidelines 2020
Kokosar et al. Infectious Diseases, 50:6, 429-435
Ajdler et al Frontiers Med 2018
Bisharat N et al. Am J Med Sci. (2012) 344:431–35.
Friedrich et al. VASGRA cohort. unpublished

Empirical therapy for abdominal VGEI

Do not treat if patient is hemodynamically stable until microbiological sampling

Gram positive Cocci:

- Coverage of Methicillin resistant bacteria (prevalence in Europe 16%)
- Bactericidal against bacteria in stationary growth phase
- Good tissue and biofilm penetration
- Good safety profile

Gram negative Bacilli

- Standardized empirical therapy difficult due to different resistance profiles

Clinical situation	First line	Second line Allergy to penicillin
Abdominal VGEI without sepsis	Piperacillin/tazobactam + Vancomycin or Daptomycin ± Gentamicin	Cefepime + Metronidazol + Vancomycin or Daptomycin ± Gentamicin
Abdominal VGEI with sepsis	Ceftazidim + Metronidazol + Vancomycin or Daptomycin ± Gentamicin	Meropenem or Imipenem + Vancomycin or Daptomycin ± Gentamicin

Barbier F et al , J Infect Dis 2010:202;:270-81
Revest et, al Int Journal of Antimicr Agents 2015
Szcot et al, J Infect 2011;62:204-11

Second imaging modality is often required to support VGEI diagnosis

Angio CT=Gold standard!

Pooled sensitivity and specificity rates 67% and 63%. In low-grade infections sensitivity descends to 55%

CTA depicts:

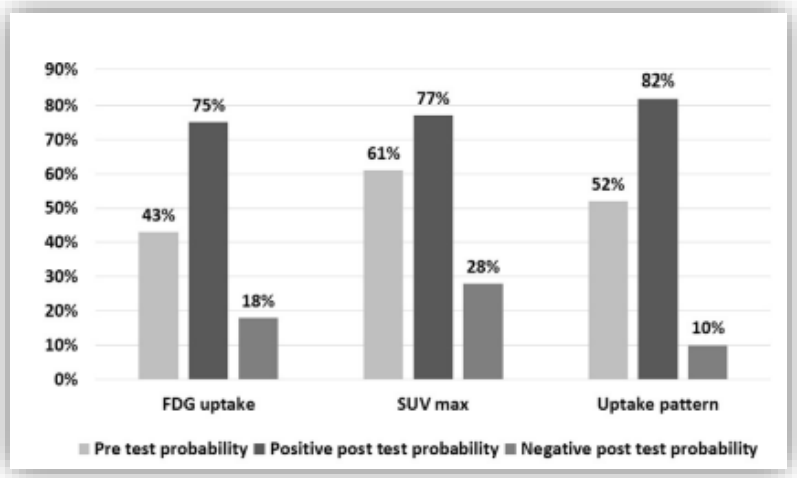
- Perigraft fluid
- Gas
- Other findings (e.g. pseudo-aneurysm, leaks at anastomotic sites

Included in the **MAGIC criteria**

PET/CT

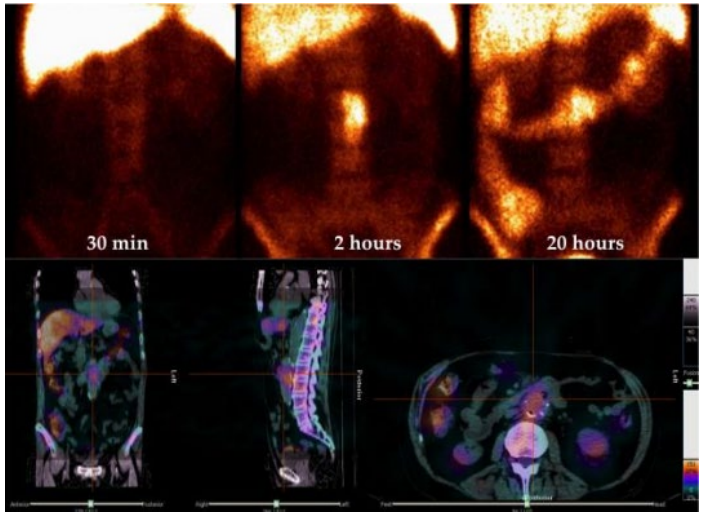
Pooled sensitivity of ≥ 90% for all evaluation methods

- Visual FDG intensity uptake
- Visual uptake pattern
- SUVmax



111In or 99m Tc- white-blood-cell (WBC)-scintigraphy

- Sensitivity and specificity rates of 90% and 88%, respectively
- Higher rates when combined with SPECT

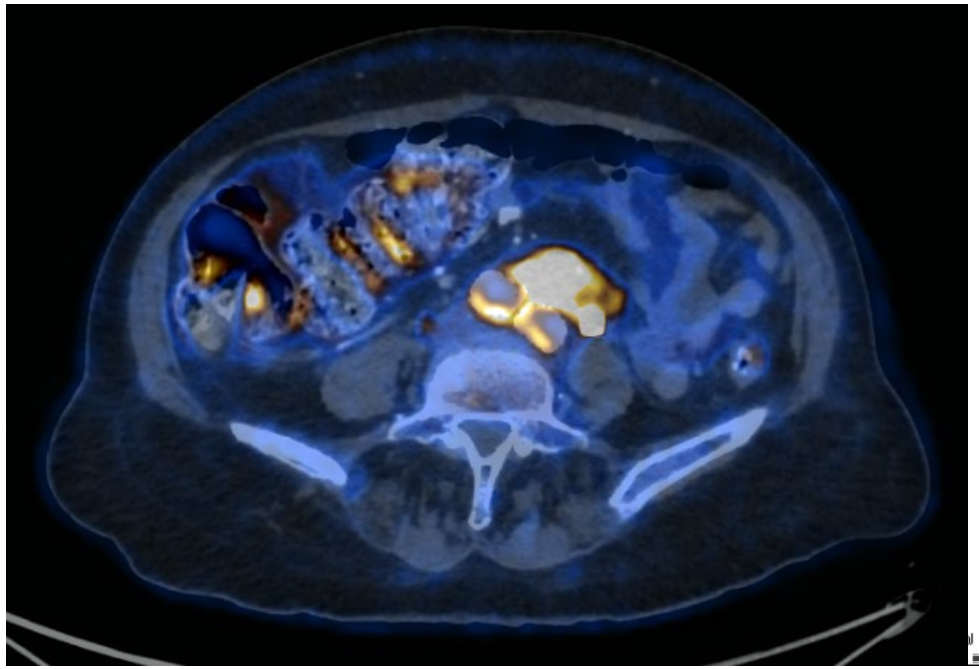


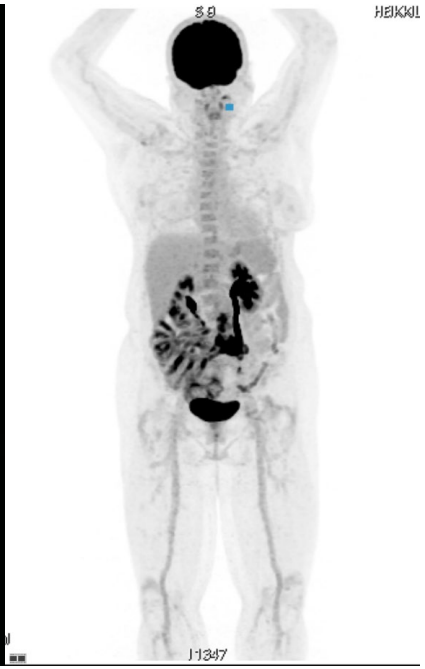
Reinders Folmer EI, et al. Eur J Vasc Endovasc Surg. 2018;56:719-729.
Jamar F, et al J Nucl Med. 2013;54:647-658
Lauri C et al. J. Clin. Med. 2020, 9, 1510

Follow up history #1: Where do we stand with the patient?

PET/CT

- Highly metabolically active pannus tissue surrounding the abdominal Y-graft (SUVmax 15.2)
- Beginning of urinary retention.
- Extensive fecal impactation





No antimicrobial treatment

Microbiology

- All blood cultures: no growth

Timely diagnosis of a VGI remains one of the main challenges

	CLINICAL / SURGICAL	RADIOLOGY	LABORATORY
MAJOR CRITERIA	• Pus (confirmed by microscopy) around graft or in aneurysm sac at surgery • Open wound with exposed graft or communicating sinus • Fistula development e.g. aorto-enteric or aorto-bronchial • Graft insertion in an infected site e.g. fistula, mycotic aneurysm or infected pseudoaneurysm	• 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 of 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; pseudoaneurysm formation; focal bowel wall thickening; discitis/ osteomyelitis; suspicious metabolic activity on FDG PET/ CT; radiolabelled leukocyte uptake ✔	• Blood culture(s) positive and no apparent source except AGI • Abnormally elevated inflammatory markers with AGI as most likely cause e.g. ESR, CRP, white cell cou ✔

VGEI diagnosis:
1 major criterion + ANY other criterion

VGEI suspected:
ONLY 1 major criterion OR >=2 minor criteria

Management of Aortic Graft Infection Collaboration

Lyons et al ESVS 2016
Chafke et al. European Society of Vascular Surgery (ESVS) Guidelines 2020

Question #2

You are the vascular surgeon. What are your considerations towards surgery?

- Removal of the endograft and in situ reconstruction with biological material
- Removal of the endograft and extraanatomical reconstruction
- Percutaneous drainage, irrigation and retention of implant
- Removal of the endograft and in situ reconstruction with crypopreserved allograft

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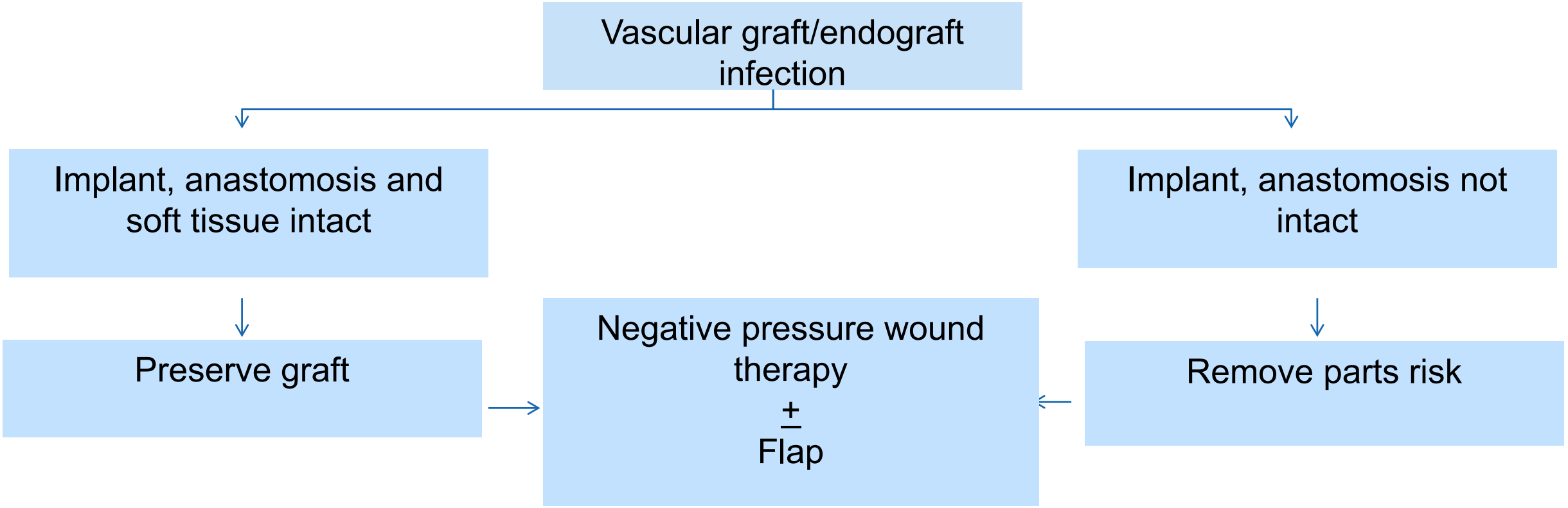
VGEI qualifying for implant preservation/conservative treatment

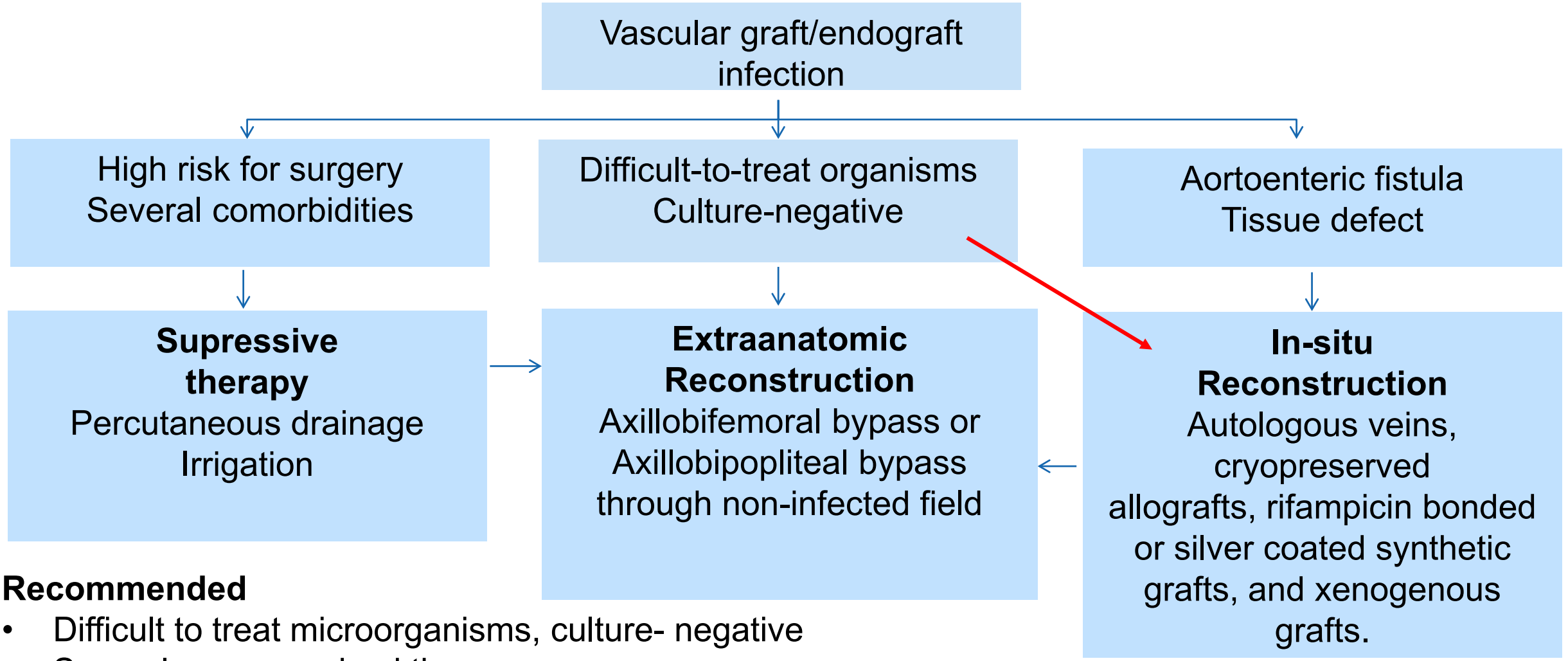


Prerequisites

- Condition of implant, anastomosis and soft tissue good
- **Perioperative culture positive**
- Susceptibility to antimicrobial agents with activity against surface-adhering microorganisms

Chafke et al. European Society of Vascular Surgery (ESVS) Guidelines 2020

VGEI not qualifying for implant preservation/conservative treatment



Recommended

- Difficult to treat microorganisms, culture- negative
- Severely compromised tissue
- Comorbidities

Chafke et al. European Society of Vascular Surgery (ESVS) Guidelines 2020

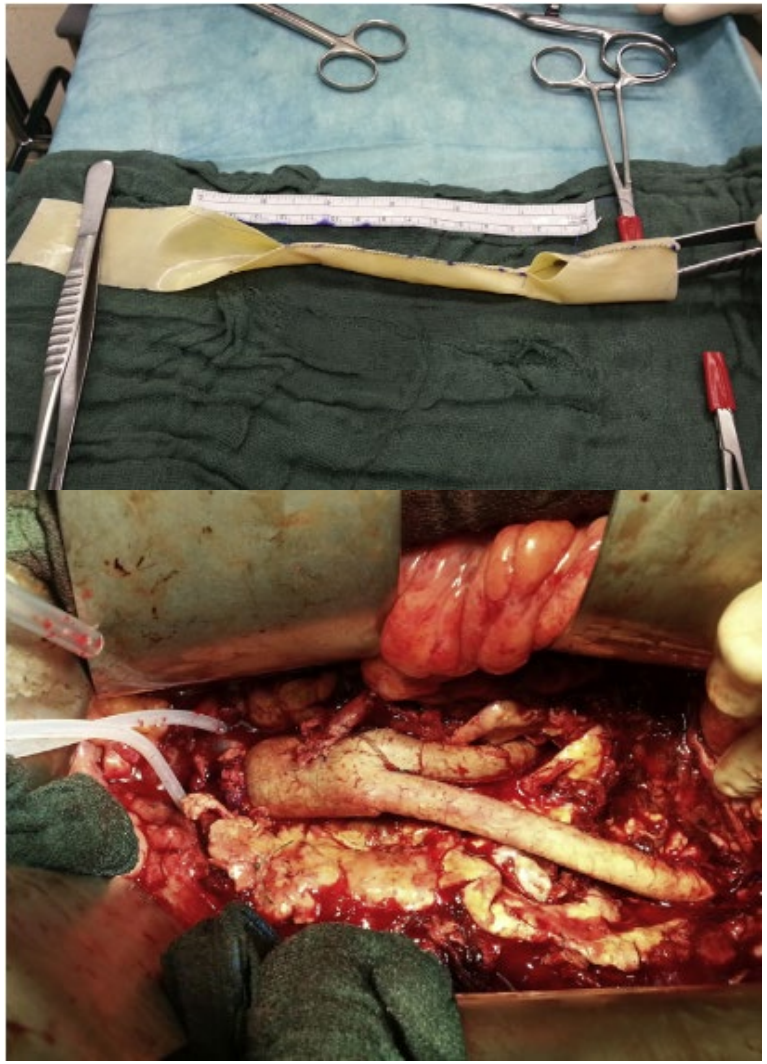
Follow up history #2

Surgery

- Explantation of the aortic endovascular stent-prosthesis
- Resection of the inflamed aortic wall
- Reconstruction of the aorta using xenogeneic, infrarenal aortobiiliac pericardial bovine prosthesis

Infectious Diseases management

- Postoperative start of piperacillin/tazobactam and vancomycin



Lutz et al. Ann Vasc Surg 2017; 41: 118–126

Chafke et al. European Society of Vascular Surgery (ESVS) Guidelines 2020

Medical history #2

PET/CT

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- Beginning of urinary retention.
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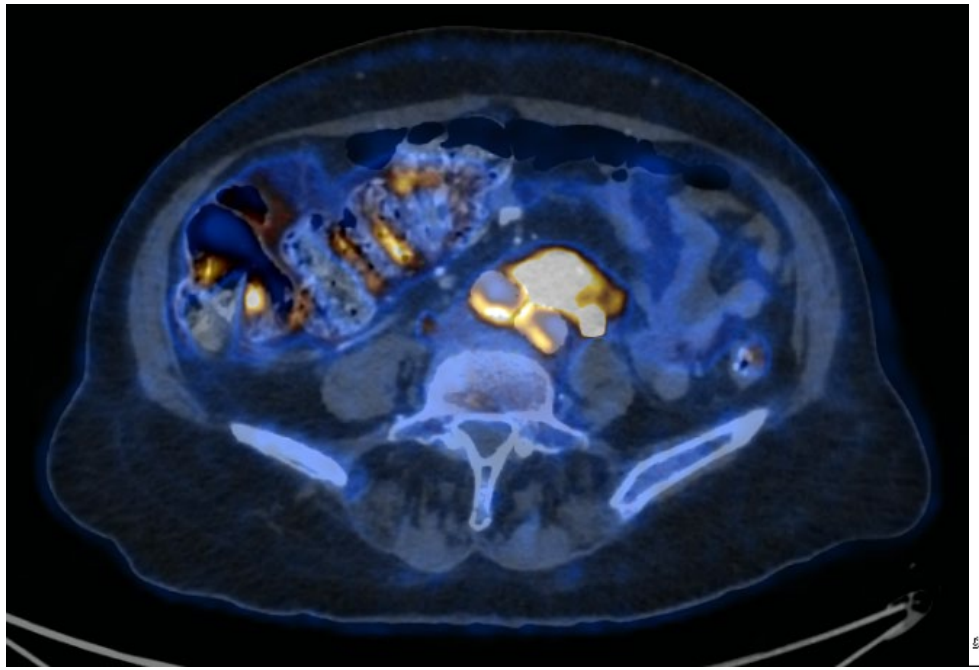
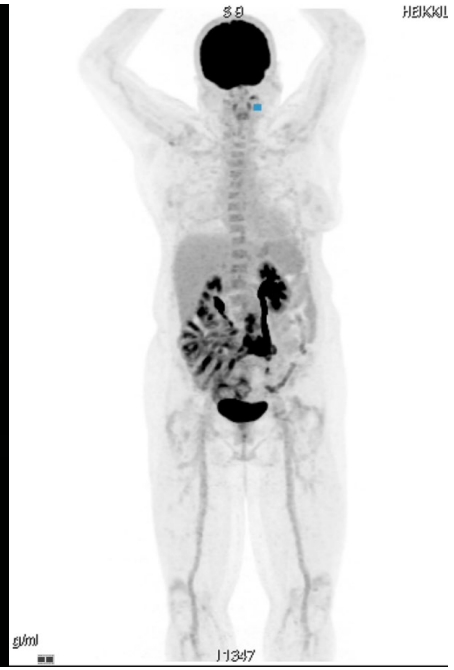
Microbiology

- All blood cultures: no growth
- Smear aortic prosthesis: no growth
- Tissue retroperitoneum: no growth
- Aortic prosthesis: no growth
- PCR negative





Question #3

You are the Infectious Diseases consultant. What are your recommendations towards antimicrobial therapy and further management?

- Continue Vancomycin and Piperacillin/Tazobactam for six weeks, followed by four weeks Ciprofloxacin and Clindamycin; no further microbiological work up needed
- Continue Vancomycin and Piperacillin/Tazobactam for six weeks; Work-up for culture-negative pathogens
- Continue Vancomycin and Piperacillin/Tazobactam for six weeks; no further microbiological work up needed
- Switch to Ceftriaxon and Doxycyclin. Work-up for culture-negative pathogens

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Targeted antimicrobial therapy for VGEI

Prerequisites

- Bactericidal against bacteria in stationary growth phase
- Good tissue and biofilm penetration
- Good safety profile

Analogy to prosthetic valve endocarditis

- Infection of endovascular material
- Production of biofilm
- Patients with multiple comorbidities, impaired renal function
- Similar pathogens (Exception: Enterobacteriacea, anaeobes, fungi, mixed infection)

Medical treatment influenced by

- Pathogen
- Surgical procedure (excision, all or part of prosthesis left in place)
- Material (prosthetic graft, biograft, cryopreserved graft)
- Anatomical site (thoracic aorta, abdominal aorta, peripheral)

Legout L et al. Clin Microbiol Infect 2012:18:352-8
Barbier F et al , J Infect Dis 2010:202;:270-81
Revest et, al Int Journal of Antimicr Agents 2015
Szcot et al, J Infect 2011;62:204-11

Duration of treatment in VGEI

AHA SCIENTIFIC STATEMENT

Vascular Graft Infections, Mycotic Aneurysms, and Endovascular Infections

A Scientific Statement From the American Heart Association

1. For patients with Samson class I or II VGI, a trial of antimicrobial therapy with or without surgical débridement for 2 or 4 weeks is reasonable *(Class IIa; Level of Evidence B)*.
2. For Samson class III or IV VGI, postoperative antimicrobial therapy for 4 to 6 weeks is reasonable *(Class IIa; Level of Evidence B)*. After the initial therapy, a course of oral antimicrobial therapy for 6 weeks to 6 months may be considered *(Class IIb; Level of Evidence B)*.
3. For Samson class V VGI, postoperative antimicrobial therapy for 4 to 6 weeks administered parenterally followed by at least 6 months of therapy administered orally may be considered *(Class IIb; Level of Evidence B)*.
4. For Samson class III, IV, or V VGI, long-term suppressive antimicrobial therapy may be considered for infection caused by MRSA, *Pseudomonas*, multidrug-resistant microorganisms, *Candida*, or other fungal species; for those patients who have undergone emergency or multiple surgeries; for patients with graft preservation or in situ reconstruction with extensive perigraft infection; or for

Eur J Vasc Endovasc Surg (2020) 59, 339–384

CLINICAL PRACTICE GUIDELINE DOCUMENT

Editor's Choice – European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines on the Management of Vascular Graft and Endograft Infections☆

4.1.2. Duration of treatment. There is no consensus on the optimal length of antimicrobial therapy for VGEI. If prosthetic material can be removed and a thorough debridement of all infected tissue can be performed, a minimum of two weeks of intravenous therapy, if possible, followed by an oral regimen for another two to four weeks is indicated. If the infected material is replaced by a new VG, four to six weeks of intensive antimicrobial therapy is usually proposed to prevent recurrent infection. Many authors favour a total treatment time of three to six months in this situation, and some even advocate one year of treatment. In those patients in whom general conditions preclude any surgery, lifelong treatment should be considered.[64,65] This can be an option in patients at higher risk of surgery, especially in low grade infections with less virulent infecting organisms, susceptible to suitable antibiotics, and without other complications. In some cases, the infection cannot be totally eradicated but kept under control by year long or even lifelong therapy.[66]

Duration of antimicrobial treatment

European Guidelines (1)	**Complete resection** 2 weeks i.v., + 2-4 weeks oral If replaced by a new vascular graft: 4-6 weeks	**Patients in poor conditions deemed unfit for surgery** Lifelong suppressive AB treatment for
American Guidelines (2)	**Intraabdominal** • 6 weeks i.v. + 3-6 months oral • If extensive perigraft infection or MRSA, Pseudomonas, multidrug resistant strain: consider lifelong suppressive	**Intrathoracic** • 4-6 weeks i.v. • Oral AB or suppressive course in selected cases and MDT discussion
Revest et al (3)	**Complete resection** • 6 weeks i.v.	**Partial removal** • MRSA, MSSA: 6 weeks + suppressive • Enterobacteriacea: 6 weeks + suppressive • Streptococci: 6 weeks • Enterococci: 6 weeks + oral extended time • Pseudomonas: MDT decision • Obligate anaerobes: suppressive oral

1 Chafke et al. European Society of Vascular Surgery (ESVS) Guidelines 2020
2 Wilson et al , AHA Statement Circulation 2016
3 Revest et al. Int J Antimicrob Agents. 2015;46:254-265.

Follow up history #3

Microbiology

- All blood cultures: no growth
- Smear aortic prosthesis: no growth
- Aortic prosthesis: no growth (including sonication)
- 3x tissue retroperitoneum: no growth
- Broad range PCR: negative
- EDTA Blood: species-specific PCR for T. whipplei, Bartonella, Brucella, Mycoplasma Legionella
- Serology for Brucella, Bartonella, Coxiella

Infectious Diseases management

- Switch to Ceftriaxone und Doxycyclin
- Switch to Doxycycline and Hydroxychloroquine

Lutz et al. Ann Vasc Surg 2017; 41: 118–126

Chafke et al. European Society of Vascular Surgery (ESVS) Guidelines 2020

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- Serology for Brucella, Bartonella **negative**

Infectious Diseases management

- Switch to Ceftriaxone und Doxycyclin
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Serology for *Coxiella burnetii* positive

	Phase 1 IgG	Phase 1 IgM	Phase 2 IgG	Phase 2 IgM
07/2019	1280	40	2560	<40

Lutz et al. Ann Vasc Surg 2017; 41: 118–126

Chafke et al. European Society of Vascular Surgery (ESVS) Guidelines 2020

Coxiella burnetii

Acute infection "query"

- Incubation period about 3 weeks
- Symptoms often mild or absent
- Self-limiting flu-like illness
- Fever, headache, myalgia, non-productive cough
- X-ray with mild, bilateral infiltrates ("viral pneumonia")
- Hepatitis: elevated transaminases
- Maculopapular exanthema (10%)

Therapy

- Acute Q fever often self-limiting (2 weeks)
- Doxycycline: reduces disease duration
- Duration of therapy: 2 weeks
- Alternatives: macrolides, quinolones

Chronic infection

1-5% of patients, subacute manifestation

Classic "culture-negative" endocarditis

- Especially with previously damaged heart valves
- Vegetation typically very small

Vascular infections

- Graft infections
- Mycotic aneurysms

Bone infection

- Osteomyelitis, PJI

Therapy

- Doxycycline and Hydroxychloroquine
- Alternative: doxycycline and quinolone
- Duration of therapy: 18 months (native valves), 24 months (artificial valves, graft infection)
- Possibly surgery (graft infection poor prognosis without surgery)

Parker et al., Lancet, 2006
Eldin et al., Clin Microbiol Rev, 2017
Million et al., Lancet, 2010

Follow up history #4

Supplementary medical history:

- Comes from Finland
- Lives in the city of Zurich for years
- No animal contact/farm
- Occasionally eats raw milk cheese from France

Good recovery from surgery, well being

After 2 years of therapy, a 4-fold titer reduction was achieved Therapy stop →

Follow –up serology for *Coxiella burnetii*

	Phase 1 IgG	Phase 1 IgM	Phase 2 IgG	Phase 2 IgM
07/2019	1280	40	2560	<40
11/2019	2560	<40	5120	<40
02/2020	2560	<40	10’240	<40
08/2020	1280	<40	10’240	<40
11/2020	1280	<40	2560	<40
05/2021	1280	<40	2560	<40
08/2021	320	<40	2560	<40
12/2021	**640**	**<40**	**2560**	**<40**

Lutz et al. Ann Vasc Surg 2017; 41: 118–126

Chafke et al. European Society of Vascular Surgery (ESVS) Guidelines 2020

Prognostic value of serological Coxiella burnetii titers for outcome and treatment questionable

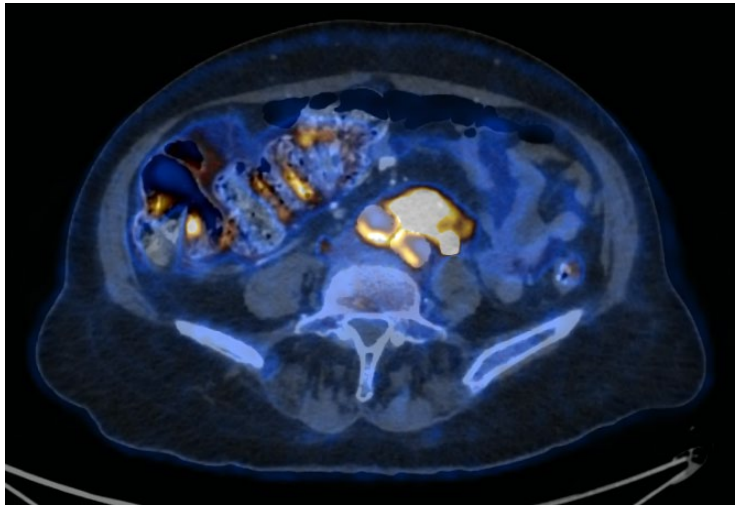
Retrospective cohort analysis from the Netherlands

- 337 patients with proven/probable Q fever
- Phase IgG ≥1024 + focus/risk factor
- 264 patients treated for at least 1 year
- 95% with doxycycline and hydroxychloroquine
- 99 patients (37.5%) with 4-fold decline in phase 1 IgG at 1 year
- Clinical endpoints
  - Q fever-associated complications in 190/337 (56%)
  - Mortality in 71/337 (21%) patients

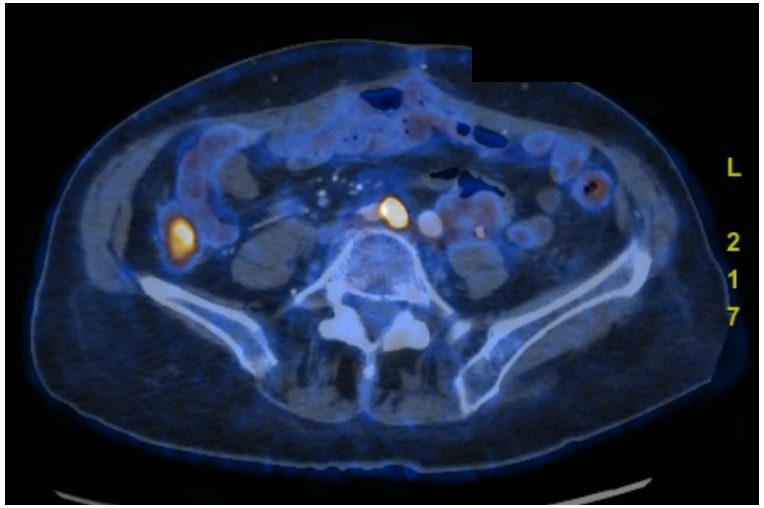
> No association with phase 1 IgG
-> Association with PCR serum positivity

Buijs et al. Clinical Microbiology and Infection 27 (2021) 1273-1278

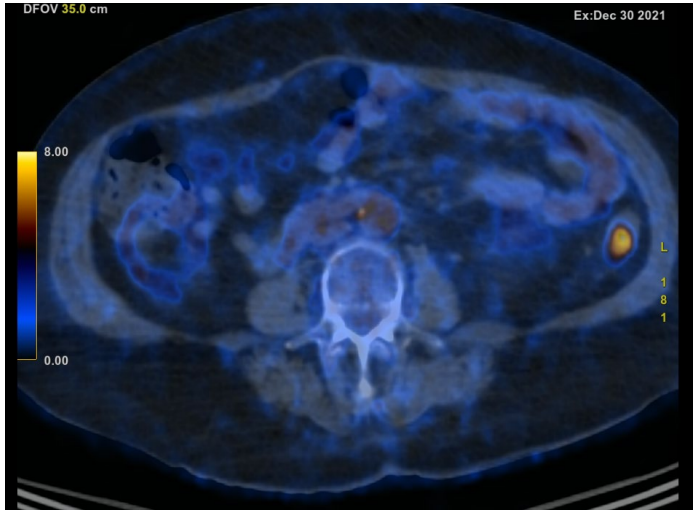
Follow up PET/CT



07/2019

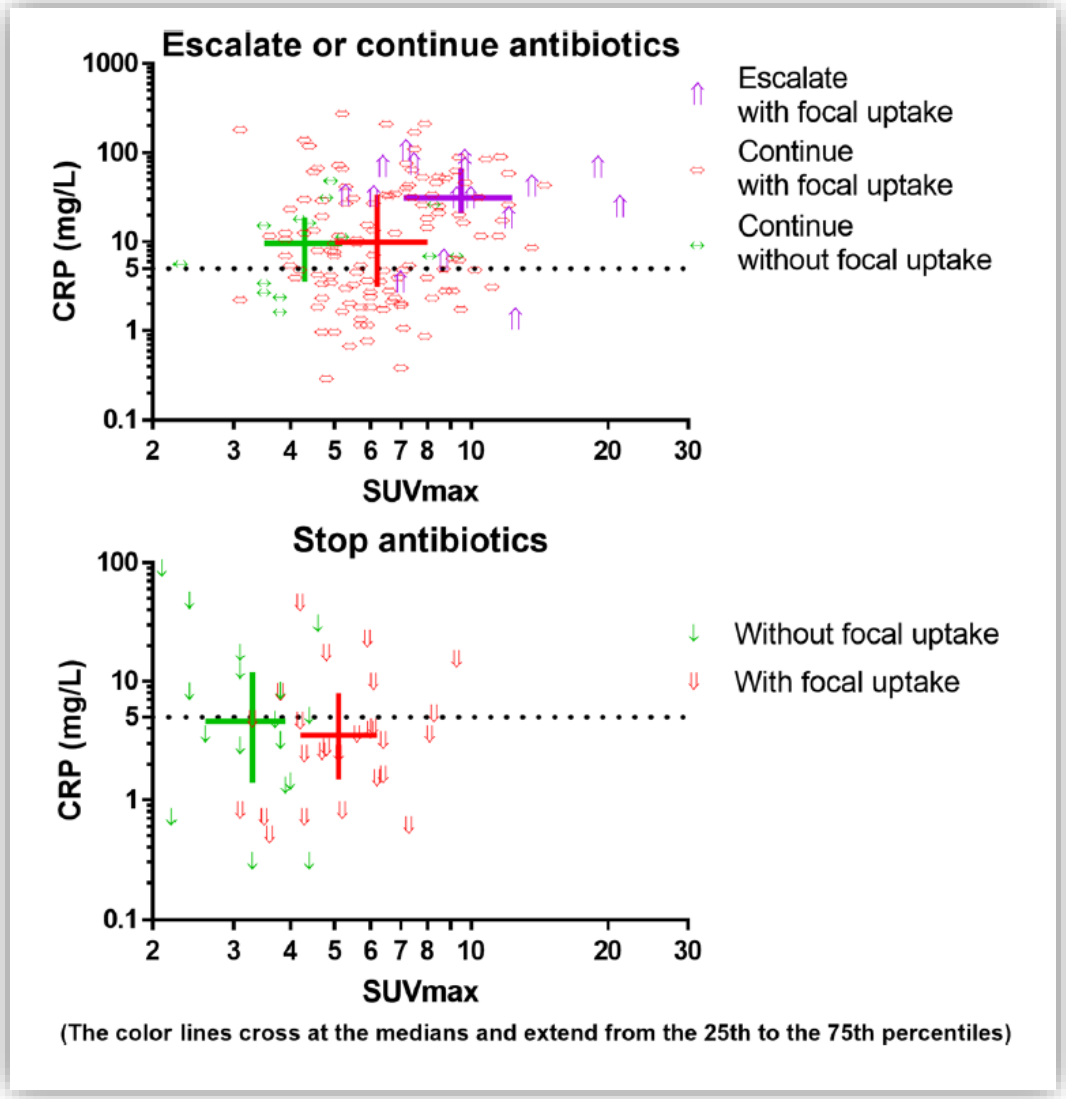


10/2019



12/2021

The role of PET/CT in therapy control in aortic graft infections



Consequences on antimicrobial therapy in relation to C-reactive protein, SUVmax, and focal signs

- In 12.5% PET/CTs treatment was escalated with normal CRP.
- Treatment was continued in 35.7% despite normal CRP and
- Treatment was stopped although 36.4% of CRP values were still
- abnormal.

- **Continue antimicrobial therapy in case of imaging non-response or imaging partial response if elevated inflammatory markers and/or clinical signs of infections are still present.**
- **In case of complete response in follow-up PET/CT scans, absence of clinical signs of VGEI and normal inflammatory markers treatment can be stopped.**

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VASGRA Vascular Graft Cohort Study

Husmann L et al. European Journal of Nuclear Medicine and Molecular Imaging 2018; https://doi.org/10.1007/s00259-018-4069-1

Take home messages

Use **MAGIC criteria** for diagnosis considering clincal factors, imaging and laboratory paramters

Antimicrobial treatment should be given after microbiological sampling - given a hemodynamically stable patient.

Treat according to pathogen, location of VGEI and depending on the surgical strategy.

Surgical strategy should be discussed in a multidisciplinary group

C. burnetii is rare culture-negative reason for VGEI. Treat for two years and use PET/CT and blood-PCR and/or serology for follow up control.

Thank you

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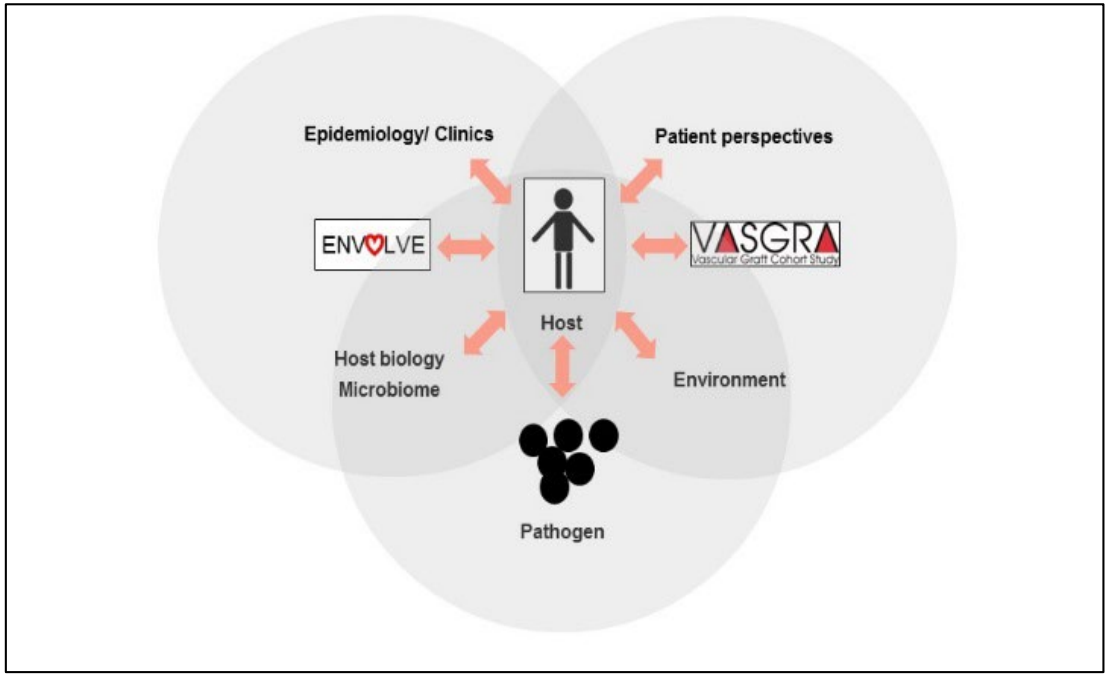

Clinical research priority program UZH
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FNSNF

VASGRA Vascular Graft Cohort Study