Imagerie métabolique en coupe dans la prise en charge des infections musculo-squelettiques

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SFMN, La Rochelle, 29th May, 2015

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NM in musculo-skeletal Infections
Outline

- Introduction
- Choice of tracer
- Clinical indications of ^{18}F-FDG-PET
  - Acute (haematogenous) osteomyelitis / chronic OM
  - Infection of prosthetic material/metallic hardware
  - Vertebral osteomyelitis
  - Diabetic foot
- Summary

NM in musculo-skeletal Infections

Introduction: scope

Question 1: infection or not?

Specificity of the signal

Question 2: bone or soft tissue?

Anatomical localization: hybrid imaging

Question 3: evaluation of therapy

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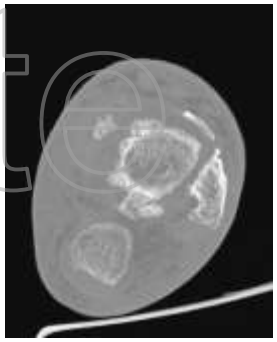
NM in musculo-skeletal Infections
Introduction: pathogeny

- Extremely **complex phenomenon** involving
  - Bacterial colonization and growth
  - Inflammation
  - Bone destruction and destruction of the vasculature resulting in compression, formation of pus, spread and exacerbated bone necrosis (sequestrae)
- **Haematogeneous** (children & elderly): bacteremia
- **Contiguous:** transmission from local infection
- **Direct injury:** trauma, surgery, prostheses

NM in musculo-skeletal Infections
Introduction: pathogeny

- **Pyogenic bacterias** are the most frequent
  - Staphylococcus *aureus*: 37-67%
  - Coagulase (-) Staphylococci (esp. *epidermidis*): 3-16%
  - Other pyogenic: Pseudomonas, Salmonella, Haemophilus, Streptococcus spp., E *Coli*,…
- **Non pyogenic:** Brucella *mellitensis*, Mycobacterium spp.
- **Staph. *aureus*** accounts for ~50% of surgical infections (UK Health Protection Agency 2008)

NM in musculo-skeletal Infections
Introduction: diagnostic challenge



- Incidence is increasing for prosthetic material and DM
- Treatment is difficult and prolonged, hence expensive
- X-Ray (and CT) is only positive when 20-50% of the bone matrix has gone (10-21 days) and often lacks specificity
- Antibiotic resistance is (more) frequent ('small colony')
- MRI and 3P-BS are nonspecific in the early stages
- Nuclear medicine offers …so (too?) many options

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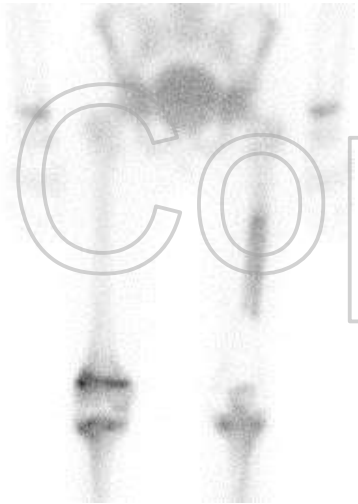
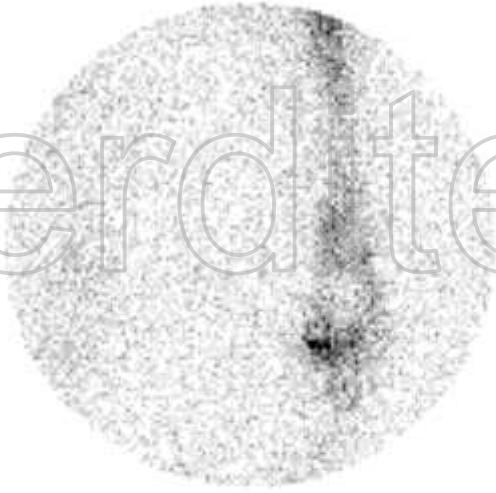
NM in musculo-skeletal Infections

Tracers: which one?



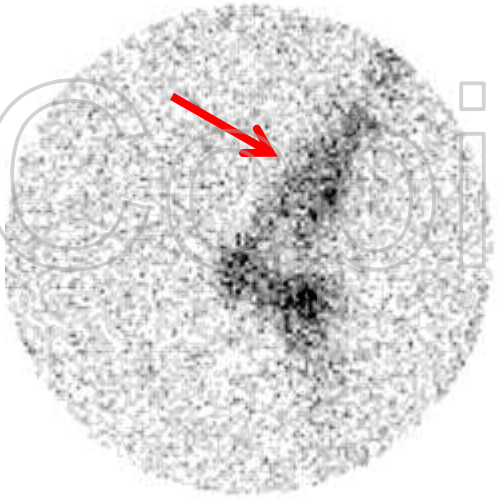
^{99m}Tc bone scan



^{99m}Tc-colloid + ^{111}In-WBC

NM in musculo-skeletal Infections

Tracers: which one?



^{111}In-WBC

^{18}F-FDG PET-CT

NM in musculo-skeletal Infections
Tracers: the ideal one

- **Targets the enemy!**
- Available, easy to use, cheap
- Good physical properties (T1/2, energy, rad. dose)
- In vivo and in vitro stability
- High sensitivity and specificity (*vs* inflammation)
- Rapid imaging (duration and delay)
- Marketing authorization

NM in musculo-skeletal Infections

Tracers: the ideal one

Staph. *aureus* accounts for ~50% of surgical infections

(UK Health Protection Agency 2008)

The target is **bacteria!**

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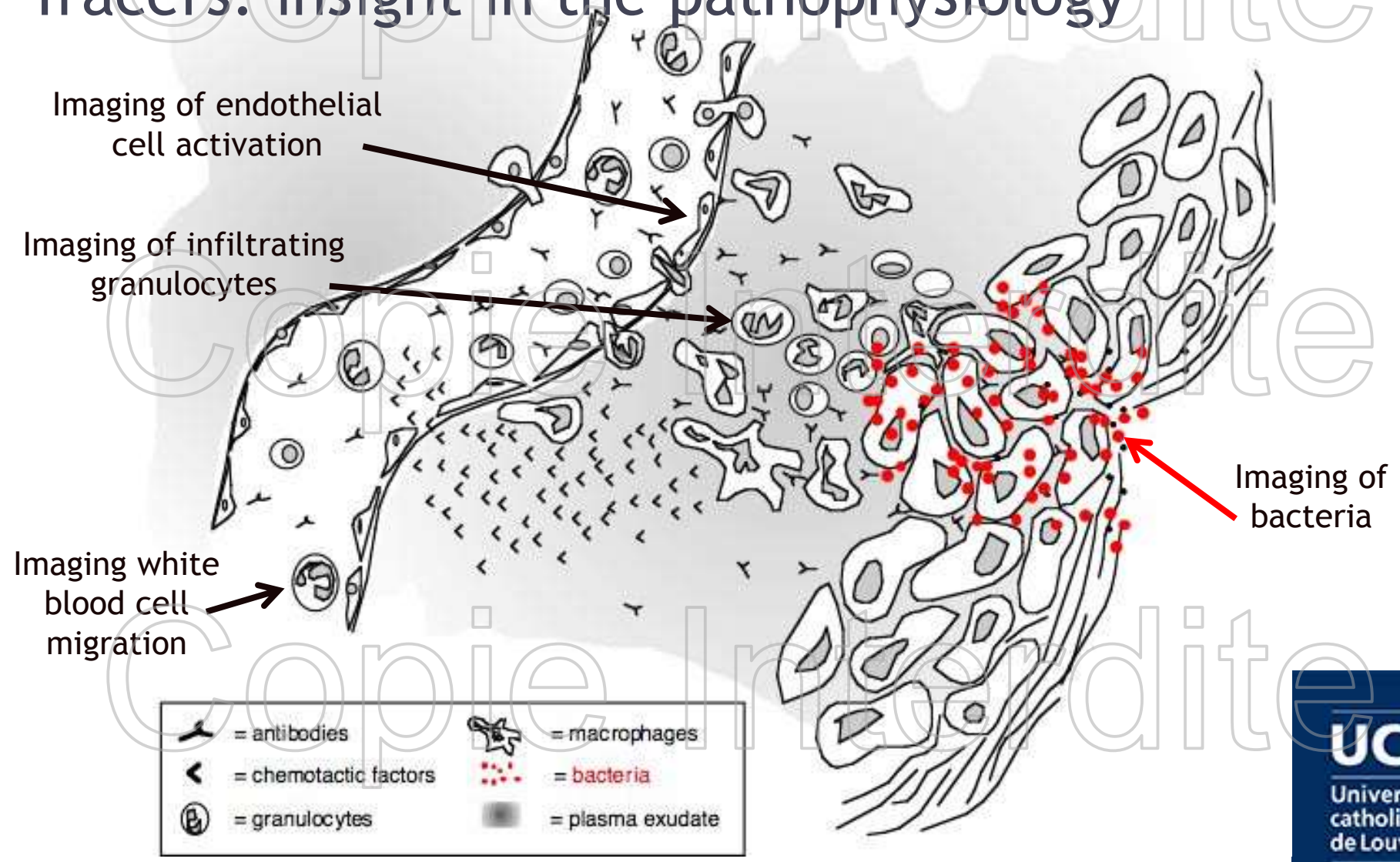
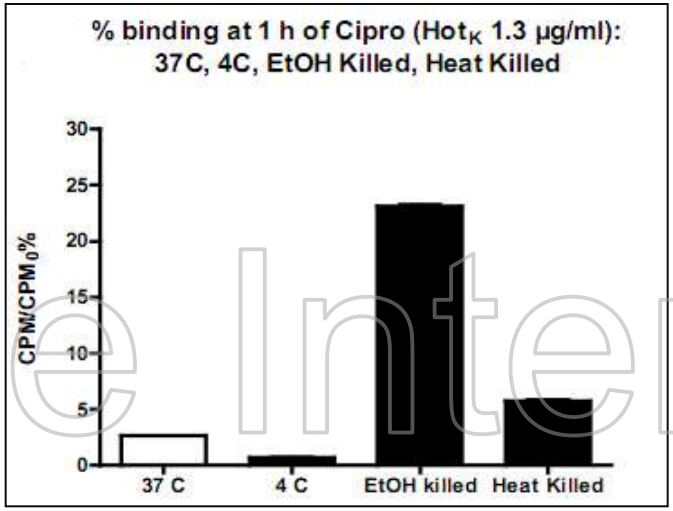
NM in musculo-skeletal Infections

Tracers: insight in the pathophysiology



NM in musculo-skeletal Infections

Tracers: targeting bacteria?



Take home message

Bacteria are dispersed, low mass, low binding of radiopharmaceuticals that do not allow their in vivo detection

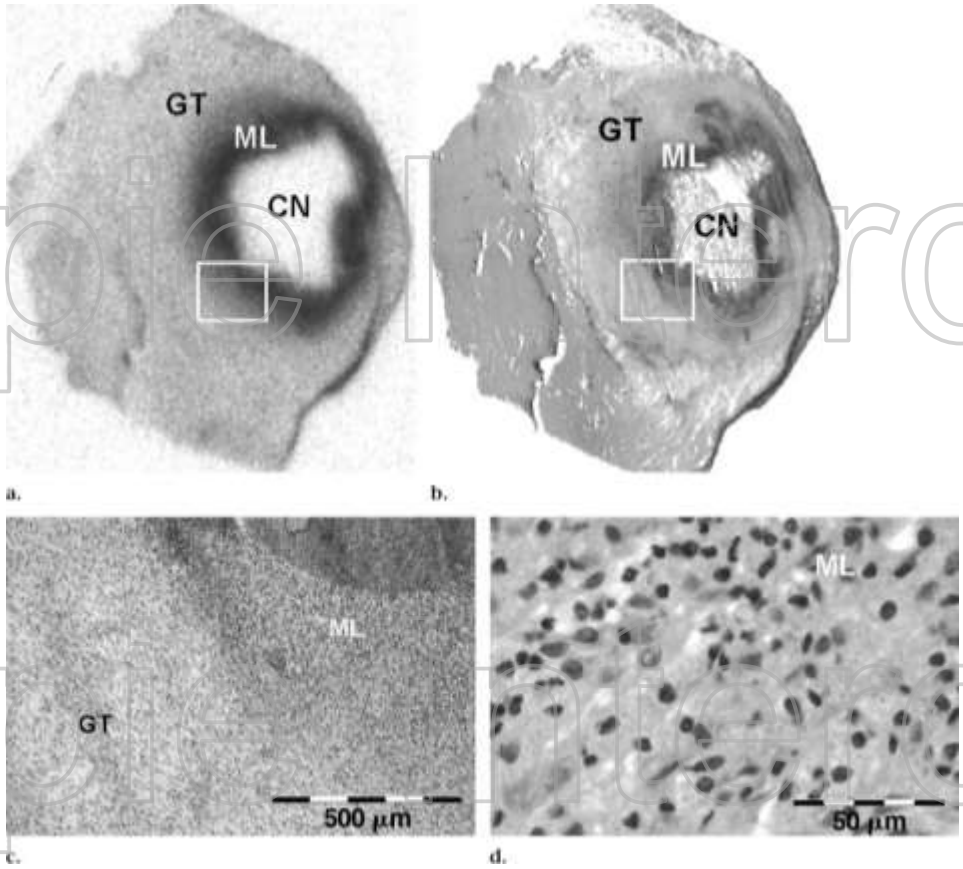
NM in musculo-skeletal Infections
Tracers

- Labelled WBC (^{111}In or ^{99m}Tc)
- ^{99m}Tc-labelled antigranulocyte moAb
- ^{67}Ga
- ^{111}In/^{99m}Tc-human immunoglobulin G
- ^{18}F-FDG
- Others... (^{18}F-FDG-WBC, ^{68}Ga-citrate)

NM in musculo-skeletal Infections

Tracers: ^{18}F-FDG – a by-product of oncology

Soft tissue Staph. *aureus* in rats Day 9 (Kaïm et al, Radiology, 2002)



NM in musculo-skeletal Infections

Tracers: ^{18}F-FDG BUT!!!!

Sterile inflammation (turpentine oil)
Day 4 (Yamada et al. , JNM 1995)

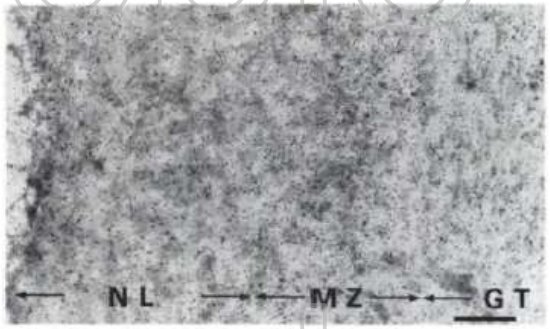
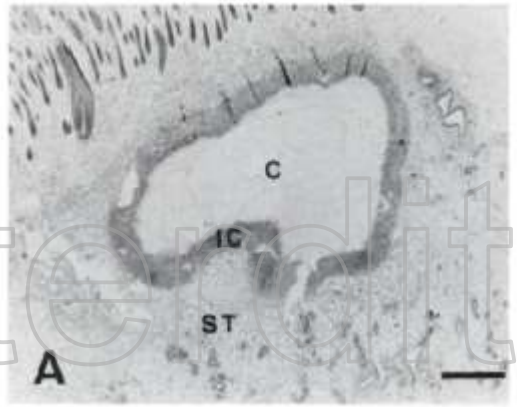
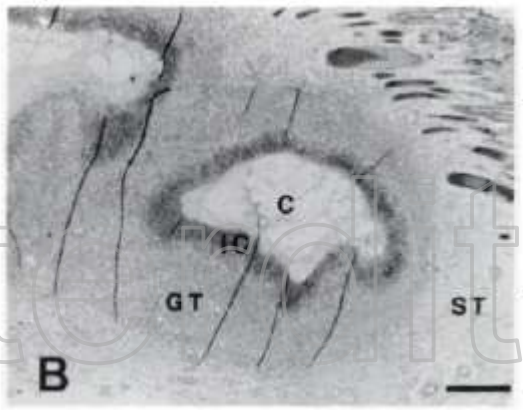


FIGURE 6. Micro-autoradiogram of abscess wall 4 days after inoculation with turpentine oil corresponding to Figure 5. Scale bar: 40 μm.





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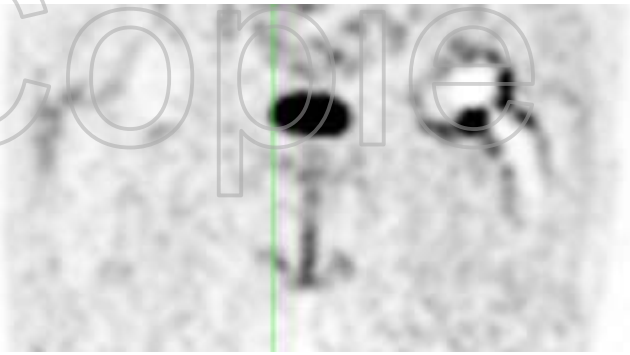
NM in musculo-skeletal Infections
Tracers: ^{18}F-FDG

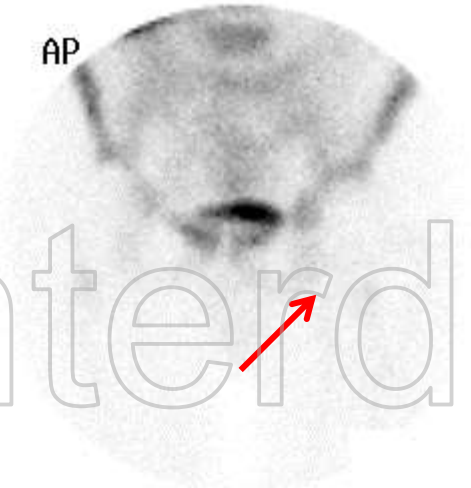
- Nonspecific targeting (neutrophils, monocytes-macrophages, fibroblasts,…)
- High quality whole-body imaging
- No blood handling
- Results in less than 2 hours
- Relatively cheap
- Multiple session imaging complicated

NM in musculo-skeletal Infections

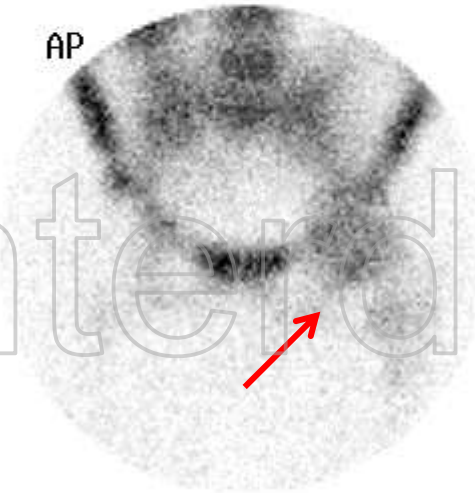
Tracers: bone marrow signal



^{18}F-FDG



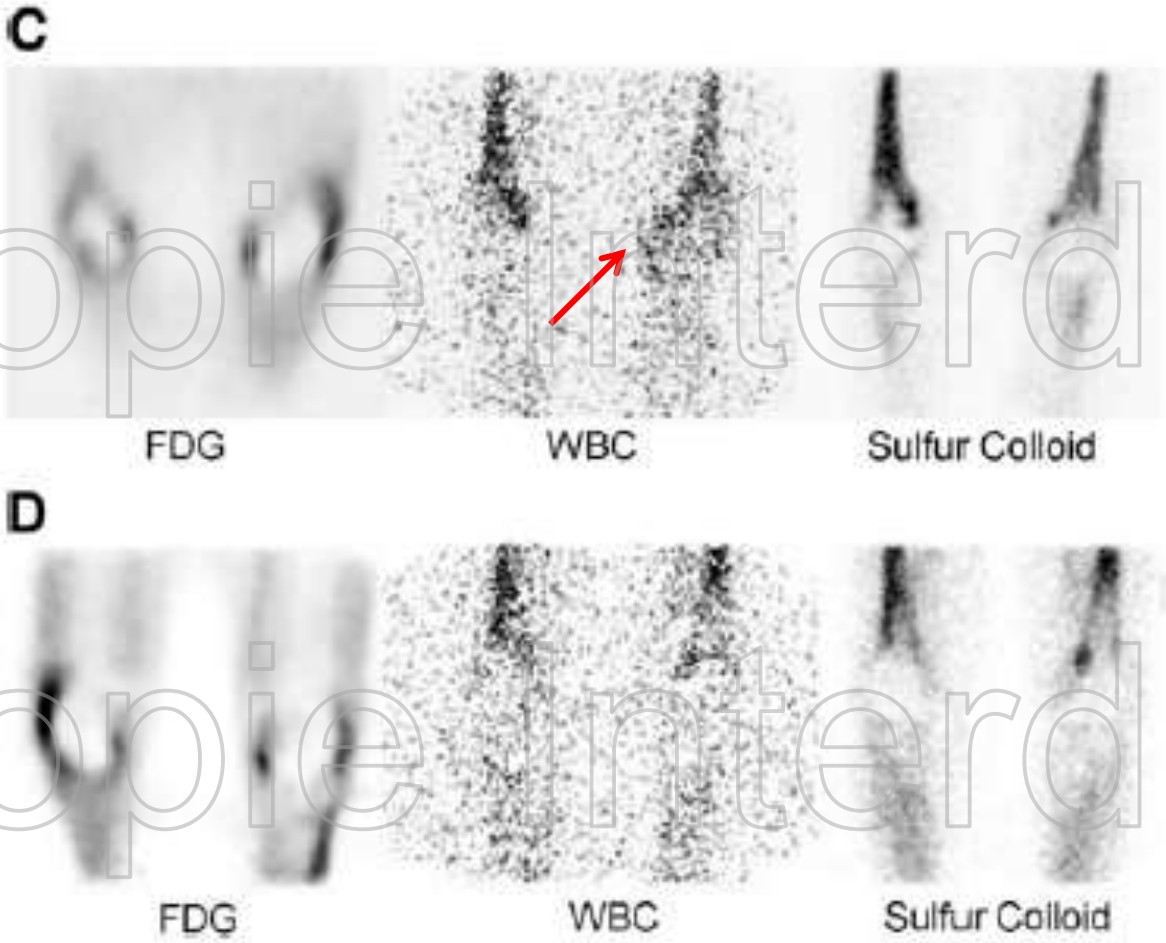
^{99m}Tc-colloid



^{111}In-WBC

NM in musculo-skeletal Infections

Tracers: but another problem with ^{18}F-FDG!



NM in acute osteomyelitis

- Plain X-Ray is the first-line method (MR if available)
- 3-Phase bone scanning is highly sensitive
- Labelled WBC + colloid (and antigranulocyte moAb) scintigraphy is highly sensitive and specific (~100%/95%)
- The added value of ^{18}F-FDG PET-CT is limited
  - No blood manipulation
  - Higher spatial resolution than BS or SPECT
  - Combination with CT for localization

NM in chronic osteomyelitis

Meta-analysis of published papers up to December 2011 on FDG-PET

Disease	Cases	Sens.	Spec.	Acc.
^{18}F-FDG	287	94.6	91.5	94.5

Meta-analysis of published papers up to December 2005 on WBC

Disease	Cases	Sens.	Spec.	Acc.
Primary osteomyelitis	617	85.4	75.5	74.0
Secondary osteomyelitis	376	88.2	80.3	79.3
Osteo-muscular infections	1803	84.8	78.9	81.6
Sternal wound infections	369	83.9	67.3	75.3

Prandini et al, Nucl Med Commun, 2006

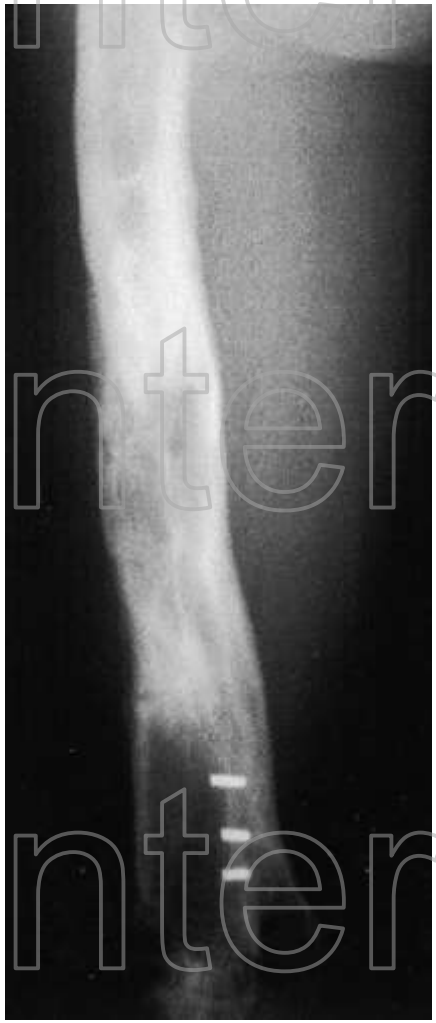
Jamar et al. J Nucl Med, 2013

NM in chronic osteomyelitis
^{18}F-FDG PET-CT

- Globally, **high sensitivity** (94-100%) after exclusion of dual-head coincidence scanning
- **Specificity** is also high with full ring PET(-CT) 87-100%
- Specificity depends on accurate clinical information
- Most studies deal with chronic OM

NM in chronic osteomyelitis

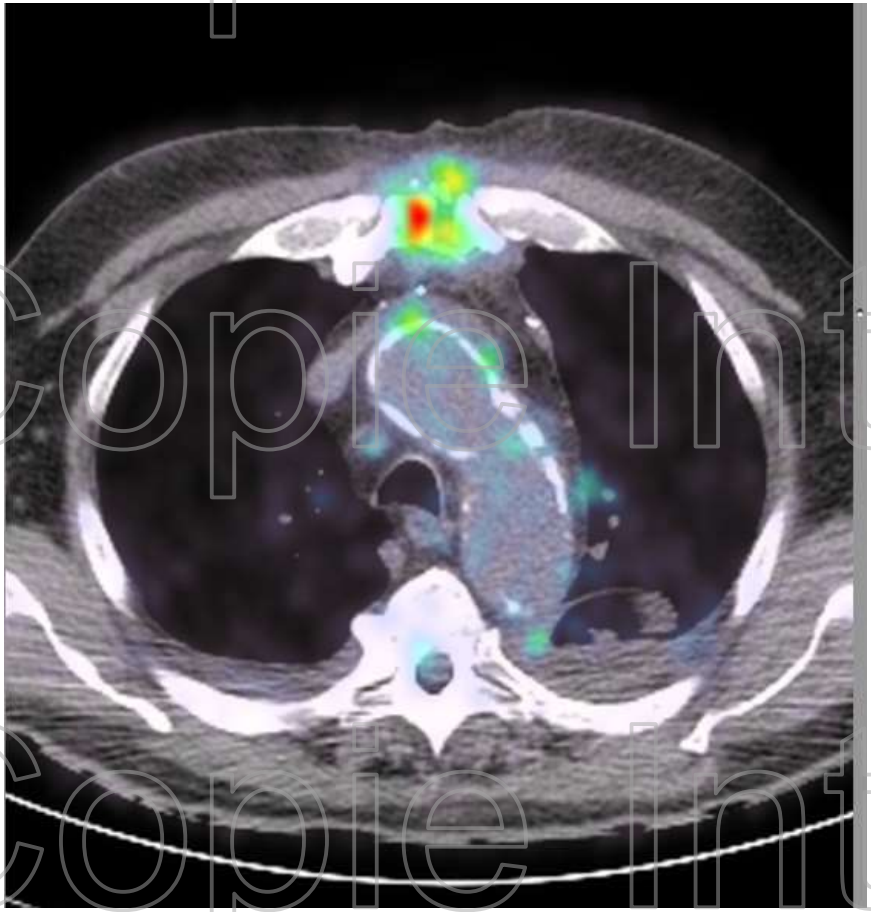
^{18}F-FDG PET-CT



De Winter JBJS 2001, 83: 651

NM in subacute/chronic osteomyelitis

^{18}F-FDG PET-CT



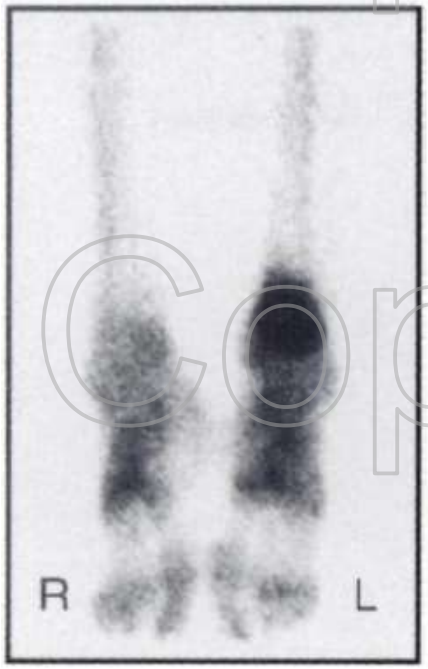
^{18}F-FDG PET-CT 9 mo after open-chest surgery

NM in chronic osteomyelitis
^{18}F-FDG PET-CT

Author	year	no	Sens.	Spec.	Acc.	Proof	comparator
Guhlmann	1998	31	100	92	97	All	-
Guhlmann	1998	51	98	95	96	All	>moAb
Stumpe	2000	18	100	83	99	17	-
De Winter	2001	60	100	88	93	18	-
Meller	2002	30	100	92	96	16	>^{111}In
Zhuang	2006	22	100	88*	91	18	-
Rini	2006	43	87	82	84	31	=^{111}In
Hakim	*2006*	*42*	*64*	*78*	-	*30/34*	***Bone SPECT***
Hartmann	2007	33	94	87	91	All	>^{111}In

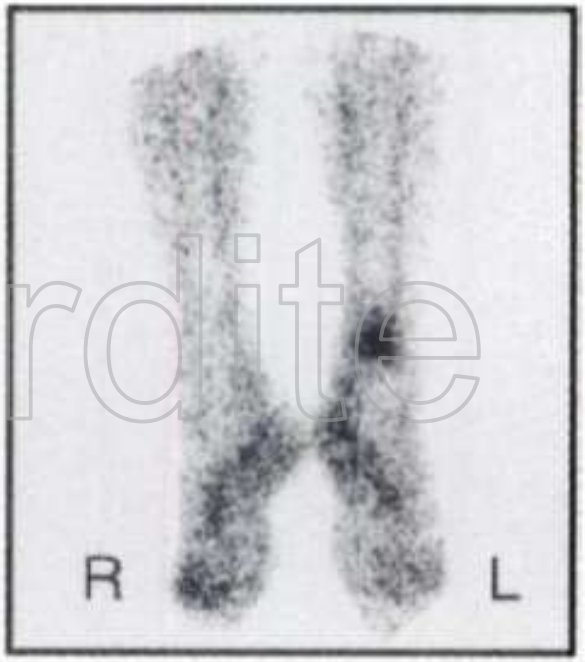
*: 2 FP due to recent osteotomy

NM in chronic osteomyelitis
^{18}F-FDG PET-CT



Bone scan

^{18}F-FDG-PET



moAb scan

Guhlmann, JNM1998, 39: 245-52

NM in chronic osteomyelitis
^{18}F-FDG PET-CT

TABLE 1
Data on Patients Suspected to Have Chronic Osteomyelitis in the Peripheral Skeleton

Patient/ Age (y)/ Sex	Site of Suspected Osteomyelitis	Cause of Suspected Osteomyelitis	FDG PET Rating*	Final Diagnosis	Results of Bacteriologic Culture†	Accuracy of FDG PET‡	SUV§
1/27/M	Distal femur	Fracture	4/4	Osteomyelitis	*S aureus*	TP/TP	2.8
2/63/M	Tibia	Fracture	4/4	Osteomyelitis	*S epidermidis*	TP/TP	2.7
3/42/M	Patella	Traumatic dislocation	0/0	Synovitis	No growth	TN/TN	0.2
4/37/M	Tibia	Orthopedic device	4/4	Osteomyelitis	*S aureus, E faecalis*, α-hemolytic streptococci	TP/TP	6.6
5/36/M	Tibia	Orthopedic device	4/4	Osteomyelitis	*S aureus*	TP/TP	3.4
6/36/M	Hand	Fracture	4/4	Osteomyelitis	*S aureus*	TP/TP	2.4
7/44/F	Hand	Fracture	4/4	Osteomyelitis	*S aureus*	TP/TP	2.1
8/37/M	Tibia	Orthopedic device	4/4	Osteomyelitis	*S epidermidis*	TP/TP	1.9
9/66/M	Tibia	Fracture	4/4	Osteomyelitis	*S aureus*	TP/TP	3.6
10/34/M	Knee joint	Injury, arthroscopy	0/0	Synovitis	No growth	TN/TN	0.1
11/32/F	Distal femur	Fracture	0/0	No infection	No growth	TN/TN	0.3
12/41/M	Tibia	Orthopedic device	0/0	Soft-tissue infection	*S aureus*	TN/TN	0.2
13/75/M	Tibia	Shin splint injury	1/1	Soft-tissue infection	*S aureus*, β-hemolytic streptococci	TN/TN	0.5
14/20/M	Tibia	Orthopedic device	4/4	Osteomyelitis	*S aureus*	TP/TP	3.8
15/69/F	Knee joint	Avascular necrosis, empyema	0/0	Synovitis	*S aureus*	TN/TN	0.2
16/56/M	Distal femur	Fracture	4/4	Osteomyelitis	*S aureus*	TP/TP	8.6
17/36/M	Tibia	Fracture	3/4	Osteomyelitis	*S aureus*	TP/TP	3.0
18/63/M	Calcaneus	Orthopedic surgery	0/0	Soft-tissue infection	No growth	TN/TN	0.2
19/46/F	Calcaneus	Orthopedic surgery	0/0	Soft-tissue infection	*S aureus*	TN/TN	0.3
20/76/F	Ankle joint	Orthopedic surgery	0/0	No infection	No growth	TN/TN	0.1
21/32/M	Tibia	Fracture	4/4	Osteomyelitis	*S aureus*	TP/TP	2.2

*Rating of reader 1/rating of reader 2.
†*E faecalis* = *Enterococcus faecalis* (group D streptococci), *S aureus* = *Staphylococcus aureus*, *S epidermidis* = *Staphylococcus epidermidis*.
‡Rating of reader 1/rating of reader 2. TN = true-negative (score of 0 or 1), TP = true-positive (score of 3 or 4).
§SUV = standardized uptake value (intraosseous).

SUV
Periph+: 3.6 (2.0)
Central+: 6.2 (2.7)

Periph-: 0.2 (0.1)
Central-: 0.9 (0.2)

Guhlmann, Radiology 1998, 206: 749-54

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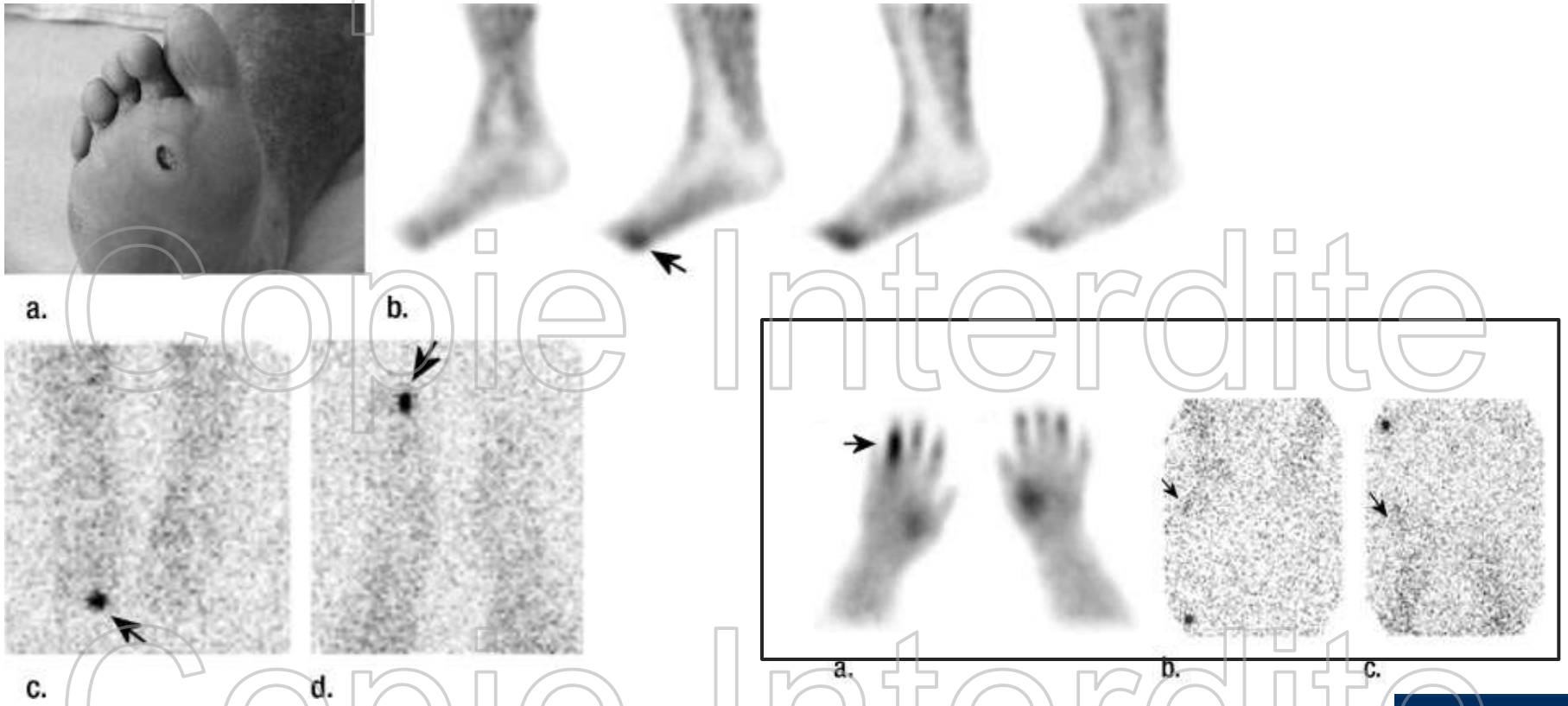
NM in chronic osteomyelitis

^{18}*F-FDG* PET-CT



^{18}F-FDG-WBC PET vs ^{111}In-WBC:
sensitivity (87% *vs* 73%), specificity (82% *vs* 86%)

Rini, Radiology, 2006, 238: 978-87

NM in chronic osteomyelitis

^{18}F-FDG PET-CT

FDG-PET appears globally equivalent to or slightly less performant than labelled WBC scintigraphy

Advantages	Inconvenients
Rapid imaging	Access limited
No blood handling	Lack of funct spec.
Not impaired by metallic implants	Artifacts with metal (CT)
All-in one technique	Lower sens. in diabetics?
Low BM uptake	Cost
Solute physiology	Reimbursement

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NM in chronic osteomyelitis
^{18}F-FDG PET-CT

- **Limitations**
  - The level of evidence remains low (2b at best)
  - No clear report on the diagnostic impact of CT
  - Limited information about acute OM
  - Perfomances may be different in selected groups
  - Limited direct comparison with MRI

- ***At this stage*, overall substitution of WBC scan by ^{18}F-FDG-PET(CT) cannot be recommended**

NM in prosthetic joint infection

- Becomes extremely frequent nowadays
- 8% will require revision
- 5-15% may be infected (70% mech. loosening)

- Major impact on treatment (success, symptoms, costs,…)
- **3-Phase bone scan** available everywhere

Sensitivity / specificity: 78% / 84% (hip)

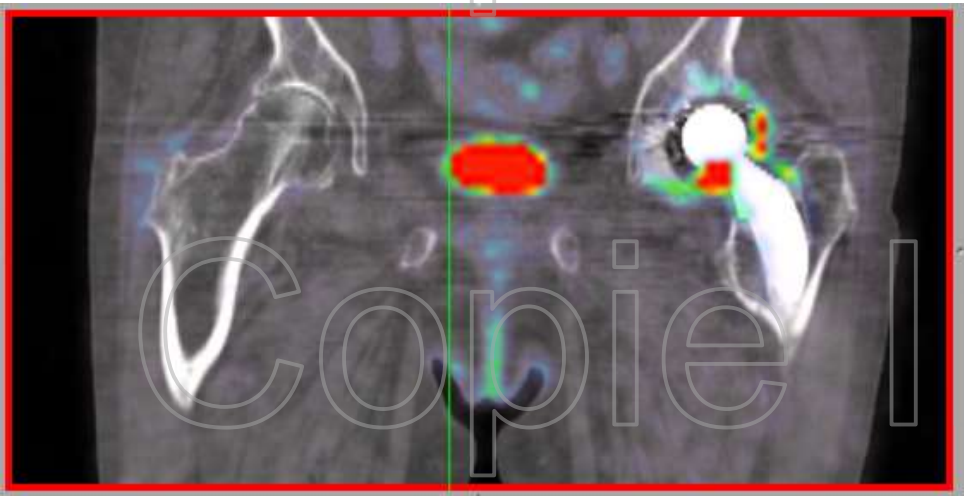
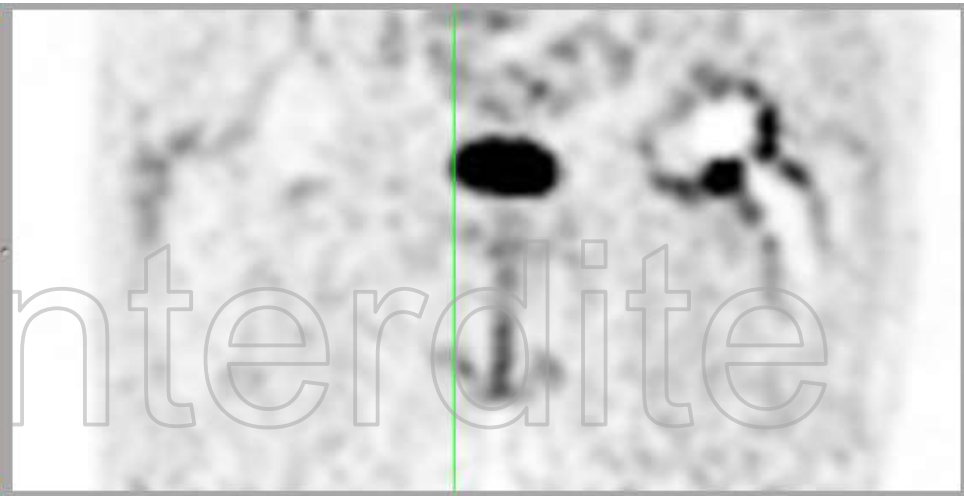
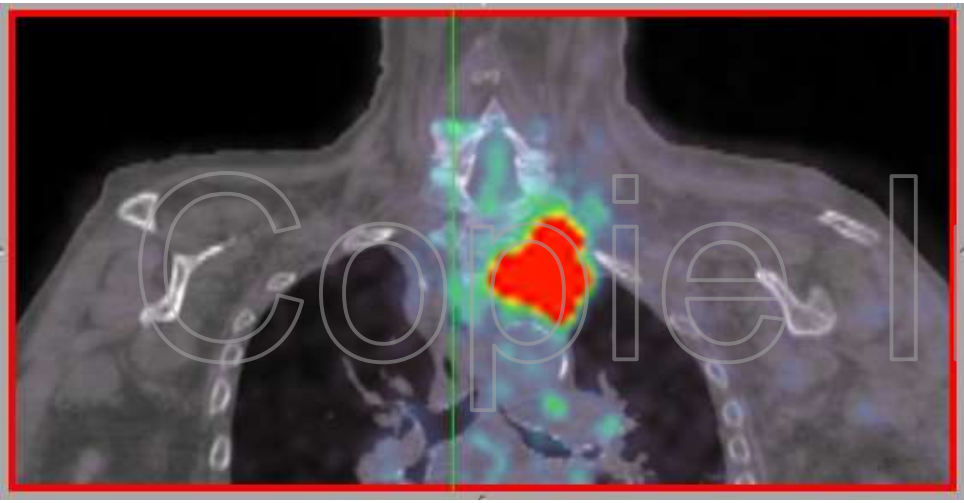
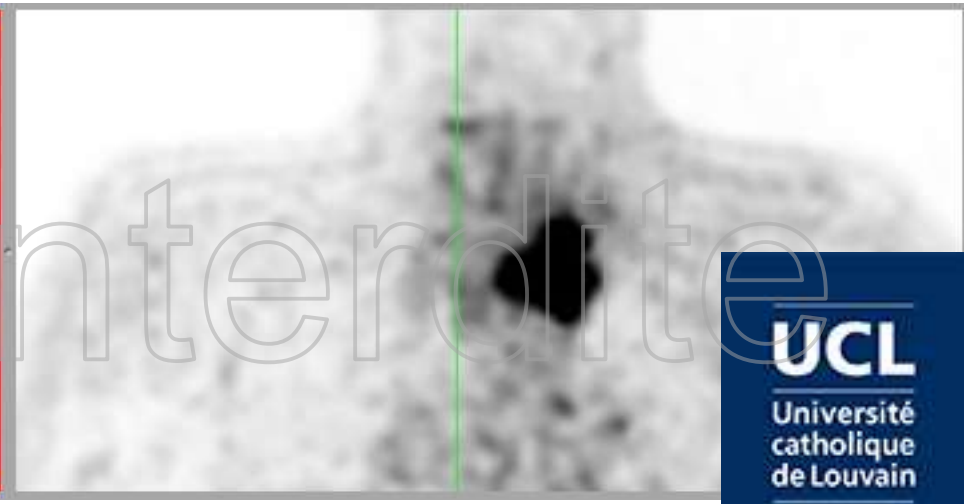
Sensitivity / specificity: 87% / 71% (knee)

NM in prosthetic infection
WBC scanning

- sensitivity - alone: 88% +colloids: 97%
  specificity - alone: 78% +colloids: 97%
- Very little data in low prevalence groups

NPV before revision probably around 85-90%

NM in prosthetic infection
^{18}F-FDG-PET?

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NM in prosthetic infection
^{18}F-FDG-PET

Table III. Analysis of the ability of PET and TPBS to differentiate between loosening and infection. An incorrect diagnosis of infection rather than loosening was considered as a false positive while a diagnosis of loosening rather than infection was regarded as a false negative

	PET*	TPBS†
True positive	31	17
True negative	56	51
False positive	3	16
False negative	2	8
Total	92	92
Sensitivity	0.94	0.68
Specificity	0.95	0.76
Negative predictive value	0.97	0.86
Positive predictive value	0.91	0.52
Accuracy	0.95	0.74

* PET, positron-emission tomography
† TPBS, triple-phase bone scanning

Reinartz et al., JBJS, 2005

NM in prosthetic infection
^{18}F-FDG-PET

- Very variable sensitivity and specificity
- Sens: 22-100%
- Spec: 61-100%
- Criteria for assessment vary from study to study

Jiue et al., Nucl Med Commun, JBJS, 2015

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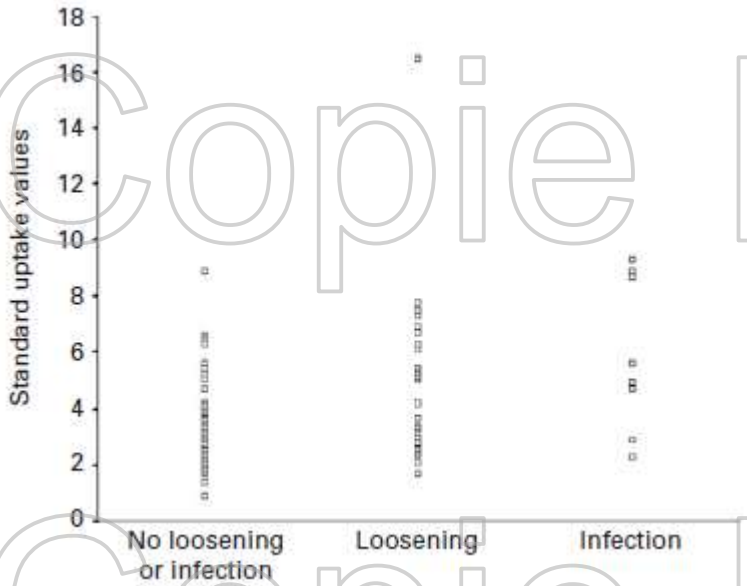
NM in prosthetic infection

^{18}F-FDG-PET - Interpretation criteria



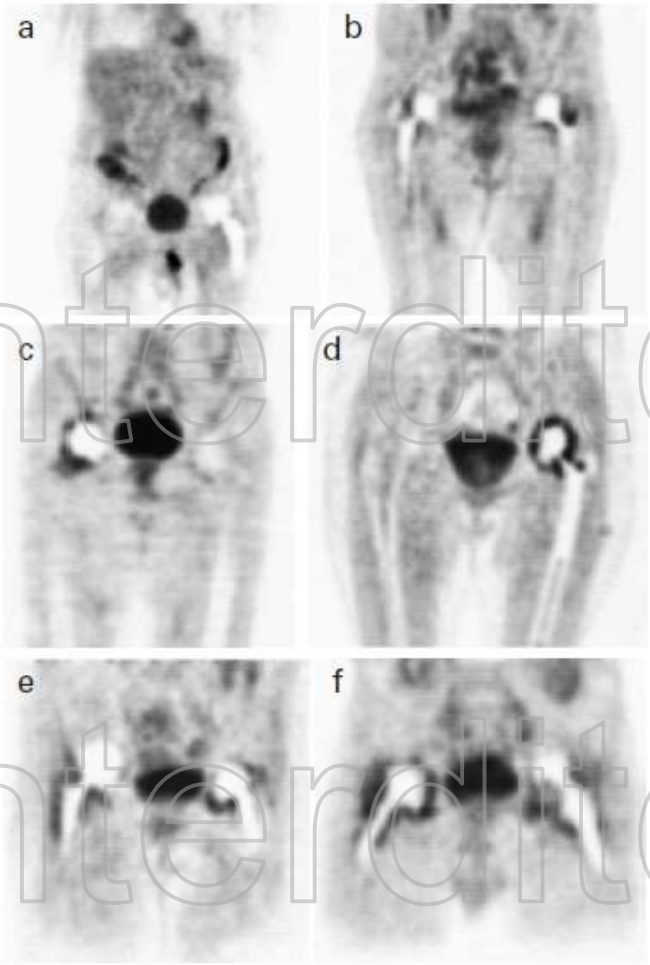


Fig. 1

Reinartz et al., JBJS, 2005

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NM in prosthetic infection
^{18}F-FDG-PET - Interpretation criteria

Table I. Patterns of PET* findings and their clinical correlates in patients with a THA

Pattern	Description	Clinical correlation
1	No increased uptake of FDG† in the prosthesis-tissue interface	No loosening
2	Increased uptake of FDG in the area of the femoral neck	
3a	Increased uptake of FDG in the area of the femoral neck and in parts of the prosthesis-bone interface of the acetabular cup without covering the whole cup	
3b	Increased uptake of FDG in the area of the femoral neck and in parts of the prosthesis-bone interface of the proximal stem	
3c	Pattern 3a and 3b	
4a	Increased uptake of FDG in the area of the femoral neck and in the whole prosthesis-bone interface of the acetabular cup	Loosening
4b	Increased uptake of FDG in the area of the femoral neck and in wide parts of the prosthesis-bone interface of the stem	
4c	Pattern 4a and 4b	
5	Uptake of FDG in the periprosthetic soft tissue	Infection

^{18}F-FDG: most publications since 2001 w/o CT

Hip: Sensitivity 85% / Specificity 90%

Knee: Sensitivity 85% / Specificity 98%

Reinartz et al., JBJS, 2005

NM in prosthetic infection
^{18}F-FDG-PET

FDG-PET in patients with painful hip and knee arthroplasty: technical breakthrough or just more of the same?

P. Reinartz, QJNM, 2009

…data indicate that PET is highly effective … Whether this holds true for PET-CT has yet to be proven…

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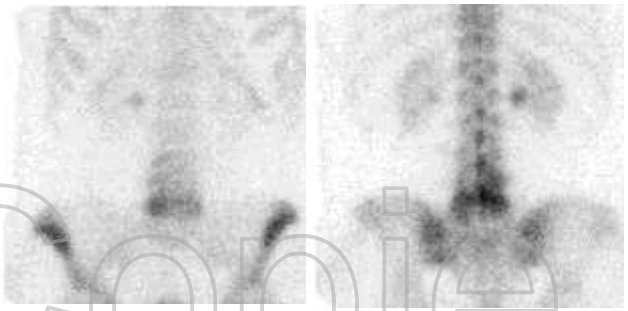
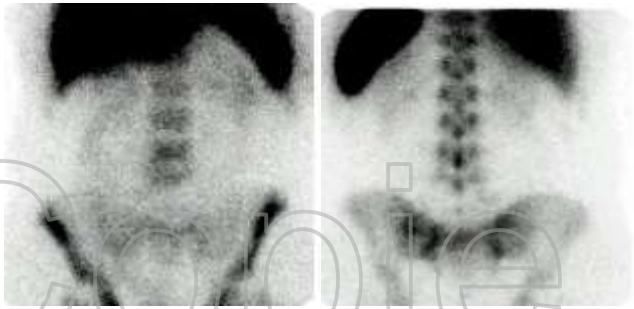
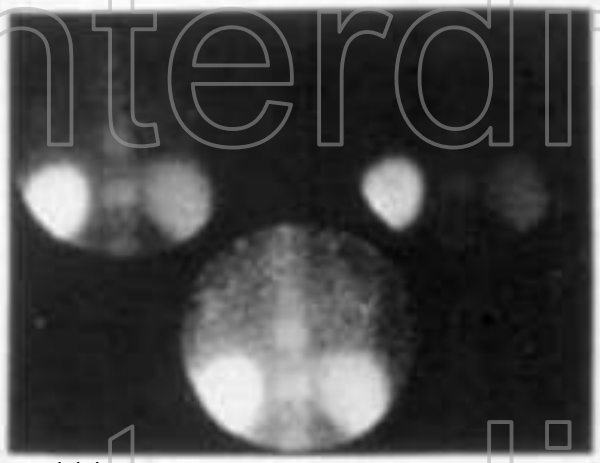
NM in vertebral osteomyelitis /(spondylo)discitis



^{99m}Tc-HDP scintigraphy



^{99m}Tc-HMPAO-WBC scintigraphy



^{111}In- WBC scintigraphy

NM in vertebral osteomyelitis/(spondylo)discitis

- Can involve the **disk alone** or both **the disk and adjacent vertebra(e)**
- **Haematogenous** or **post-injury** (surgery)

- **WBC scanning is inadequate** because of the vascular spasm that results in no migration of living leukocytes

Sensitivity -	**hyper: 39%**	hypo: 54%	**total: 93%**
Specificity -	hyper: 98%	**hypo: 32%**	**total: 50%**

- MRI is clearly more performant but limited due to access and metallic implants in postoperative cases

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NM in vertebral osteomyelitis/(spondylo)discitis

^{18}F-FDG PET

- Prospective, 57 patients with previous spinal surgery
- 15 with infection, no bacteriology in all cases

Sensitivity: 100%

Specificity: 81% overall

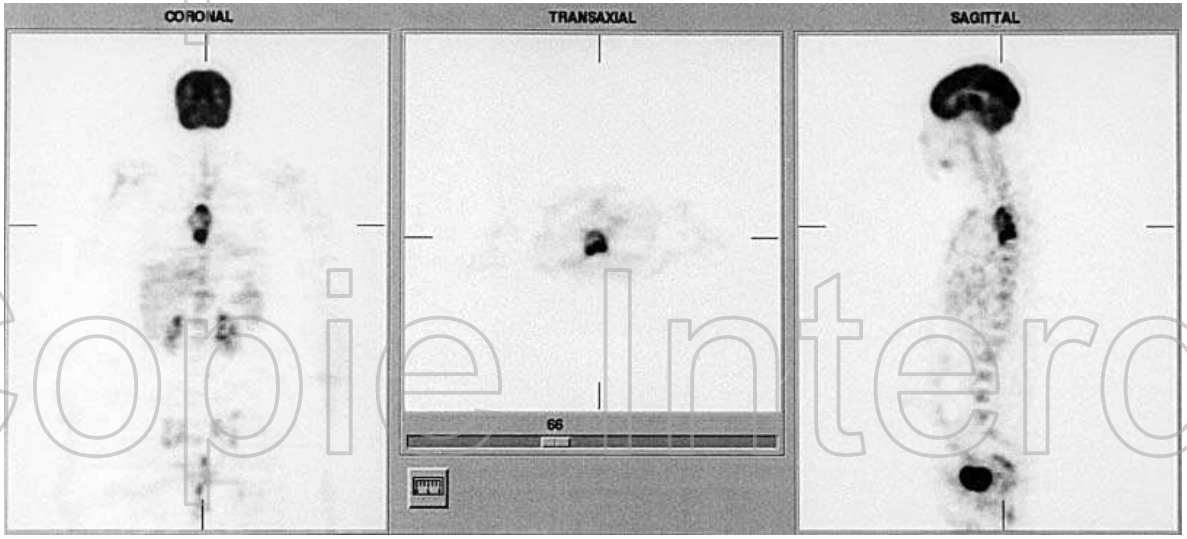
- No metallic implants (n=27): **2 FP** within 6 mo of surgery
- Metallic implants (n=30): **6 FP** overall

De Winter et al. Spine 2003,28:1314-19

NM in vertebral osteomyelitis/(spondylo)discitis

^{18}F-FDG PET

- Differential diagnosis of **compression fractures** is a difficult challenge
- Preliminary data suggested that SUV could discriminate with osteoporotic fracture
  SUV (spondylo): 7.5 (3.8) *vs* 1.4 (0.7) (osteoporotic)



Schmitz *et al.* (Osteoporosis Int 2002 and Eur J spine 2001)

NM in vertebral osteomyelitis/(spondylo)discitis

^{18}F-FDG PET

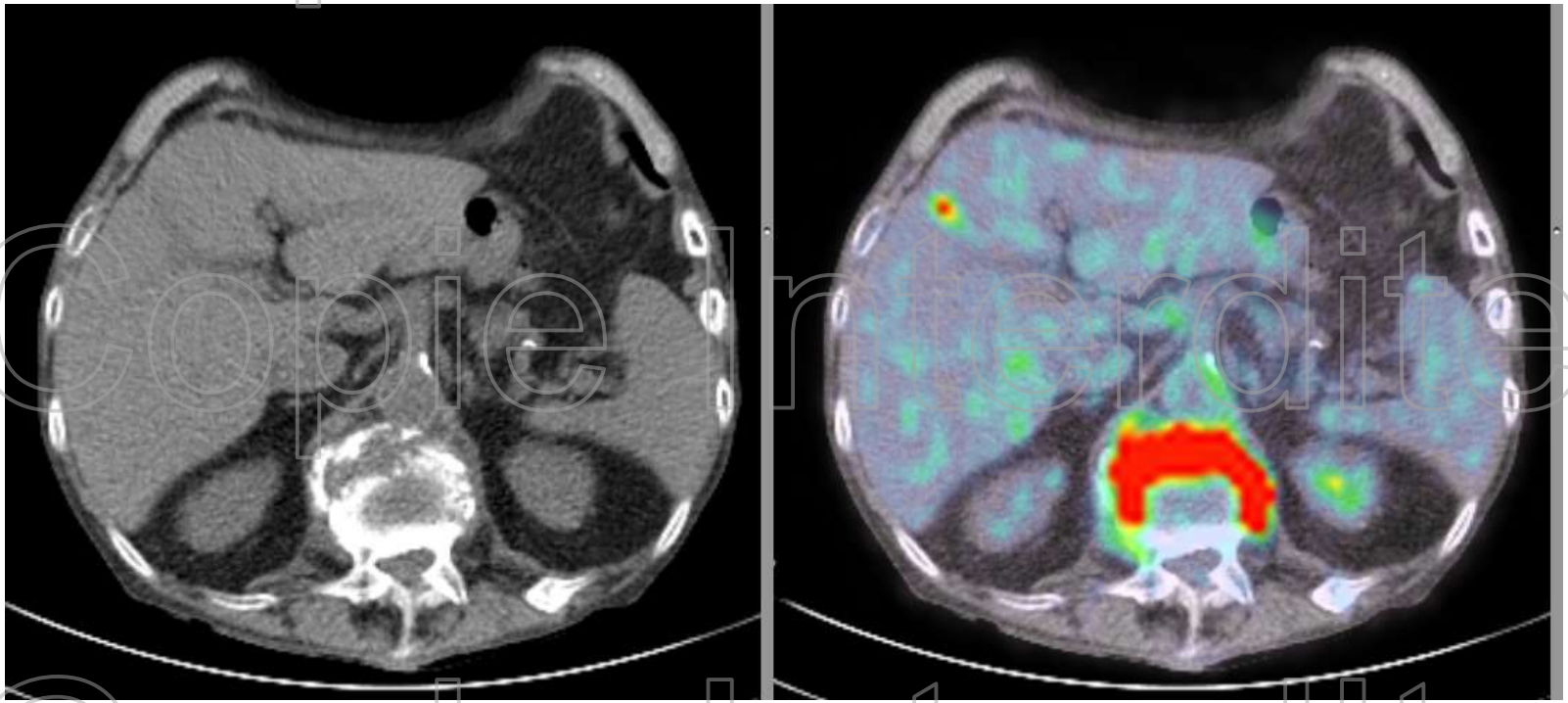
True Negative

True Positive

Stumpe, Am J Roentgenol, 2002, 179: 1151-7

NM in vertebral osteomyelitis/(spondylo)discitis

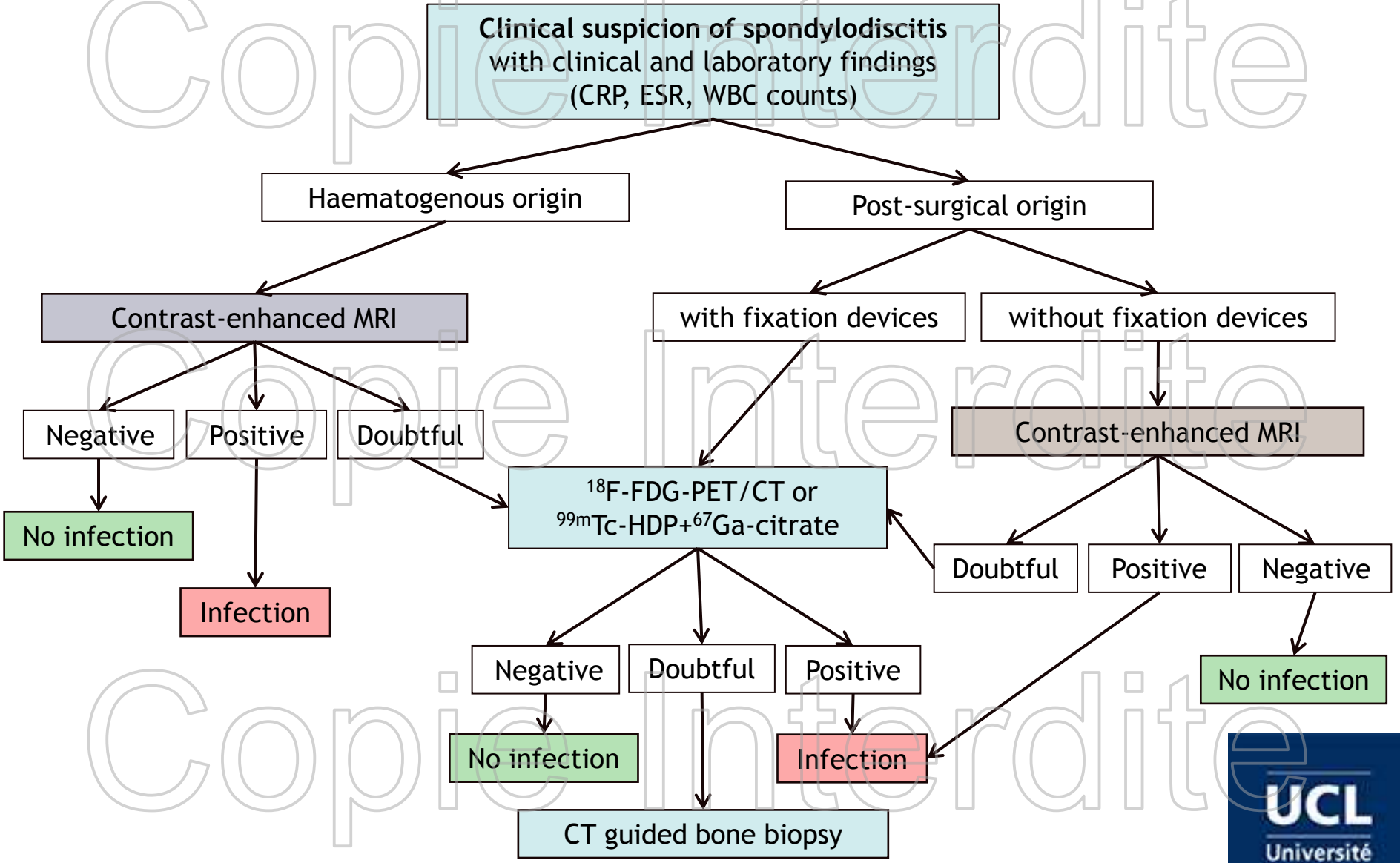
^{18}F-FDG PET



NM in vertebral osteomyelitis/(spondylo)discitis
^{18}F-FDG PET

- Limited information in the literature
- All go in the same (good) direction for FDG-PET
- One study in low back pain and patients with Modic type 1 signal (low T1/high T2), showed 100% sensitivity and 100% specificity (Ohtori, Spine 2010, 35:1599-603)

- **The evidence seems sufficient for second-line use and PET-CT can be recommended when MRI is not accessible/feasible**
- Also interesting in FUO / / CAVE SUV *vs* tumor



Jutte et al. Q J Nucl Mol Imaging 2014;58:2-19

NM in diabetic foot infection

NATURE REVIEWS | ENDOCRINOLOGY VOLUME 6 | JANUARY 2010 | 43

Management of osteomyelitis of the foot in diabetes mellitus

Fran Game

« Identifies MRI as superior to X-ray and CT, prior to biopsy, before deciding for surgical or conservative treatment of suspected OM in diabetic foot that may occur in ~20% of DM patients with ulcers and Charcot osteoarthropathy »

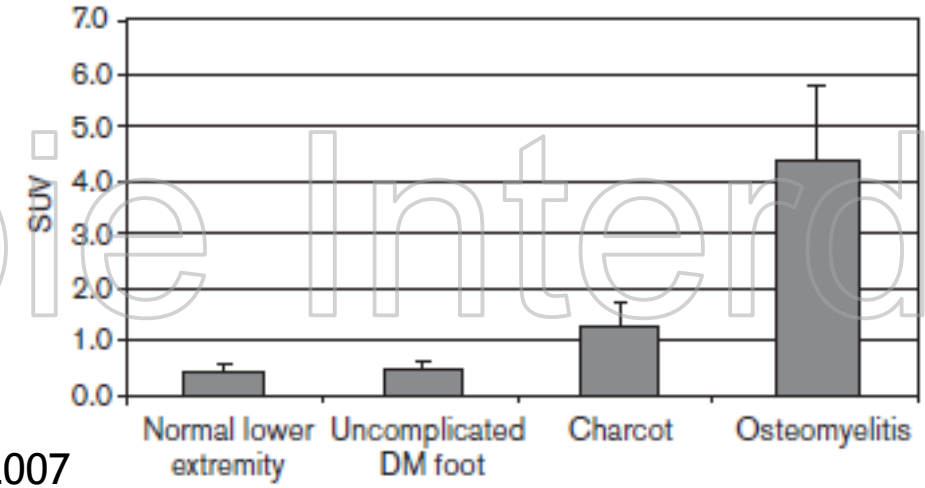
FDG PET-CT even not cited…

NM in diabetic foot infection

- Bone scan is very sensitive but nonspecific (*vs* Charcot!)
- WBC scanning is sensitive and specific but lacks anatomical resolution
- ^{18}F-FDG PET/CT is promising but data are conflictual (clearly helps with anatomic delineation, bone *vs* soft tissue infection)

NM in diabetic foot infection
^{18}F-FDG PET

Author	Year	Pts/sites	OM/STI	Sens.	Spec.	Acc.	comparator
Höfner	2004	16/39	0	–	0	–	
Keidar	2005	14/18	8/5	100	80	94	
Basu	2007	22	6/7	100	89	94	> MR
Schwegler	2007	20	7/–	29	92	70	< MR
Nawaz	2010	110	27/–	81	93	90	S>MR, Sp<MR
Familliari	2011	13	7/2	43	67	54	< ^{99m}Tc-WBC



Basu et al.,Nuc Med Comm, 2007

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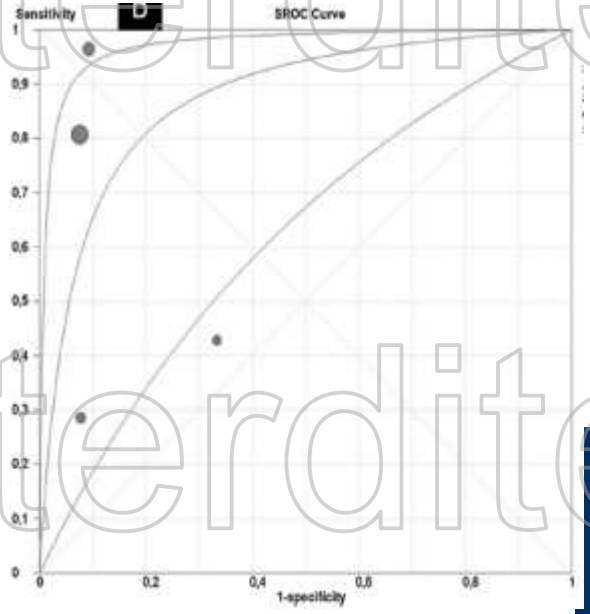
NM in diabetic foot infection
^{18}F-FDG PET : A meta-analysis (4/44 studies)

- Highly variable sensitivity — 29-100% (Pooled sensitivity: 74%)
- Variable specificity — 67-93% (Pooled specificity: 90%)

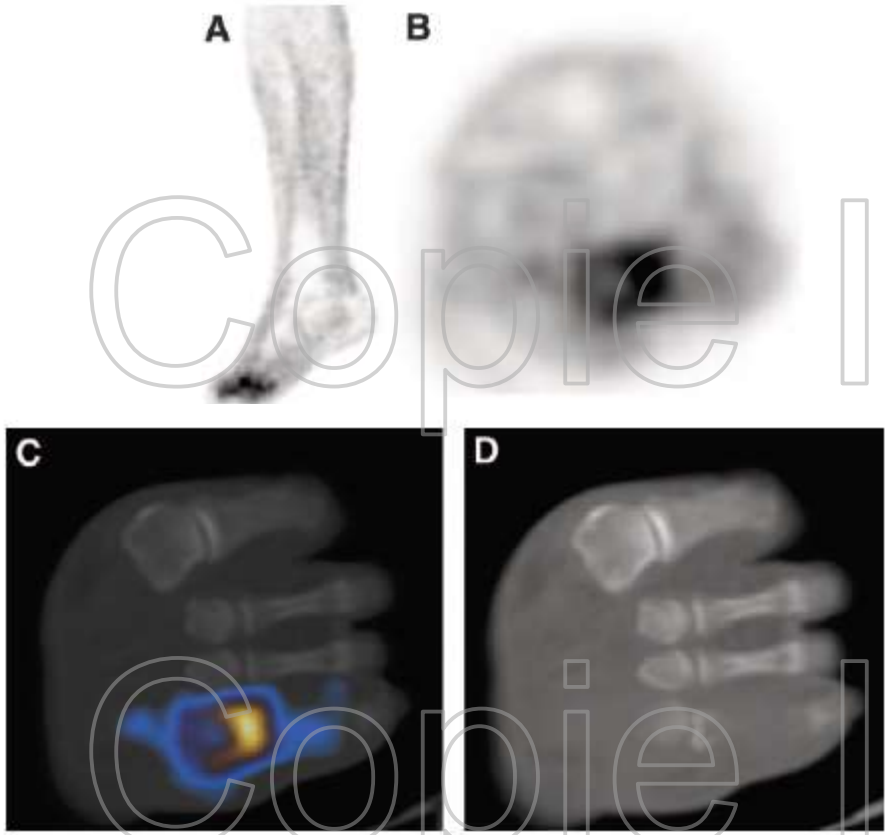
- Most (other) studies lack biopsy as a proof for biopsy

- Nawaz et al. (level 2) – best study
  - 106 patients
  - prospective
  - consecutive
  - 37 biopsies



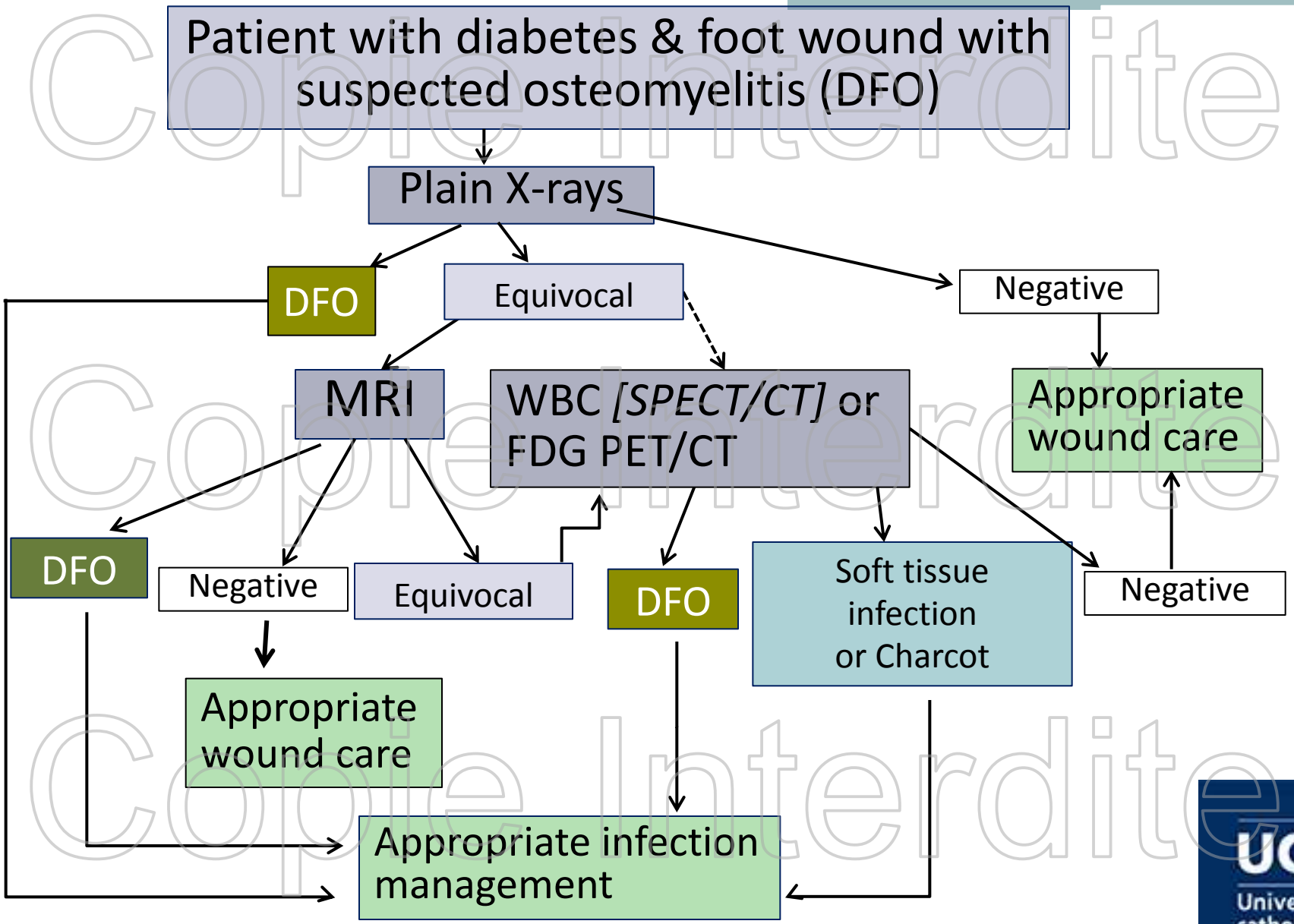
Treglia et al., The Foot, 2013

NM in diabetic foot infection
^{18}F-FDG PET



Keidar et al, JNM, 2005

Nawaz et al. Mol Imaging Biol, 2010



NM in musculoskeletal Infections
Summary on the role of ^{18}F-FDG PET

- **Acute OM** limited role (BS / WBC)
- **Chronic OM** WBC++ (FDG?)
- **Prostheses** WBC++ (FDG: **no**)
- **Vertebral OM** BS nonspecific / FDG++
- **Diabetic foot** WBC with BS ++ /FDG controversial

NM in musculoskeletal Infections
Perspectives of molecular imaging

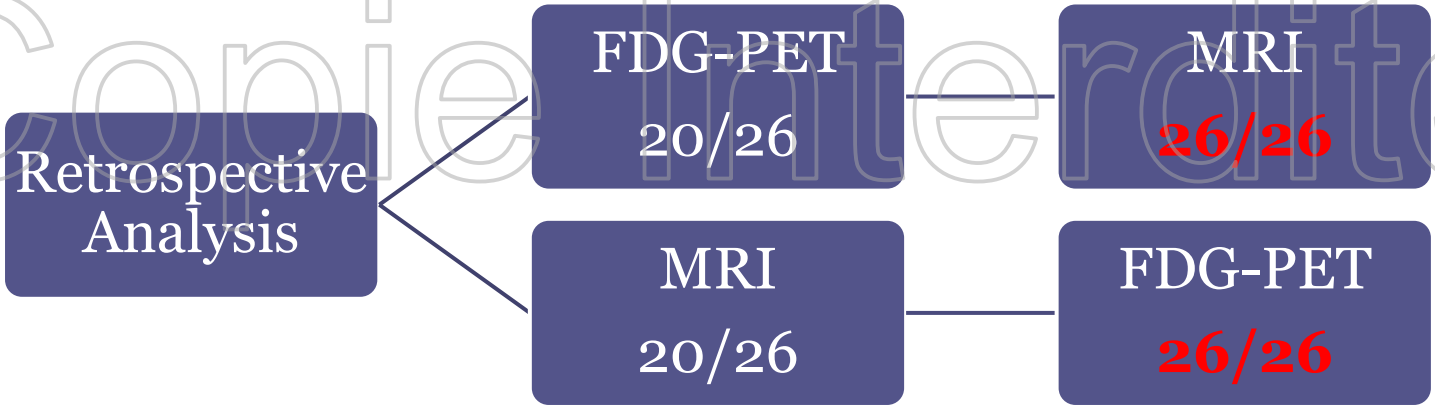
- ^{68}Ga-citrate? 18F-FDG-WBC??
- ^{18}F-FDG-PET/MRI
- Innovative tracers for infection (antibiotics, ^{18}F, ^{89}Zr)
- Large prospective trials with standardized protocols and diagnostic criteria and blinded review
- This is being started under the umbrella of EANM

NM in musculoskeletal Infections
Perspectives: ^{18}F-FDG-PET/MRI?

Patient with bacteraemia and lucent zone on X-Ray

Demirev et al., Skeletal Radiol, 2014

NM in musculoskeletal Infections
Perspectives: ^{18}F-FDG-PET/MRI?



Demirev et al., Skeletal Radiol, 2014