Algorithme diagnostique des infections de prothèse vasculaire

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JAC

Diagnosis and treatment of prosthetic aortic graft infections: confusion and inconsistency in the absence of evidence or consensus

S. F. FitzGerald[1]*, C. Kelly[2] and H. Humphreys[1]

- No standardized diagnostic strategy
- Variable according to centre
- Based on:
  - Clinical assessment: variable (early- / late-onset infections)
  - Imaging: CT is the imaging modality of choice
  - Microbiological investigations
- A provisonal set of diagnostic criteria could be formulated

Diagnosis of Aortic Graft Infection: A Case Definition by the Management of Aortic Graft Infection Collaboration (MAGIC) - *Lyons OTA et al, Eur J Vasc Endovasc Surg 2016*

	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 ≥ 1 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 count

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AGI is suspected in the presence of:

- any isolated **major** criterion,
- or **minor** criteria **from two of the three** categories: clinical/surgical, radiological, or laboratory.

AGI is diagnosed in the presence of a **single major criterion, plus any other criterion** (major or minor) from another category.

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Clinical/surgical criteria

Minor criteria

- Clinical manifestations are often non-specific
- Variable with time elapsed since graft implantation
- ➢ **Local clinical features of AGI** may represent postoperative wound inflammation or superficial soft tissue infection
- Lack of specificity of systemic inflammatory response syndrome
- ➢ **Fever ≥38°C without other focus of infection**

Clinical/surgical criteria

Major criteria

- Presence of pus (confirmed by microscopy) around the graft
- direct communication between a non-sterile site and the vascular prosthesis itself
- exposed grafts in deep open wounds
- endovascular stent-graft into an already infected field

Laboratory criteria

Major criteria

Positive microbiology obtained from:

- surgically explanted grafts or other intraoperative specimens
- percutaneous aspirate of perigraft fluid/pus using radiological guidance

[Where standard laboratory culture is negative, highly sensitive molecular techniques ("broad range" PCR) were considered to have significant diagnostic value]

Minor criteria

- Positive blood cultures
- Elevated inflammatory markers
- with vascular graft infection as most likely cause

Imaging: computed tomography (CT)

- First-line imaging modality
- Discrimination between post-operative remodelling and infection is challenging

Major criteria

- 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

Imaging: computed tomography (CT)

Minor criteria

- perigraft soft tissue abnormalities
- secondary involvement by contiguous spread of infection involving adjacent structures
- pseudoaneurysms

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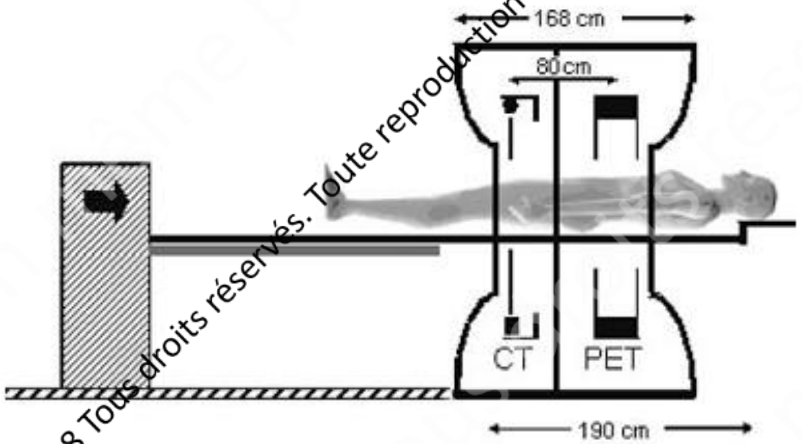
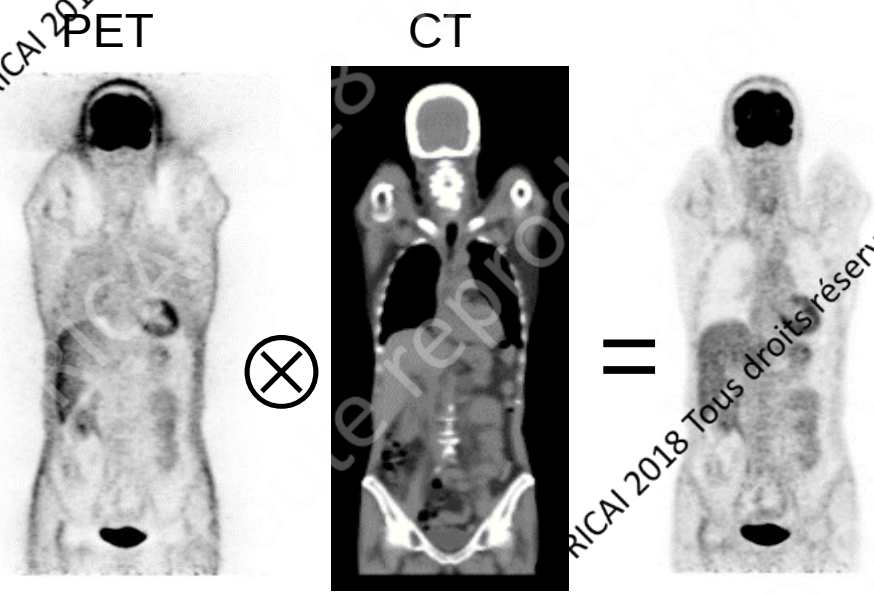
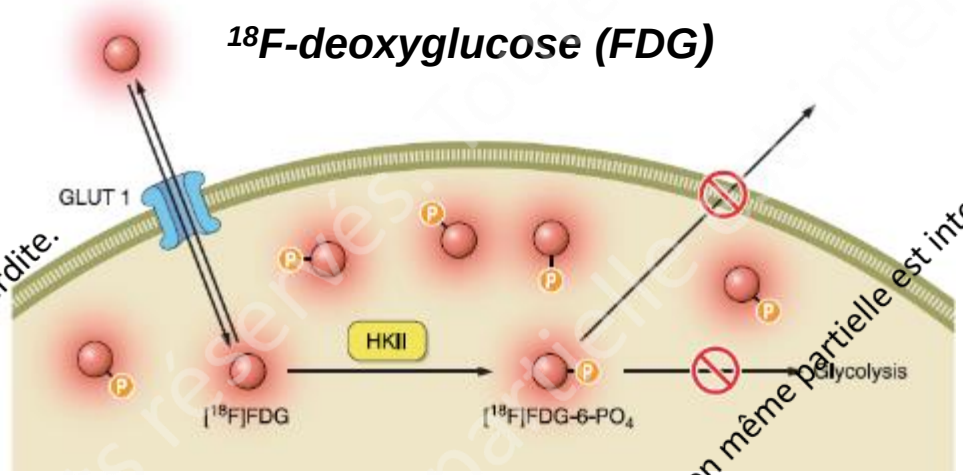
FDG PET/CT: technical aspects

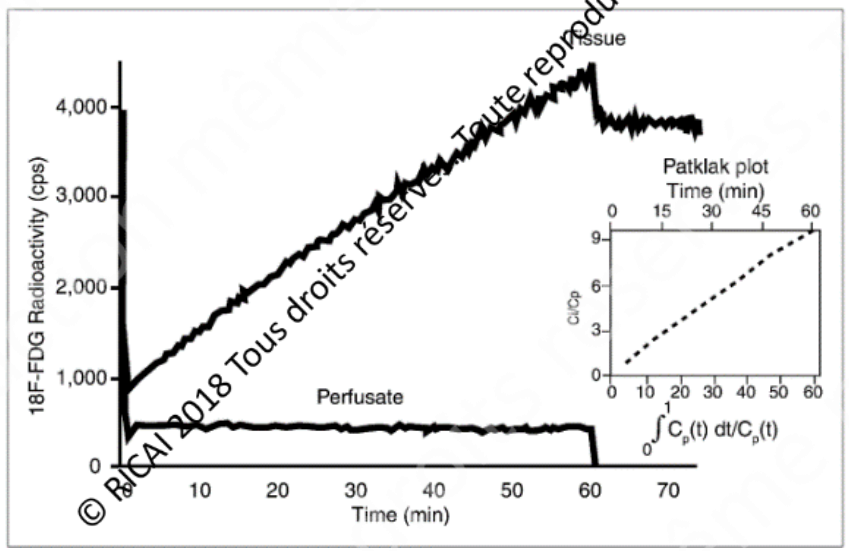
1. **High sensitivity / Whole body**
2. **Absolute quantification**





^{18}F-deoxyglucose (FDG)





Nguyen et al., Am J Physiol 1990

FDG PET/CT

Diagnostic value of FDG PET/CT

Mutiple small sample studies

TABLE 1: Summary of literature data regarding the use of ^{18}F-FDG PET imaging requested in suspected vascular graft infection.

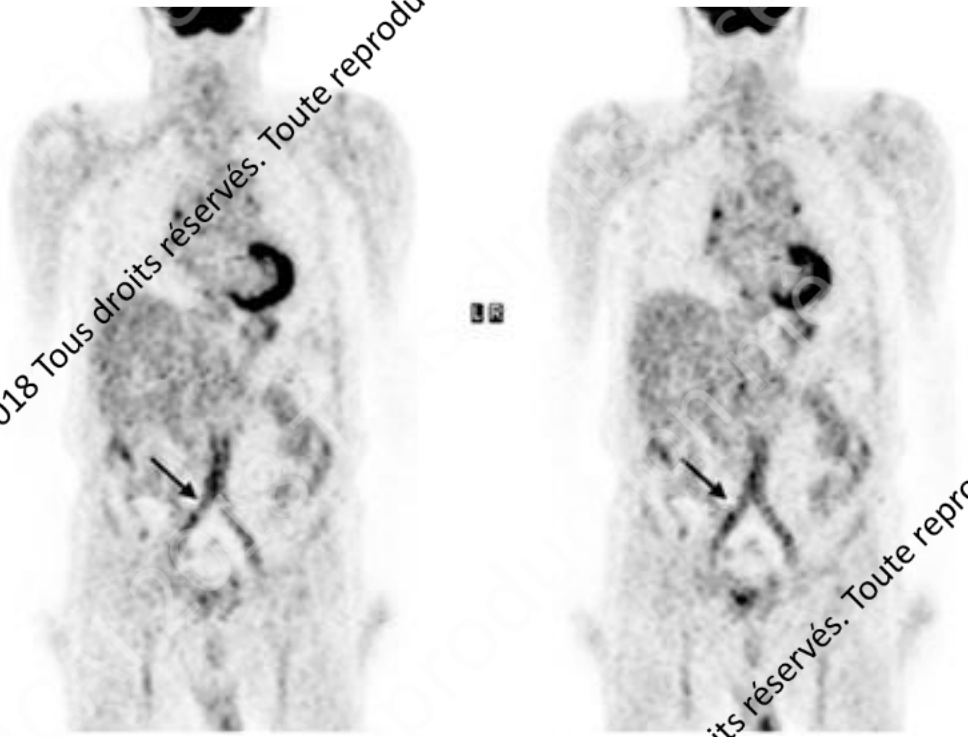
Study	Year	Study Design	Number of patient's	Imaging modality	Interpretation criteria	TP[1]	TN[2]	FP[3]	FN[4]	Sens* %	Spec* %
Fukuchi et al. [10]	2005	prospective	33	PET	Semiquantitative[a]	10	14	8	1	91	64
Keidar et al. [13]	2007	prospective	39	PET/CT	Visual	14	22	2	1	93	91
Lauwers et al. [14]	2008	case series	4	PET	Visual	3	0	1	0	—	—
Spacek et al. [15]	2009	prospective	76	PET/CT	Semiquantitative[b]	54	31	10	1	78.2	92.7
Bruggink et al. [16]	2010	retrospective	25	PET and PET/CT	Semiquantitative[c]	15	10	0	0	93[†]	70[†]
Tokuda et al. [17]	2013	retrospective	9	PET/CT	Semiquantitative[d]	4	5	0	0	—	—

- Good sensitivity, variable specificity

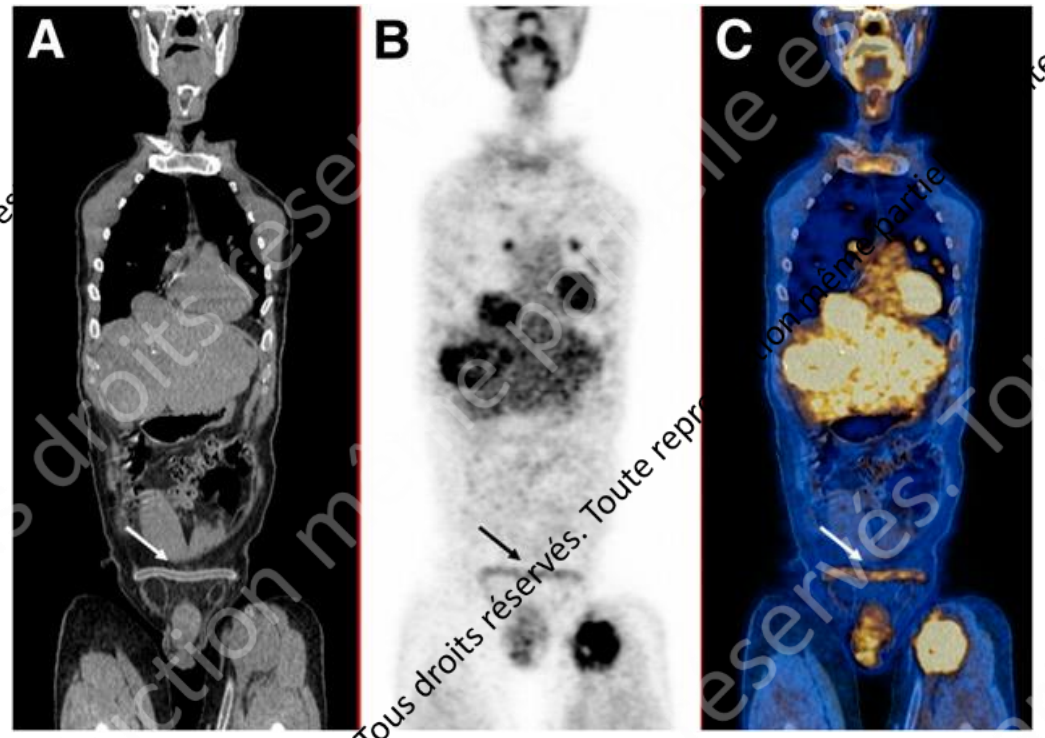
Saleem BR et al, Biomed Res Int 2014

FDG Uptake in Noninfected Prosthetic Vascular Grafts

Incidence, Patterns, and Changes over Time



16 years after implant of aorto-bifemoral Dacron graft



3 years after insertion of femoro-femoral Gore-Tex graft

Keidar Z et al, J Nucl Med 2014

FDG Uptake in Noninfected Prosthetic Vascular Grafts

Incidence, Patterns, and Changes over Time

^{18}F-FDG Uptake Patterns and SUVmean Measurements in 107 Vascular Grafts

Graft type	Dacron	Gore-Tex	Native vein grafts
No. of grafts	67	33	7
Homogeneous uptake pattern	36	28	3
Inhomogeneous uptake pattern	29	2	0
No ^{18}F-FDG uptake	2	3	4
Focal uptake pattern	0	0	0
Average SUV-G*	2.35	1.09	1.07
Average SUV-G/SUV-M†	1.72	0.91	0.75

Keidar Z et al, J Nucl Med 2014

FDG Uptake in Noninfected Prosthetic Vascular Grafts

Heterogeneous uptake related to adhesives (bioglue) for PVG placement

Open replacement of the ascending aorta and aortic arch, with bioglue, and endoprosthesis in the descending aorta.

3D PET images and volume rendering fusion images clearly demonstrated intense uptake in the site where adhesives were deposited, indicating that the uptake was due to inflammatory changes

Bowles H et al, J Nucl Cardiol 2018

Diagnostic value of FDG PET/CT in PVGs infection

Differential FDG-PET Uptake Patterns in Uninfected and Infected PVGs

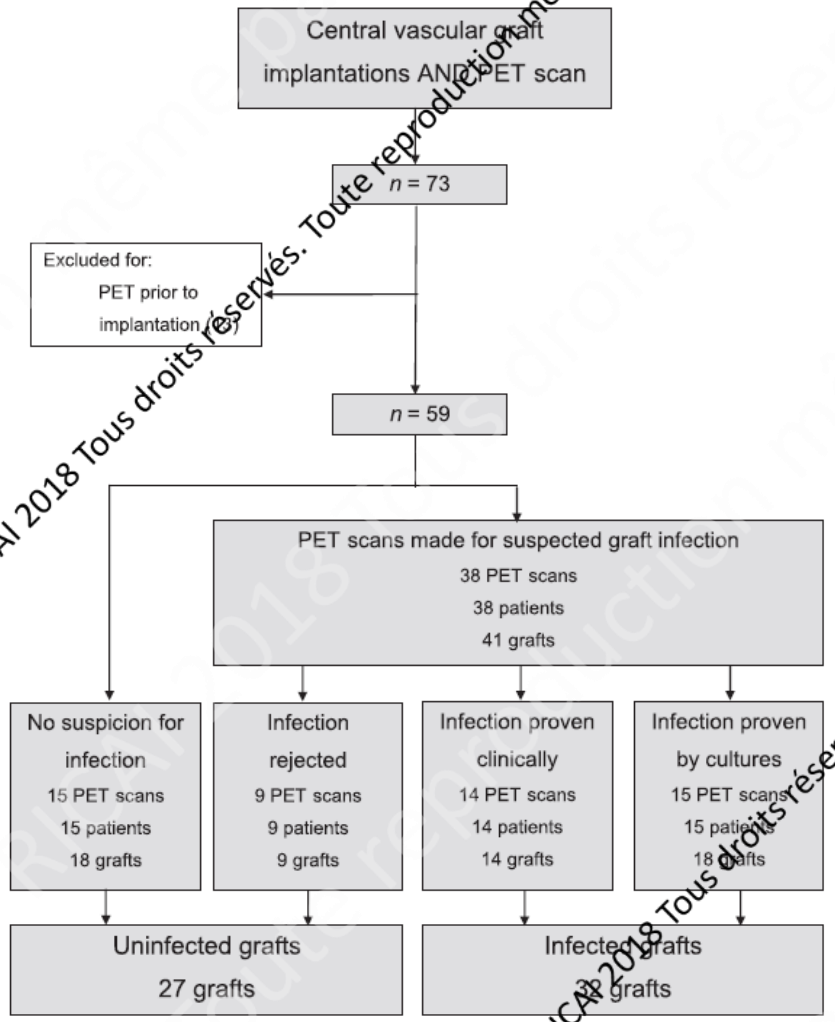


Figure 1. Data collection.

Table 3. CT findings and correlation with PET studies.

	Uninfected grafts	Infected grafts	Negative PET result	Positive PET result
Peri-graft air	0	7	0	7
No peri-graft air	4	15	7	12
Peri-graft fluid	0	11	0	11
No peri-graft fluid	3	12	7	8
>20 HU peri-graft soft tissue	3	19	7	15
<20 HU peri-graft soft tissue	1	3	1	3

HU = Hounsfield units.

Berger P et al, Eur J Vasc Endovasc Surg 2015

Diagnostic value of FDG PET/CT in PVGs infection

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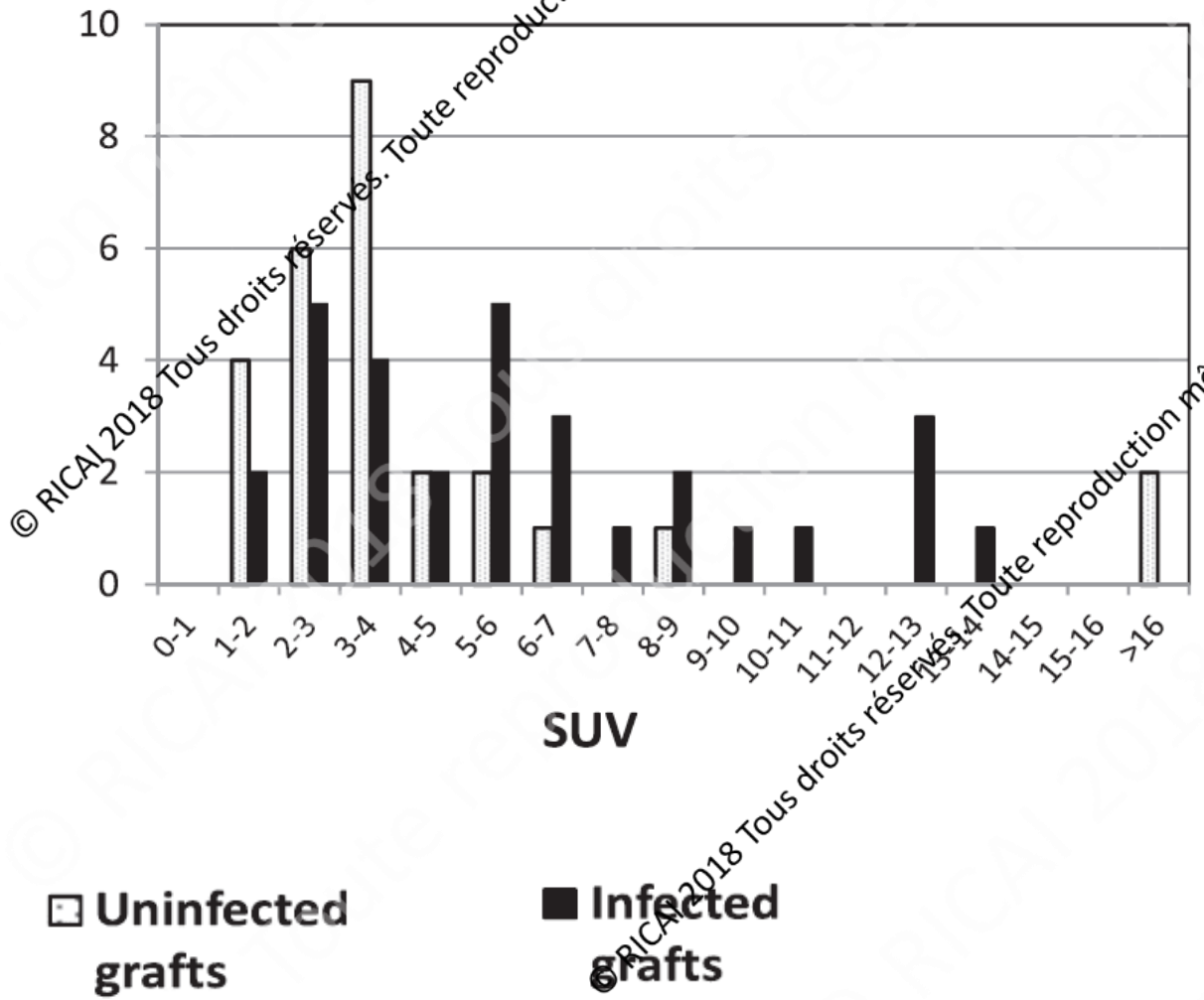
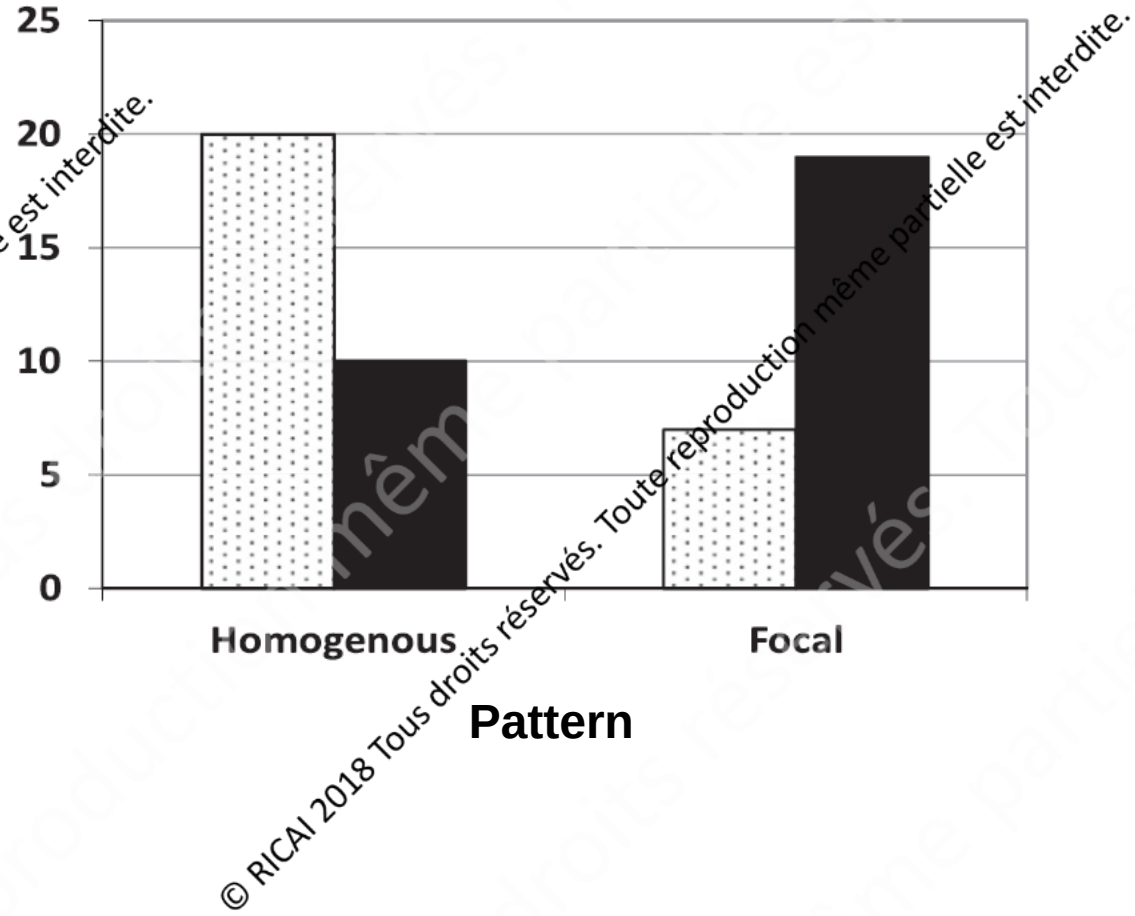


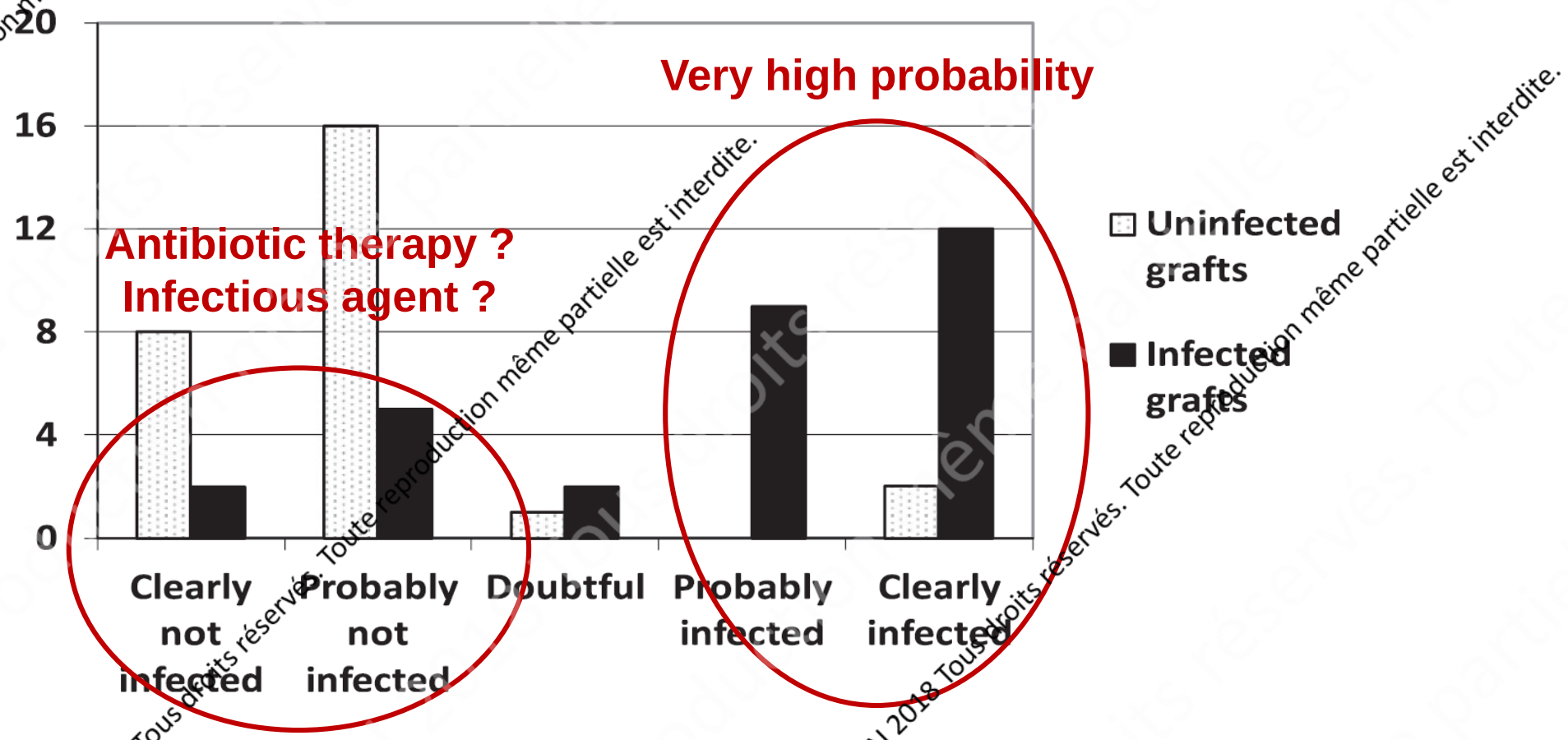


Berger P et al, Eur J Vasc Endovasc Surg 2015

Diagnostic value of FDG PET/CT in PVGs infection

Differential FDG-PET Uptake Patterns in Uninfected and Infected PVGs

Final conclusion of the PET/CT scan



- **FDG uptake patterns in uninfected PVGs overlap with those of infected PVGs**

Berger P et al, Eur J Vasc Endovasc Surg 2015

Diagnostic value of FDG PET/CT

	FDG PET		FDG PET/CT	
	Sensitivity	Specificity	Sensitivity	Specificity
Graded uptake	0.89 (0.73 - 0.96)	0.61 (0.48 - 0.74)	0.97 (0.77 - 0.99)	0.62 (0.31 - 0.86)
Focal uptake	0.93 (0.83 - 0.97)	0.78 (0.53 - 0.92)	0.97 (0.89 - 0.99)	0.89 (0.70 - 0.96)
SUVmax	0.98 (0.42 - 0.99)	0.80 (0.70 - 0.88)	0.99 (0.95 - 0.99)	0.78 (0.68 - 0.86)
TBR	0.57 (0.39 - 0.73)	0.76 (0.64 - 0.85)		
DTP	1.00 (0.48 - 1.00)	0.88 (0.68 - 0.97)		

SUVmax: maximum standardised uptake value; **TBR:** target to background ratio; **DTP:** dual time point

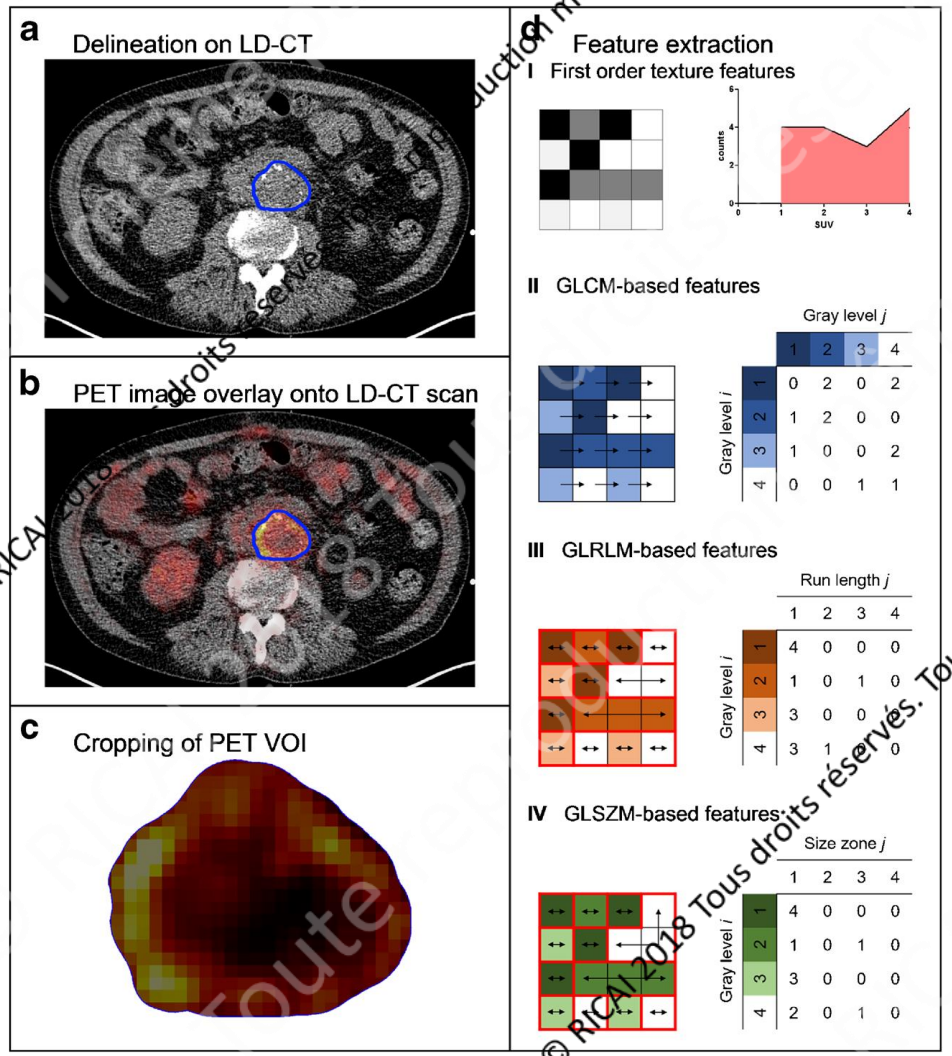
Graded uptake

1 Absent: 18F-FDG uptake similar to background uptake
2 Low: comparable to muscle and fat
3 Moderate: clearly visible and higher than inactive muscle and fat
4 Strong: but distinctly less than physiological urine bladder activity
5 Very strong: comparable to physiological urinary activity of bladder

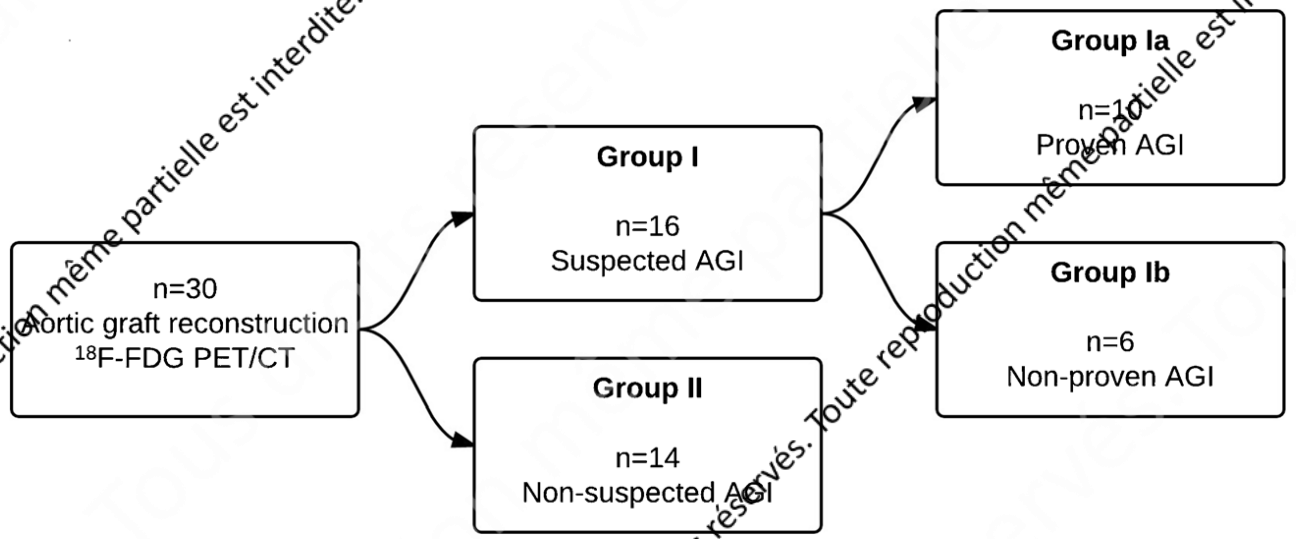
Rojoa D et al, Eur J Vasc Endovasc Surg 2018

Diagnostic value of FDG PET/CT in PVGs infection

Analysis of textural features: characterization of FDG uptake ***heterogeneity***



Flow chart of patient disposition



Saleem BR et al, EJNMMI 2017

Diagnostic value of FDG PET/CT in PVGs infection

Analysis of textural features: characterization of FDG uptake ***heterogeneity***

Variable	I vs. II		Ia vs. Ib		
	P-value	AUC	*P*-value	AUC	ICC
Conventional measures					
Maximal standardized uptake value	**0.01**	**0.87**	**0.13**	0.75	
Tissue to background ratio	**0.06**	0.78	0.35	0.70	
Visual grading scale	**<0.01**	**0.90**	0.26	0.64	
First order textural features					
Variance	**0.01**	**0.88**	0.17	0.70	**0.85**
GLRLM-based textural features					
Short run high grey level emphasis*	**0.02**	0.79	**0.07**	**0.83**	**0.75**
GLSZM-based textural features					
High grey level zone emphasis†	**0.01**	**0.87**	**0.12**	0.78	**0.83**
Small zone low grey level emphasis	**0.01**	**0.80**	0.16	0.73	**0.86**
Small zone high grey level emphasis	**0.04**	**0.81**	**0.15**	0.75	**0.79**

- **Automated analysis still at the development phase**

FDG PET/CT in PVGs infection

Impact on management: The Vascular Graft Cohort Study

Study population:

- 25 patients with a definite (FitzGerald) PVG infection
- Baseline and follow-up FDG PET/CT (time span: around 6 months)

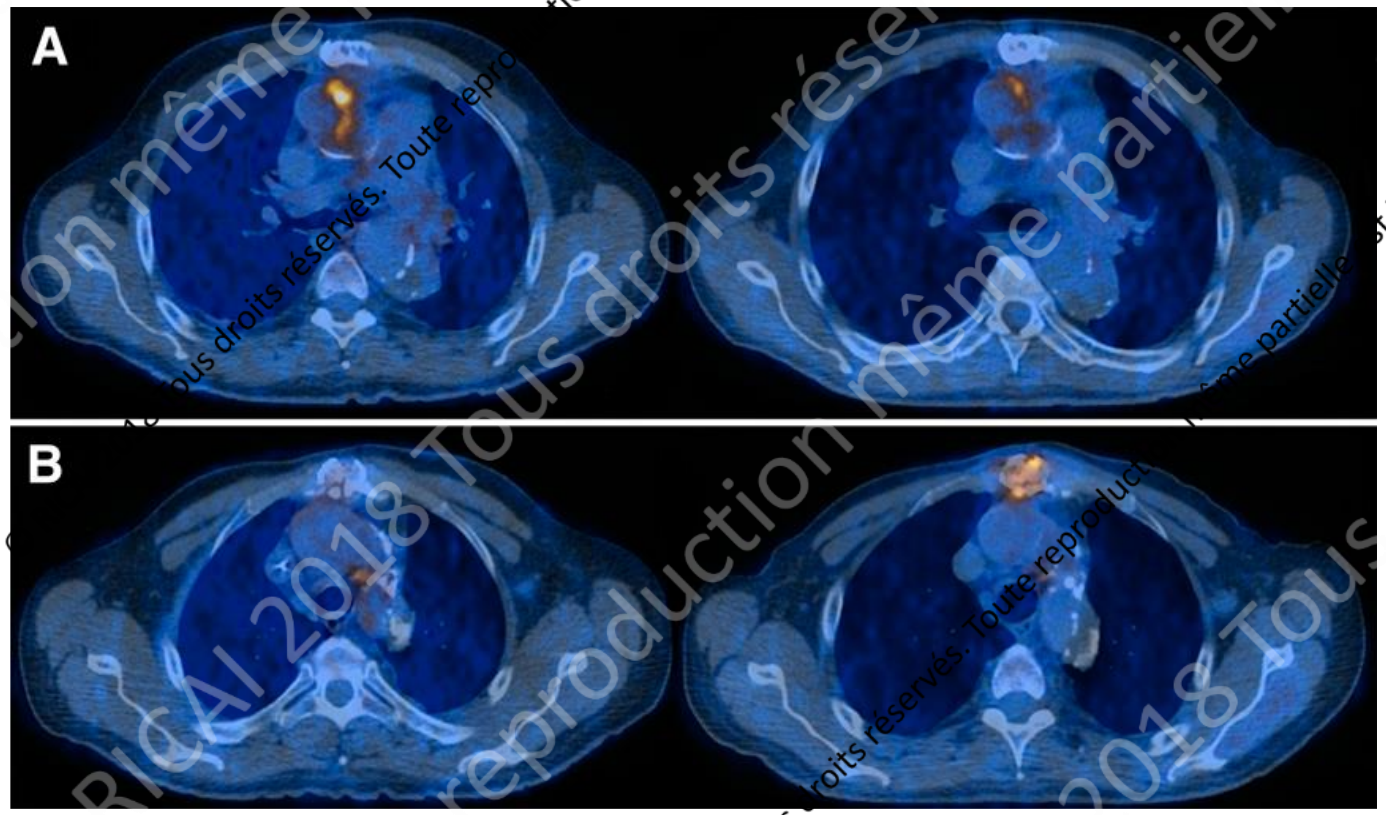
Overall results :

- In 19 of 25 patients (76%), antibiotic treatment was continued on the basis of the follow-up [18F]FDG PET/CT results;
- in 2 patients (8%), treatment was stopped;
- in 4 patients (16%), antibiotic treatment was changed.

Husmann L et al, J Nucl Med 2015

FDG PET/CT in PVGs infection

Impact on management: The Vascular Graft Cohort Study



(A) Baseline FDG PET/CT in September 2012 displays 18F-FDG–avid infection of graft (SUVmax, 7.6) and only mild 18F-FDG activity in sternum.

(B) Follow-up 18F-FDG PET/CT in June 2013 shows partial therapy response at graft (SUVmax, 5.1) but progression in sternum.

Husmann L et al, J Nucl Med 2015

Radiolabelled leukocytes: methods

Blood sample

40-50 ml

Plasma
Platelets
Leukocytes

RBC

Gradient centrifugation

^{99m}Tc-HMPAO

PMNs
+ plasma

^{99m}Tc-WBC: biodistribution

Radiolabelling procedure: 2 – 3 hours

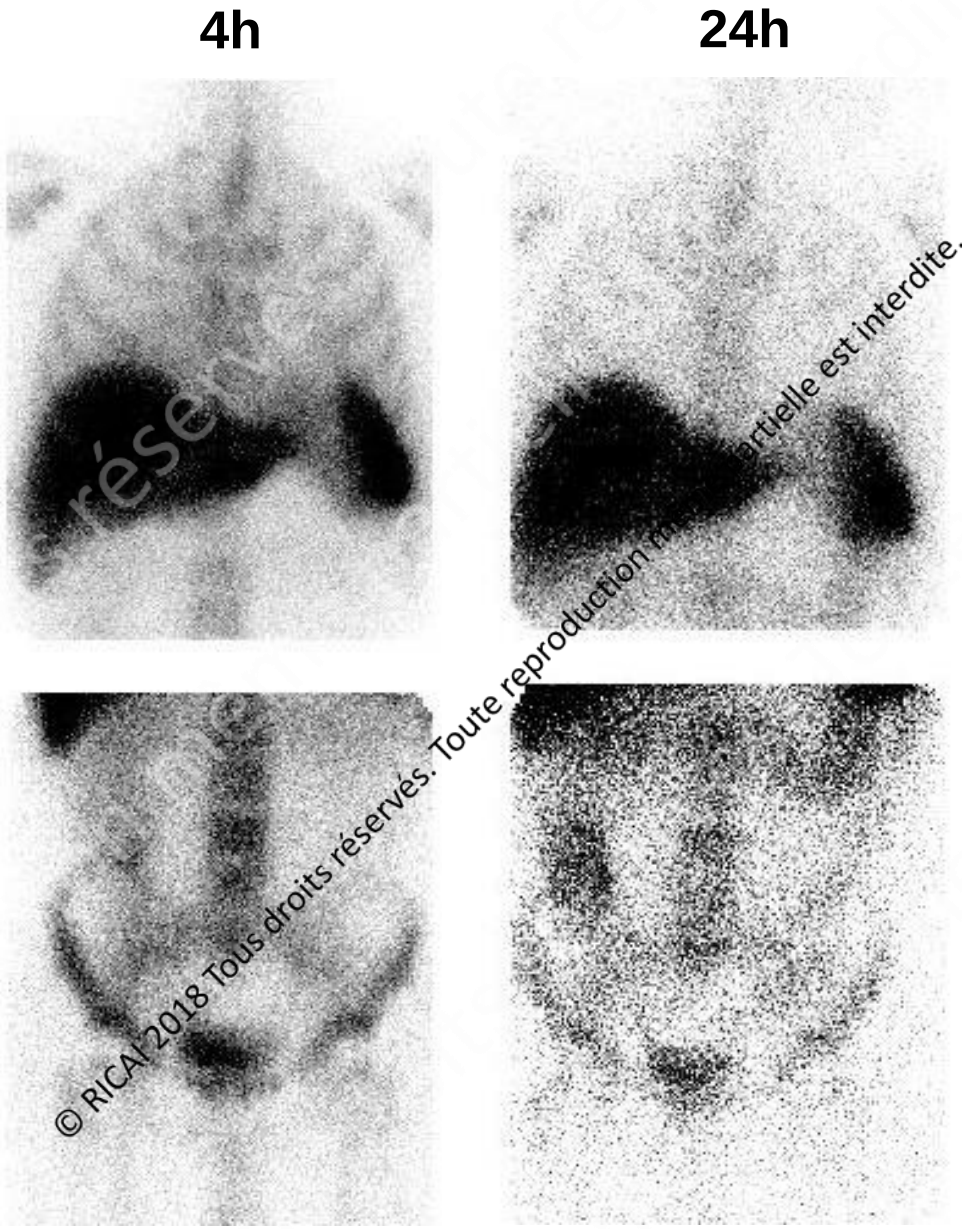
Acquisition: planar and SPECT/CT: 4h and 24h

Biodistribution: reticulo-endothelial system (liver, spleen, bone marrow)

Analysis:

Infection = increase of uptake intensity or size over time

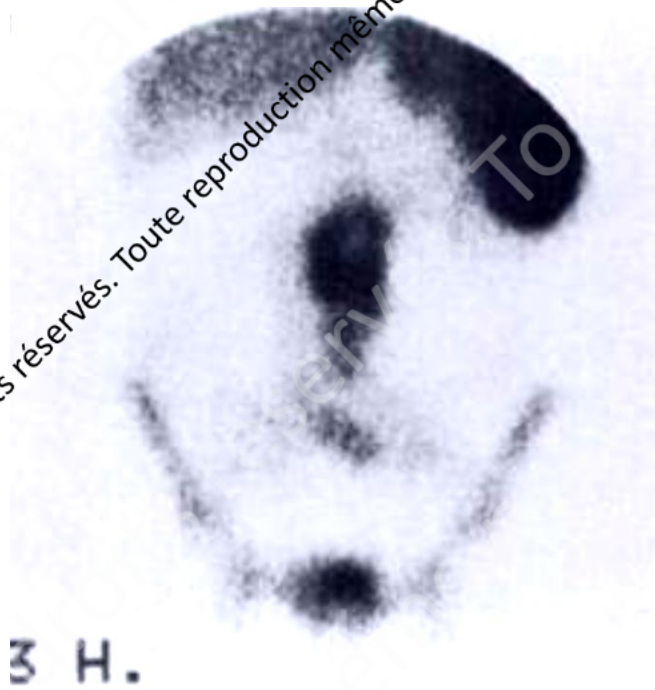
Inflammation = decrease of uptake intensity or size



Diagnostic value of WBC SPECT/CT in PVGs infection

Selected studies using ^{99m}Tc-WBCs SPECT

- Liberatore et al. J Nucl Med 1998: 129 pts
  - ***Sensitivity 100%, specificity 92% and accuracy 97%***
- Fiorani et al J Vasc Surg 1993: 37 pts
  - ***Sensitivity 100%, specificity 94%, PPV 90% and NPV 100%***
- Insall et al. Br J Surg 1990. 17 pts, 8 infected pts.
  - ***8 true positive, 1 false positive, no false negative***
- Prats et al. J Nucl Med 1994: 36 pts, 20 infected pts
  - ***Sensitivity 100%, specificity 100%***



Diagnostic value of WBC SPECT/CT in PVGs infection

Low-grade late vascular prosthesis infection

Table 4 Results of ^{99m}Tc-HMPAO-WBC scintigraphy, US, contrast-enhanced CT and the FitzGerald classification according to the final diagnosis of VPI, other concomitant infections or no infection for all the examinations performed at baseline. ^{99m}Tc-HMPAO WBC SPECT/CT performed significantly better than US (χ^2=25.48, p<0.0001, McNemar test), contrast-enhanced CT (χ^2=16.33, p<0.0001) and the FitzGerald classification (χ^2=8, p=0.004)

		VPI (n=47)	Other infections (n=8)	Sensitivity	Specificity	Accuracy	Positive Predictive Value	Negative Predictive Value
^{99m}Tc-HMPAO-WBC	Positive	47/47	8/8	100 % (91.9 – 100 %)	100 % (91.9 – 100 %)	100 % (91.9 – 100 %)	100 % (91.9 – 100 %)	100 % (91.9 – 100 %)
	Negative	0/47	0/8					
US	Positive	16/47	2/8	34 % (22.2 – 48.2 %)	75 % (70.1 – 91.7 %)	40 % (27.3 – 54.1 %)	88.9 % (76.8 – 95.2 %)	16.2 % (8.1 – 29.1 %)
	Negative	31/47	6/8					
CT	Positive	23/47	3/8	48.9 % (35.1 – 62.9 %)	83.3 % (70.1 – 91.7 %)	52.8 % (38.8 – 66.5 %)	95.8 % (85.7 – 99.2 %)	17.2 % (8.7 – 30.6 %)
	Negative	9/47	1/8					
	Non-diagnostic	15/47	4/8					
FitzGerald classification	Positive	32/47	3/8	68.1 % (54 – 79.6 %)	62.5 % (48.4 – 74.9 %)	67.3 % (72.8 – 93.1 %)	94.4 % (79.9 – 96.9 %)	25 % (14.7 – 38.8 %)
	Negative	15/47	5/8					

Erba PA et al, EJNMMI 2014

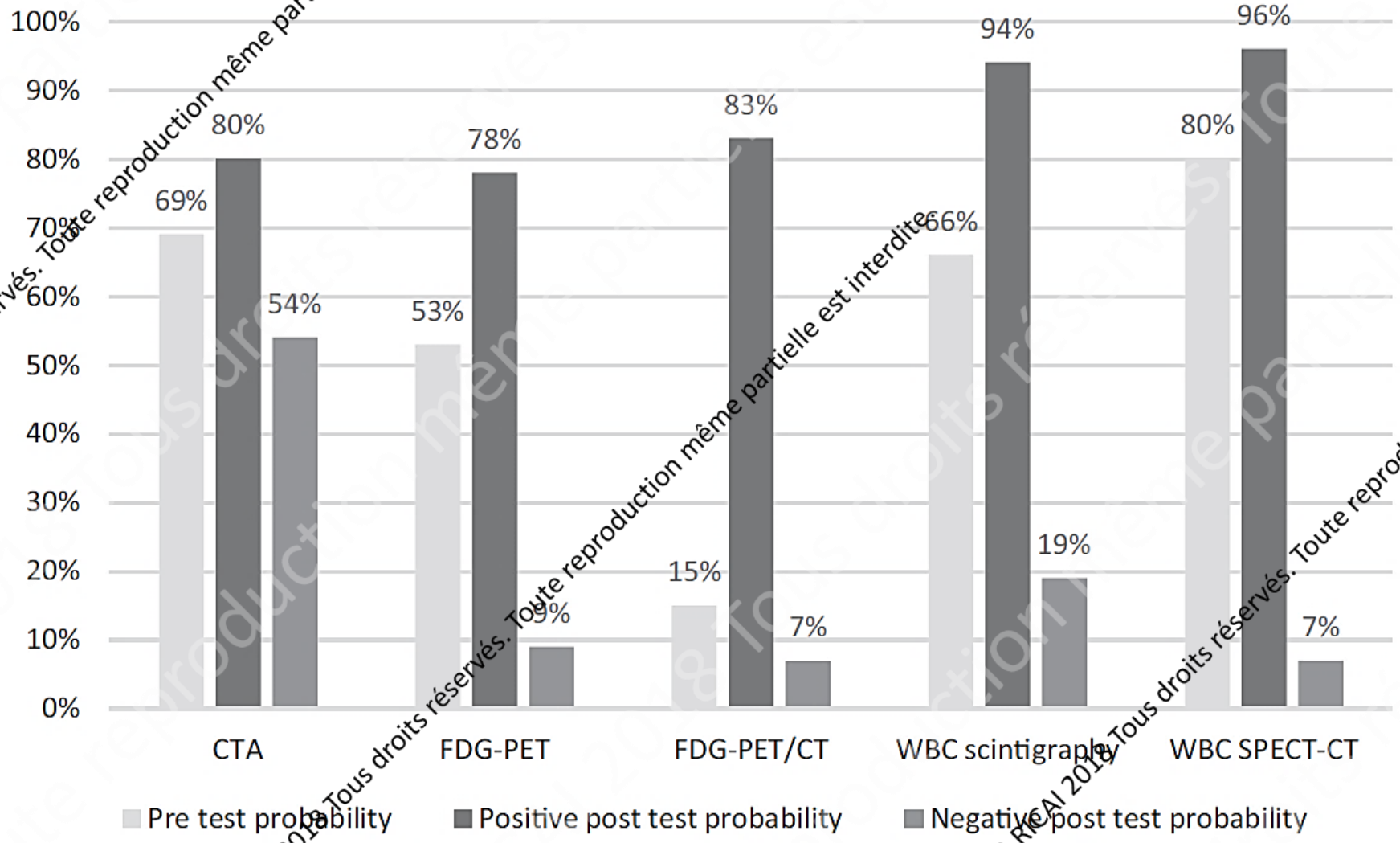
Diagnostic performance of imaging in VGI

Meta-analysis of 14 articles were included, 8 prospective and 6 retrospective

	Sensitivity	Specificity	Odds ratio
CT Angio	0.67 (0.57 - 0.75)	0.63 (0.48 - 0.76)	2.90 (1.21 - 6.98)
FDG PET	0.94 (0.88 - 0.98)	0.70 (0.59 - 0.79)	28.36 (7.83 - 102.74)
FDG PET/CT	0.95 (0.87 - 0.99)	0.80 (0.69 - 0.89)	38.04 (8.49 - 170.44)
WBC SPECT	0.90 (0.85 - 0.94)	0.88 (0.81 - 1.94)	41.84 (4.8 - 364.36)
WBC SPECT/CT	0.99 (0.92 - 1.00)	0.82 (0.57 - 0.96)	73.59 (5.35 - 1011.76)

Reinders Folmer EI et al, Eur J Vasc Endovasc Surg 2018

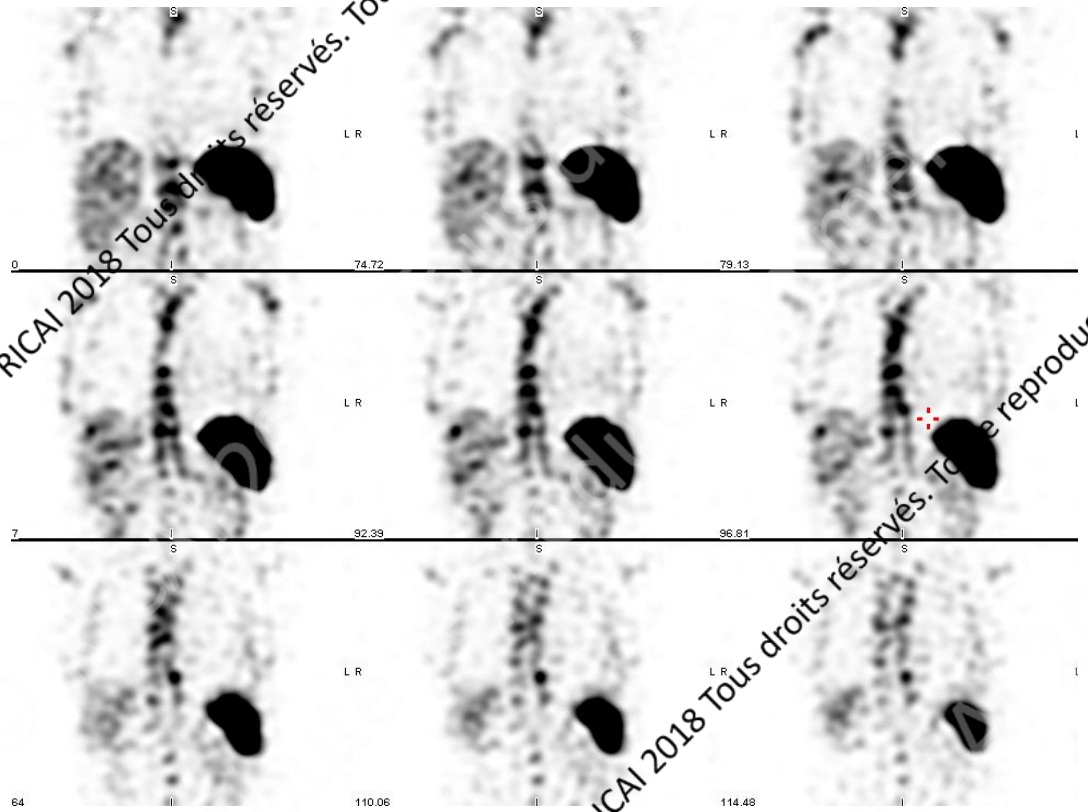
Pre- and post-test probabilities per imaging modality

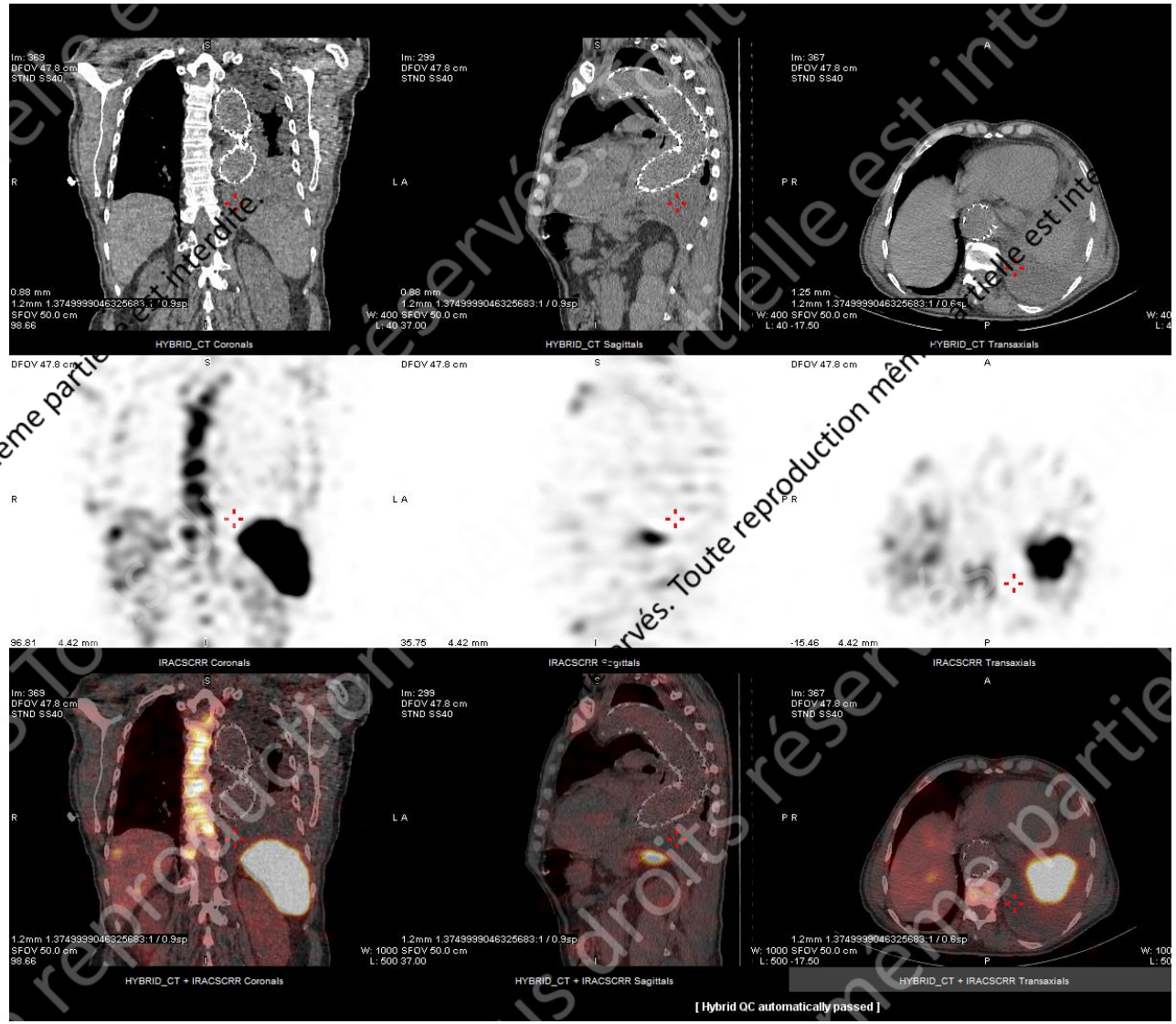


Reinders Folmer EI et al, Eur J Vasc Endovasc Surg 2018

- **Recurrent fever 2 weeks after thoracic graft implantation.**
- **CT: hematoma in contact with the lower portion of the graft**
- **Question: infection of the hematoma?**

^{99m}Tc-Leucocytes SPECT, coronal views

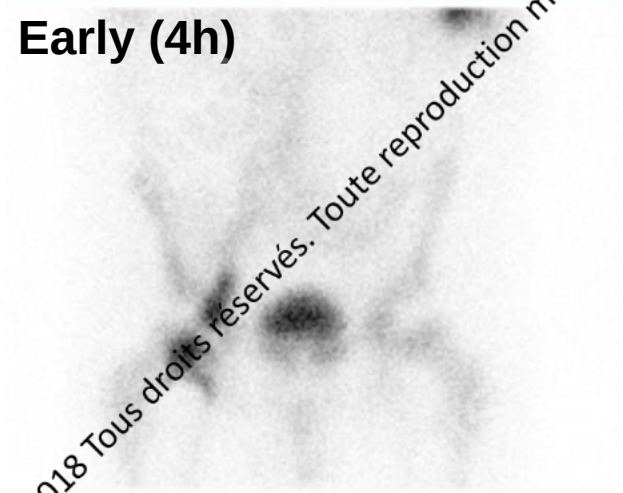




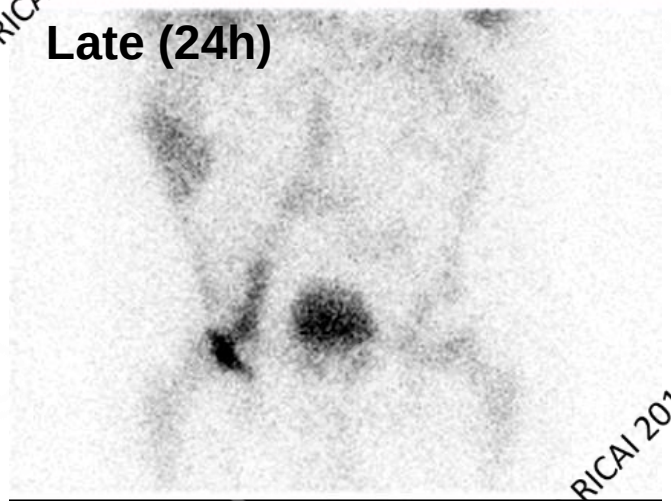
Infected ilio-femoral graft without infection of the femoro-femoral graft

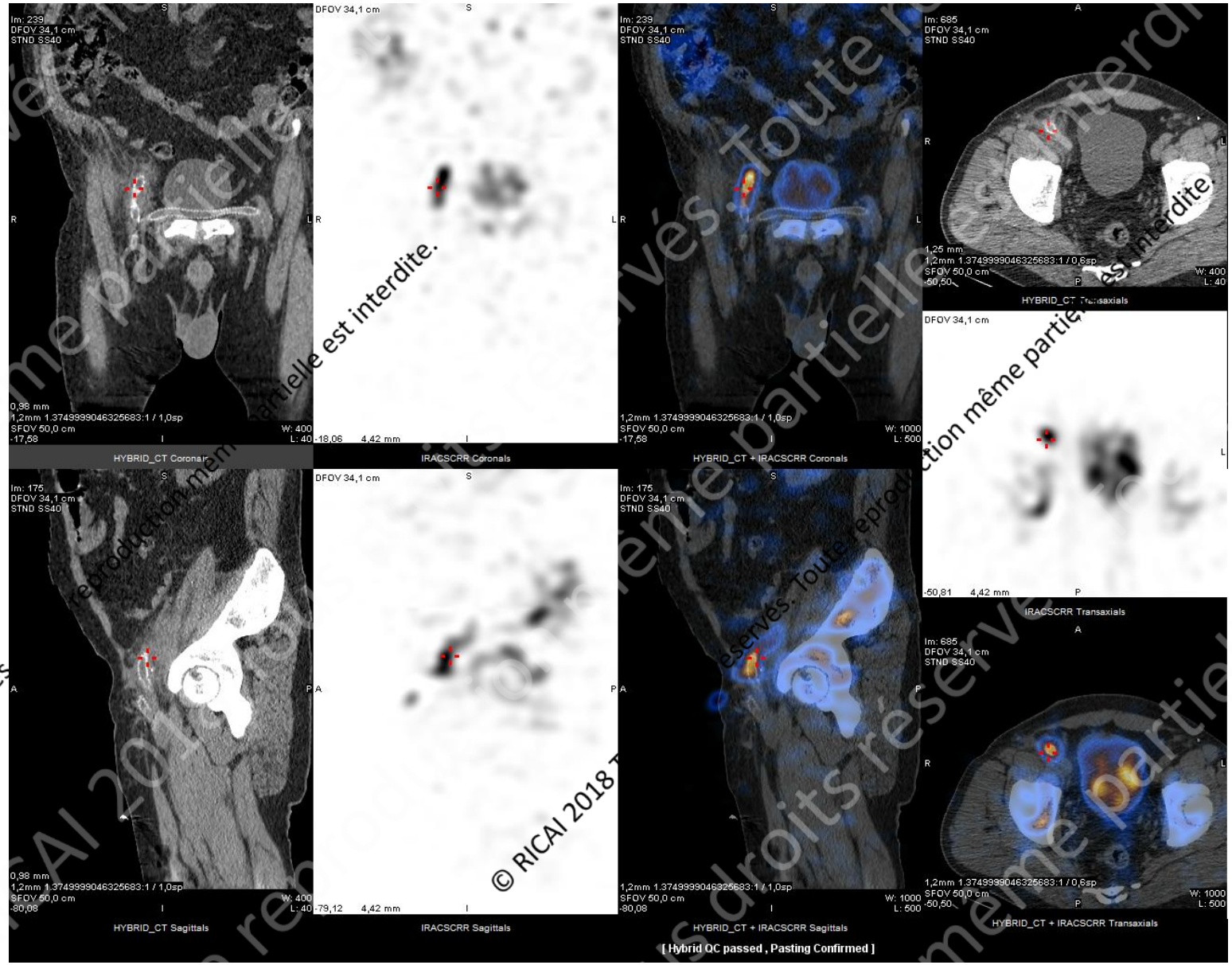
Planar acquisitions

Early (4h)



Late (24h)

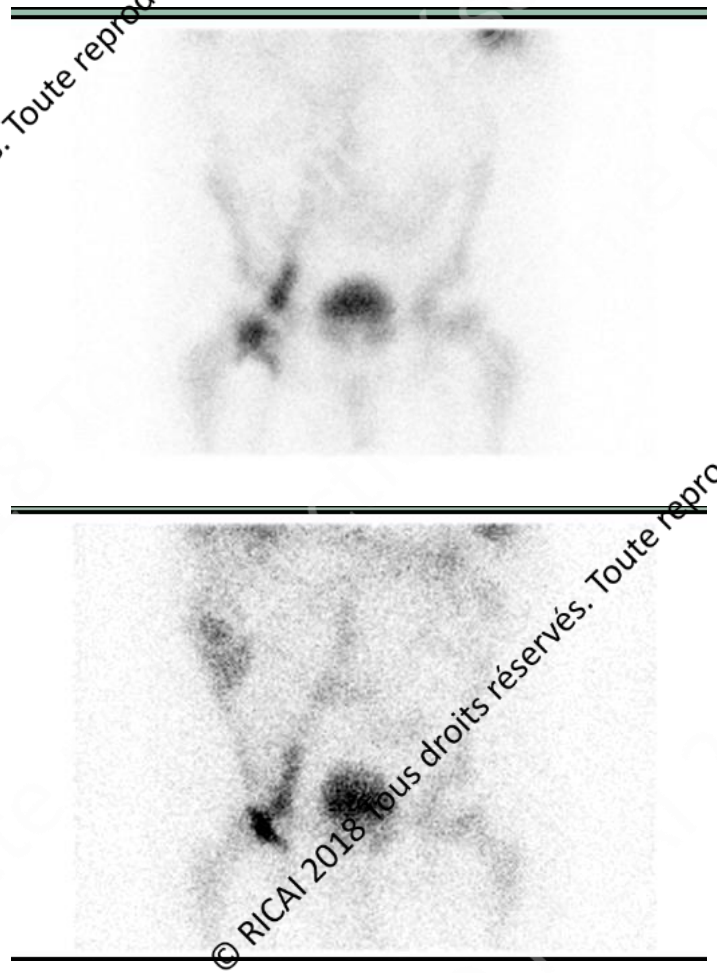




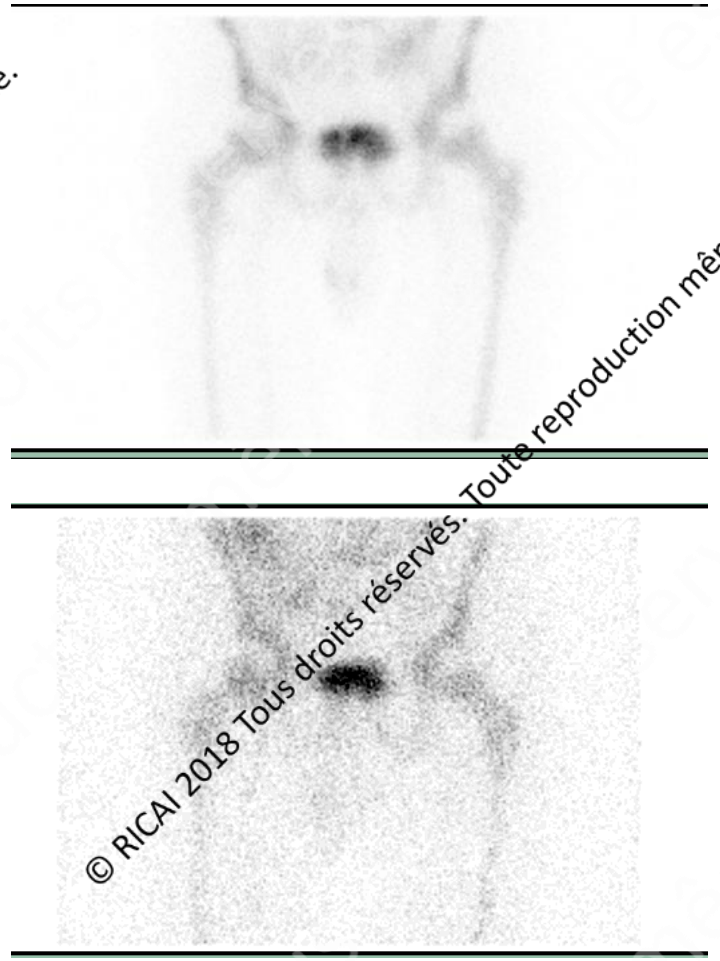
Infected ilio-femoral graft without infection of the femoro-femoral graft

- **Follow-up after surgery**

Before



After

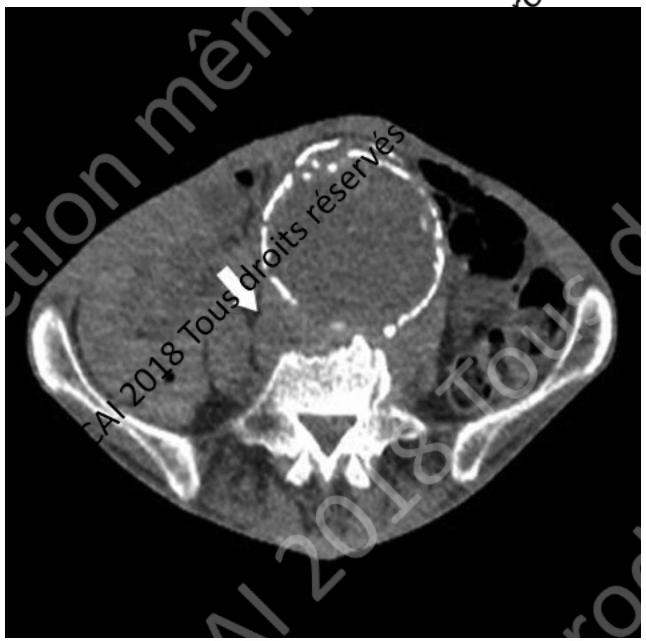


Early (4h)

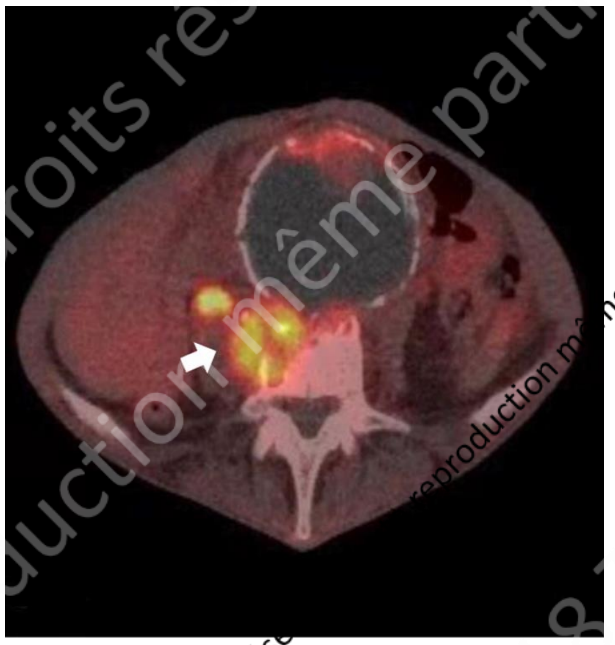
Late (24h)

Case report: 68-year-old male, who underwent open abdominal aortic graft in August 2016 owing to a ruptured large infrarenal abdominal aneurysm.
He subsequently presented 6 months later with back pain, general weakness, reduced mobility and cachexia.

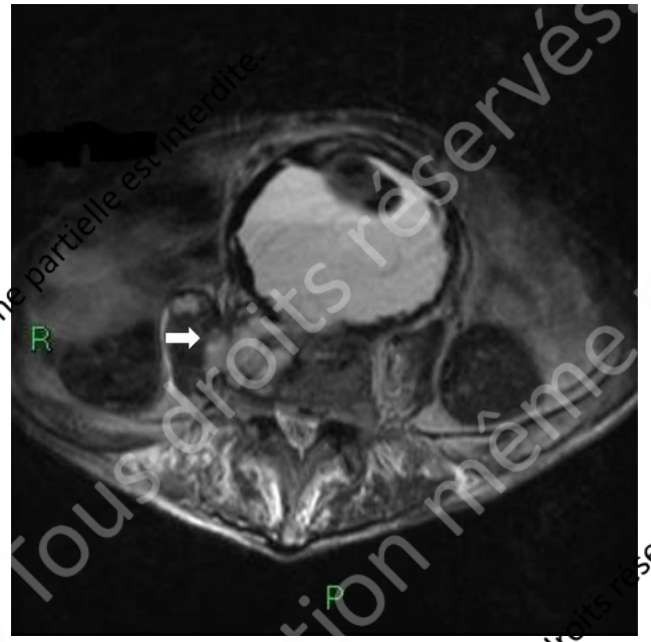
Non-enhanced CT



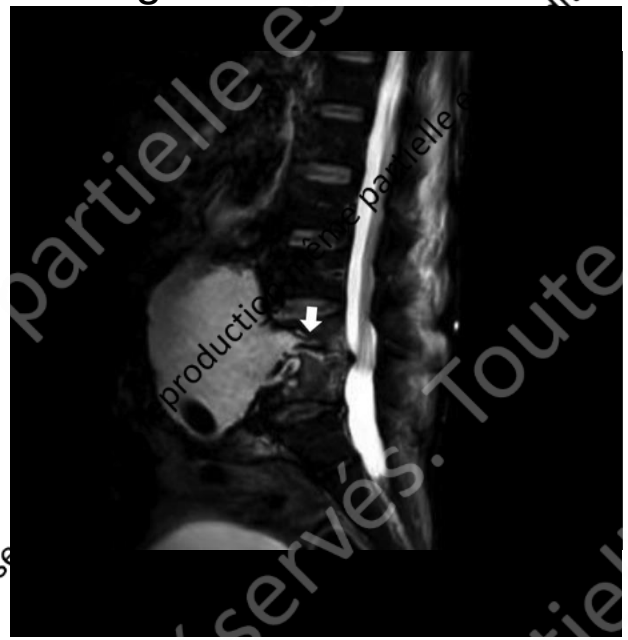
FDG PET/CT



Axial MRI T2



Sagittal MRI STIR



Conclusion: aortic graft infection complicated by L4/5 discitis

Sumrein HB et al, BJR Case Rep. 2018

Imaging modalities in PVG infections

Table 1 Advantages vs. Disadvantages for Different Imaging Modalities in Diagnosing Vascular Prosthetic Graft Infection

Imaging Modality	Advantages	Disadvantages
Ultrasound	No radiation exposure. No contrast-nephrotoxicity Easy and quick to perform	Interference with several artifacts Less differentiating ability compared to other modalities No data on sensitivity and specificity available and interobserver variability
CT	High specificity, relative high sensitivity, fast acquisition procedure Availability in most centres, less invasive Possibility for needle aspiration for microbiological analysis Three-dimensional reconstruction	Decreased sensitivity in low-grade infections Interference with normal postoperative findings in first 6 weeks after surgery
MRI	No radiation exposure. No contrast-nephrotoxicity Could differentiate in small perigraft fluid collections or surrounding inflammatory changes Less invasive and allows tissue characterization Comparable sensitivity and specificity rates to CT	Metal artifacts Diagnostic value for vascular graft infection less investigated compared to other modalities
FDG PET	At least comparable sensitivity and specificity rates to CT Can be fused with CT imaging (or PET-CT) Higher diagnostic rates compared to other modalities in case of low-grade vascular graft infections	Time-invasive investigation Less exact anatomical localization
SPECT	Specificity	Lower resolution and sensitivity compared to FDG PET

Modified from Bruggink JJ *et al*, Semin Vasc Surg 2011

Summary

MAGIC diagnostic criteria

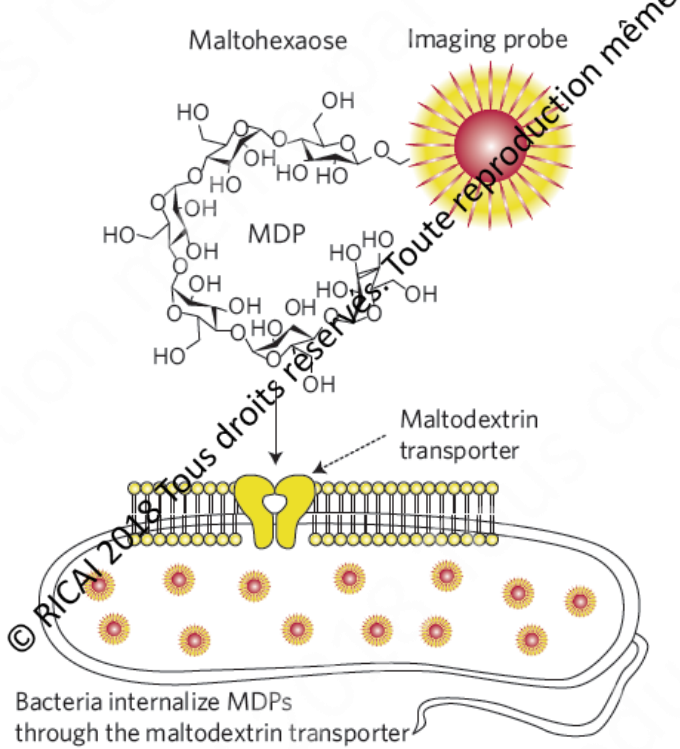
- Major: site-specific evidence of infection
- Minor: systemic signs, alternative sources of infection should be excluded

Contrast-enhanced CT is the first-line imaging modality

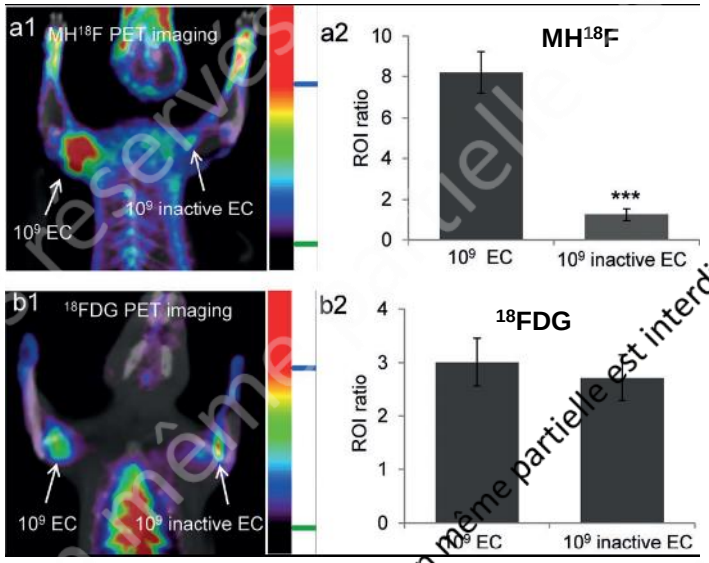
In case of doubtful diagnosis: nuclear imaging may be useful

- FDG PET/CT:
  - + Wide availability, excellent sensitivity, identification of regional extent / portal of entry
  - – Specificity depends on the expertise of the reader
- WBC SPECT/CT
  - + Excellent sensitivity and specificity in prosthetic graft infection
  - – Limited availability, labelling and acquisition procedures cumbersome

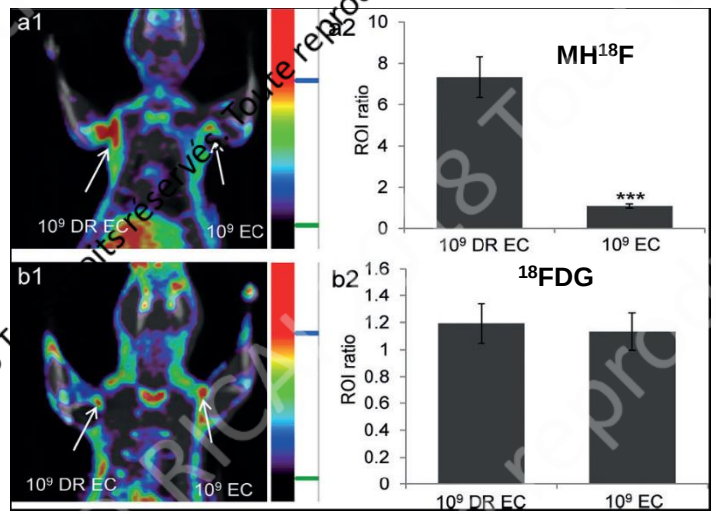
Perspectives: Maltodextrin-based imaging agents



live versus dead bacteria



drug resistance

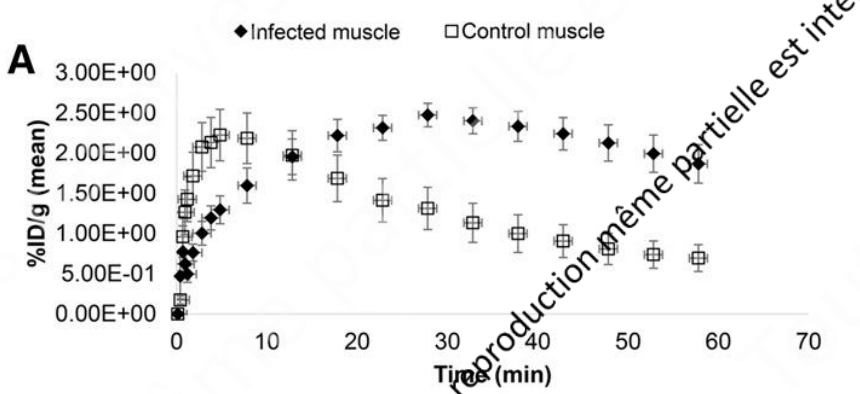


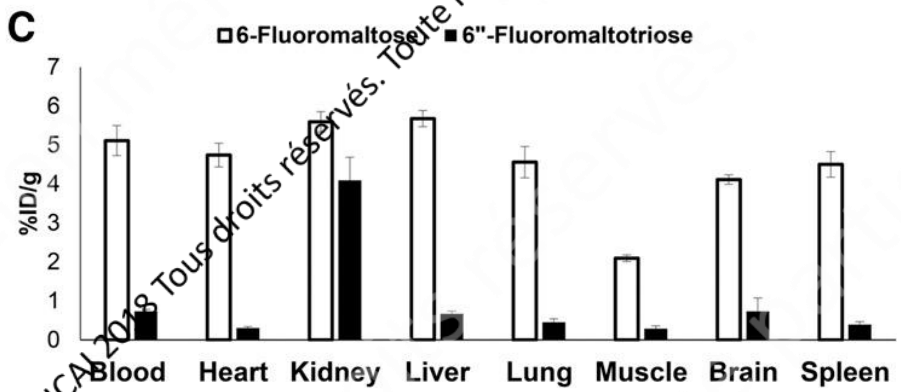
Ning X et al, Nat Mater 2011

Ning X et al, Angew Chem Int Ed Engl. 2014

6”-18F-fluoromaltotriose

- **improved pharmacokinetics**





Gowrishankar G et al. J Nucl Med 2017