A New Role of Nuclear Medicine in Inflammation Imaging

Bone and Joint Inflammation and Infections

Napoleone Prandini
Hospital and University of Ferrara, Italy
n.prandini@ospfe.it
Review paper

Nuclear medicine imaging of bone infections
Napoleone Prandini\textsuperscript{a}, Elena Lazzeri\textsuperscript{b}, Brunella Rossi\textsuperscript{c}, Paola Erba\textsuperscript{b}, Maria Gemma Parisella\textsuperscript{d} and Alberto Signore\textsuperscript{d}

Table 3 Results of the meta-analysis of data published between 1984 and 2004 regarding the infections of peripheric bone and of prosthetic joint implants

<table>
<thead>
<tr>
<th>Technique</th>
<th>Lesions</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Lesions</th>
<th>Accuracy</th>
<th>Lesions</th>
<th>PPV</th>
<th>NPV</th>
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<tr>
<td>$^{67}$Ga</td>
<td>569</td>
<td>70.1</td>
<td>81.8</td>
<td>396</td>
<td>78.2</td>
<td>343</td>
<td>50.0</td>
<td>89.5</td>
</tr>
<tr>
<td>$^{111}$In-WBCs</td>
<td>2147</td>
<td>82.8</td>
<td>83.8</td>
<td>1327</td>
<td>84.6</td>
<td>845</td>
<td>60.9</td>
<td>92.4</td>
</tr>
<tr>
<td>$^{99m}$Tc-WBCs</td>
<td>1453</td>
<td>89.0</td>
<td>89.1</td>
<td>960</td>
<td>89.1</td>
<td>768</td>
<td>75.1</td>
<td>91.6</td>
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<tr>
<td>$^{99m}$Tc-BS</td>
<td>1527</td>
<td>85.4</td>
<td>75.2</td>
<td>866</td>
<td>75.5</td>
<td>403</td>
<td>62.9</td>
<td>95.8</td>
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<tr>
<td>$^{99m}$MoAb BW 250/183</td>
<td>258</td>
<td>81.7</td>
<td>80.1</td>
<td>365</td>
<td>83.2</td>
<td>159</td>
<td>79.9</td>
<td>88.5</td>
</tr>
<tr>
<td>$^{99m}$MoAb MN3</td>
<td>129</td>
<td>92</td>
<td>86.0</td>
<td>106</td>
<td>86</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>$^{99m}$Tc-HIG and $^{111}$In-HIG</td>
<td>537</td>
<td>88.2</td>
<td>78.7</td>
<td>288</td>
<td>86.0</td>
<td>323</td>
<td>72.7</td>
<td>96.1</td>
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<tr>
<td>$^{18}$F-FDG PET</td>
<td>413</td>
<td>94.1</td>
<td>87.3</td>
<td>273</td>
<td>91.9</td>
<td>294</td>
<td>86.9</td>
<td>94.2</td>
</tr>
<tr>
<td>$^{99m}$Tc-nanocolloid</td>
<td>154</td>
<td>89</td>
<td>80.5</td>
<td>97</td>
<td>80.7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>MRI</td>
<td>95</td>
<td>88.2</td>
<td></td>
<td>54</td>
<td>88.7</td>
<td>19</td>
<td>69.0</td>
<td>99.5</td>
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<tr>
<td>Aspiration</td>
<td>786</td>
<td>50.7</td>
<td></td>
<td>663</td>
<td>88.4</td>
<td>614</td>
<td>91.3</td>
<td>99.5</td>
</tr>
<tr>
<td>Total</td>
<td>8180</td>
<td></td>
<td>93.9</td>
<td>5207</td>
<td></td>
<td>3907</td>
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</table>

WBC=labelled white blood cells and granulocytes; BS=bone scan (multiphase); MoAb=monoclonal antibodies against granulocytes antigens; HIG=polyclonal human immune globulin; MRI=Magnetic resonance imaging; CT=computed tomography; Lesions=number of lesions for which the data of sensitivity, specificity, accuracy, PPV and NPV were available. PPV=positive predictive value; NPV=negative predictive value; NA=Not available data. All parameters have been weighted for the number of lesions available in each study (sometimes more than one for each patient). The numbers in bold refer to the best performing technique.

Peculiarities of bone inflammation and infection

- Distribution of bone marrow
- Structure of bone
- Bone destruction
- Ischaemia, necrosis and sequestra
- Peripheric reactive hyperaemia of the sequestra
- Periosteal apposition and new bone formation
- OM requires often a surgical approach....

Lew DP & Waldvogel FA, Lancet 2004
## Bone marrow imaging

<table>
<thead>
<tr>
<th>Radiotracer</th>
<th>Principal Photon Energy (keV)</th>
<th>Physical Half-Life</th>
<th>Localization</th>
<th>Liver/Spleen Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{99m}$Tc-sulfur colloid</td>
<td>140</td>
<td>6 h</td>
<td>RES</td>
<td>+++ + + +</td>
</tr>
<tr>
<td>$^{99m}$Tc-nanocolloid</td>
<td>140</td>
<td>6 h</td>
<td>RES</td>
<td>+ +</td>
</tr>
<tr>
<td>$^{52}$Fe</td>
<td>165, 511</td>
<td>8.2 h</td>
<td>Erythropoietic</td>
<td>No</td>
</tr>
<tr>
<td>$^{111}$In-chloride</td>
<td>174, 247</td>
<td>2.8 d</td>
<td>Unclear</td>
<td>+ +</td>
</tr>
<tr>
<td>$^{111}$In-WBC</td>
<td>174, 247</td>
<td>2.8 d</td>
<td>Probably RES</td>
<td>+ +</td>
</tr>
<tr>
<td>$^{99m}$Tc-WBC</td>
<td>140</td>
<td>6 h</td>
<td>Probably RES</td>
<td>+ +</td>
</tr>
<tr>
<td>$^{99m}$Tc-NSAb</td>
<td>140</td>
<td>6 h</td>
<td>Granulopoietic</td>
<td>+</td>
</tr>
<tr>
<td>$^{18}$F-FDG</td>
<td>511</td>
<td>2 h</td>
<td>Active elements</td>
<td>+</td>
</tr>
</tbody>
</table>

## Infection and inflammation imaging

Extent of red bone marrow with age

Birth 7 Y 12 Y 12-14 Y 15 Y 16 Y 18 Y 19-20 Y 25 Y

JD Blebea et Al: Semin Nucl Med 2007
Bio-distribution of labeled leukocytes (in the same patient)

$^{99m}$Tc-nanocolloids

$^{99m}$Tc-HMPAO-WBC
Interpretation criteria: $^{111}$In-oxime WBC

Both $^{99m}$Tc-sulfur colloid and $^{111}$In-oxime labeled WBC accumulate in bone marrow but only WBC accumulate in infection.

Match: Aseptically Loosened Rt. THR

Mismatch: Infected Rt. THR

By the courtesy of CJ Palestro

Palestro CJ., J Nucl Med. 1990
Interpretation criteria for $^{99m}$Tc-HMPAO WBCs

The images obtained 1, 4 and 20 h p.i. injection give the opportunity to compare the praecox and constant distribution of WBCs's in bone marrow (empty arrows) in comparison with the increasing uptake in infections (full arrow)
Questions 1

Is NM imaging useful in suspected joint infection?

• Can NM distinguish septic from non-septic arthritis?
• Can NM imaging distinguish aseptic loosening from infection?
• Does time after surgery and antibiotic therapy affect NM imaging results?
• Can it be used to monitor response to therapy?
Can NM imaging distinguish aseptic loosening from infection?

$^{99}$mTc-HMPAO-WBC

The aspect of WBC uptake modifies with time in septic arthritis

Persistent increased activity of bone marrow in post traumatic arthritis
Can NM imaging distinguish aseptic loosening from infection?

\[ {^{99m}}\text{Tc-HMPAO-WBC} \]

The aspect of WBC uptake modifies with time in left hip prosthesis infection

Physiological expansion of bone marrow after right prosthesis implant
Can NM imaging distinguish aseptic loosening from infection?

$^{18}$F-FDG PET

PET cannot distinguish between aseptic and septic loosening of prostheses

K-St Delank: BMC Musculoskeletal Disorders 2006, 7:20
Can PET imaging distinguish aseptic loosening from infection?

The role of FDG-PET in distinguishing between septic and aseptic loosening in hip prosthesis: a review of literature

C. Zoccali • G. Teori • N. Salducca

Table 2  FDG-PET results

<table>
<thead>
<tr>
<th>Authors</th>
<th>PT</th>
<th>THR</th>
<th>SE</th>
<th>SP</th>
<th>AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhuang et al. [16]</td>
<td>62</td>
<td>38</td>
<td>90.0%</td>
<td>89.3%</td>
<td>89.5%</td>
</tr>
<tr>
<td>Chacko et al. [2]</td>
<td>32</td>
<td>41</td>
<td>91.7%</td>
<td>96.6%</td>
<td>95.1%</td>
</tr>
<tr>
<td>Vanquickenborne et al. [14]</td>
<td>17</td>
<td>17</td>
<td>87.5%</td>
<td>77.8%</td>
<td>82.3%</td>
</tr>
<tr>
<td>Stumpe et al. [12]</td>
<td>35</td>
<td>35</td>
<td>33%</td>
<td>81%</td>
<td>68.6%</td>
</tr>
<tr>
<td>Reinartz et al. [11]</td>
<td>63</td>
<td>92</td>
<td>94.0%</td>
<td>95.0%</td>
<td>95.0%</td>
</tr>
</tbody>
</table>

The results of $^{18}$F-FDG PET in distinguishing between aseptic and septic loosening are widely variable in the published papers.
Does time after surgery affect NM imaging results?

$^{99m}$Tc-HMPAO-WBC

Increased perfusion at 1 h images without increasing with time 30 days after right (upper) and left (lower) knee prosthesis implant
Does antibiotic therapy affect NM imaging results?

$^{99m}$Tc-HMPAO-WBC

Increased perfusion in all images without significant increasing or concentration with time of labelled WBC in patient during Ab therapy.
Can NM be used to monitor response to therapy?

$^{99m}$Tc-HMPAO-WBC

30/4/2009: infection of right femur and left leg in polytrauma
Can NM be used to monitor response to therapy?

12/12/2009 after surgical debridement and antibiotic treatment: no more signs of infection
Can it be used to monitor response to therapy?

\(^{18}\text{F-FDG PET}\)

Infectious Spondylodiscitis

By courtesy of A. Versari. Reggio Emilia
Can it be used to monitor response to therapy?

\(^{18}\text{F-FDG PET}\)

Infectious Spondylodiscitis: response to therapy evaluation

By courtesy of A. Versari. Reggio Emilia
Questions 2

NM imaging in Osteomyelitis

• Is NM imaging helpful to correctly diagnose OM in early and difficult cases?
• Can NM imaging distinguish soft tissue from bone infection?
• Can it be used to diagnose chronic infection?
• Does insulin resistance affect the performance of PET-CT in patients with DM?
Is NM imaging helpful to correctly diagnose early OM?

4 y old child with haematogenous OM of right femur (pin hole)
Is NM imaging helpful to correctly diagnose difficult cases?

$^{99m}$Tc-MDP SPECT CT

Sandwich pattern of spondilodiskitis

By courtesy of F. Psayca Colombes, France
Is NM imaging helpful to correctly diagnose difficult cases?

Bone SPECT/CT in spondilodiskitis

By courtesy of F. Psayca
Colombes, France
Is NM imaging helpful to correctly diagnose difficult cases?

Secondary infective spondilodiskitis of multiple lumbar vertebra: cold area can be found with both gallium and PET imaging.
Is NM imaging helpful to correctly diagnose difficult cases?

$^{99m}$Tc -MDP

$^{99m}$Tc –HMPAO WBC of the same patient: paravertebral abscess
Is NM imaging helpful to correctly diagnose difficult cases?

MRI in vertebral stabilization

$^{67}$Gallium SPECT/CT in active diskitis
Can NM imaging distinguish soft tissue from bone infection?

\[ ^{18}\text{F-FDG PET} \]

\[ ^{18}\text{F-FDG PET can distinguish osteomyelitis from soft tissue infection} \]

Can NM imaging distinguish soft tissue from bone infection?

$^{99m}$Tc-HMPAO-WBC

$^{99m}$Tc HMPAO-WBC SPECT/CT: localisation of bone or soft tissues infection in diabetic foot
Can NM imaging distinguish soft tissue from bone infection?

$^{99m}$Tc-HMPAO-WBC

SPECT/CT: septic arthritis without involvement of bone
Is NM imaging useful in the diagnosis of subacute and chronic infection?

$^{99m}$Tc-HMPAO-WBC

SPECT/CT: chronic infection of left thybia (staph aureus)
Is NM imaging useful in the diagnosis of subacute and chronic infection?

$^{18}$F-FDG PET

PET-FDG and OM in open fracture

By courtesy of prof. J.N. Talbot (Paris)
Is NM imaging useful in the diagnosis of subacute and chronic infection?

$^{18}$F-FDG PET

FDG in spinal tuberculosis

De Winter, Spine 2003

Hybrid systems: PET/CT and SPECT/CT

- Hardware fusion of PET and SPECT functional images with CT images produces
  - greater accuracy VS PET and SPECT alone;
  - better anatomical localization;
  - additional diagnostic informations provided by CT scans
  - more sensibility (improves the identification of small and deep lesions that are not discriminating from other structures in planar imaging or in PET with gadolinium attenuation)
  - more specificity (better discrimination of close structures)
  - more definition of extension and activity of the pathologic uptakes
# SPECT/CT Better localization of OM

## TABLE 1
Results of Labeled Leukocyte Scintigraphy (Planar + SPECT) and SPECT/CT: Clinical and Scintigraphic Data on 10 Patients in Whom Osteomyelitis Was Suspected and Scan Findings Were Positive (Group 1)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Suspected infection</th>
<th>Planar + SPECT findings</th>
<th>SPECT/CT findings</th>
<th>SPECT/CT contribution</th>
<th>Final diagnosis</th>
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<tbody>
<tr>
<td>1</td>
<td>OM</td>
<td>Infection in thigh</td>
<td>STI in thigh</td>
<td>Excluded OM</td>
<td>STI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(suspected femoral OM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2*</td>
<td>OM</td>
<td>Infection in thigh</td>
<td>OM and STI in thigh</td>
<td>Defined extent of STI and OM</td>
<td>STI and OM</td>
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<tr>
<td></td>
<td></td>
<td>(suspected femoral OM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>OM</td>
<td>Infection in calf</td>
<td>STI in calf</td>
<td>Excluded OM</td>
<td>STI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(suspected tibial OM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>OM</td>
<td>Infection in thigh</td>
<td>STI in thigh</td>
<td>Excluded OM</td>
<td>STI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(suspected femoral OM)</td>
<td></td>
<td></td>
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<tr>
<td>5*</td>
<td>OM</td>
<td>Infection in calf</td>
<td>OM and STI in calf</td>
<td>Defined extent of STI and OM</td>
<td>STI and OM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(suspected tibial OM)</td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td>Posttraumatic OM</td>
<td>Infection in calf</td>
<td>OM corresponding to altered bone</td>
<td>Defined OM</td>
<td>Posttraumatic OM</td>
</tr>
<tr>
<td></td>
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<td>(suspected tibial OM)</td>
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<td>7</td>
<td>Posttraumatic OM</td>
<td>Infection in thigh</td>
<td>OM corresponding to altered bone</td>
<td>Defined OM</td>
<td>Posttraumatic OM</td>
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<td>(suspected femoral OM)</td>
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<tr>
<td>8</td>
<td>Posttraumatic OM</td>
<td>Infection in right shoulder</td>
<td>OM of bone graft (humeral head)</td>
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<td>Posttraumatic OM</td>
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<td>9</td>
<td>Posttraumatic OM</td>
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<td>10</td>
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<tr>
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<td>(suspected humeral OM)</td>
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</table>

*Patient with 2 sites of infection.
OM = osteomyelitis; STI = soft-tissue infection.
Luca Filippi and Orazio Schillaci *J Nucl Med* 2006; 47:1908–1913
Increased accuracy of SPECT/CT in the study of bone infections

<table>
<thead>
<tr>
<th>Results</th>
<th>Patients</th>
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<td>Useful</td>
<td>23</td>
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<td>Determinant</td>
<td>7</td>
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<tr>
<td>Changing in diagnosis</td>
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<tr>
<td>Indifferent</td>
<td>6</td>
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<tr>
<td>Improved accuracy</td>
<td>32/38</td>
</tr>
</tbody>
</table>

N. Prandini SNM, 2009
SPECT/CT: better localisation of obturator abscess complicating an infection of a right hip prosthesis

$^{99m}\text{Tc-HMPAO-WBC}$
SPECT/CT: focal uptake of $^{67}$Gallium in the left side of L4 - L5 intervertebral disc: spondylodiscitis
Planar: cold area  SPECT/CT: cold in hot (diskitis)
PET/CT with $^{68}$Ga-citrate

MRI

Spondilodiskitis at diagnosis

$^{68}$GA CITRATE

PET/TC

Acute osteomyelitis of left thybia

By courtesy of C. Nanni SNM 2010 n 368
Biodistribution of $^{67}$Ga (scan) vs $^{68}$Ga (PET)

- 67-GA CITRATE
  1. NO BLOOD POOL ACTIVITY
  2. HIGH HEPATIC ACTIVITY
  3. MODERATE BONE MARROW ACTIVITY

- 68-GA CITRATE
  1. HIGH BLOOD POOL ACTIVITY
  2. HIGH HEPATIC ACTIVITY
  3. MILD BONE MARROW ACTIVITY

By courtesy of C. Nanni SNM 2010 n 368
Assessment of Disease Activity in Rheumatoid Arthritis with $^{18}$F-FDG PET

Catherine Beckers, MD$^1$; Clio Ribbens, MD, PhD$^2$; Béatrice André, MD$^2$; Stefaan Marcelis, MD$^3$; Olivier Kaye, MD, PhD$^2$; Luc Mathy, MD$^2$; Marie-Joëlle Kaiser, MD$^2$; Roland Hustinx, MD, PhD$^1$; Jacqueline Foidart, MD, PhD$^1$; and Michel G. Malaise, MD, PhD$^2$

$^1$Division of Nuclear Medicine, Center for Cellular and Molecular Therapy, University Hospital of Liège, Liège, Belgium; $^2$Department of Rheumatology, Center for Cellular and Molecular Therapy, University Hospital of Liège, Liège, Belgium; and $^3$Department of Bone and Joint Radiology, University Hospital of Liège, Liège, Belgium

Conclusion: $^{18}$F-FDG PET is a unique imaging technique that can assess the metabolic activity of synovitis and measure the disease activity in RA.

Key Words: $^{18}$F-FDG PET; rheumatoid arthritis; disease activity

J Nucl Med 2004; 45:956–964

FIGURE 1. $^{18}$F-FDG PET images of healthy control subject (A and B) and RA patient with active disease (C and D). (A) 3D projection image of normal tracer distribution in knee. (B) Normal distribution in hand and wrist. (C) Rheumatoid knee. (D) Rheumatoid hand and wrist.
Take home messages

• If we are looking for some inflammation or infection or if we want exclude it, we must start with a $^{18}$F FDG PET/CT as a first choice

• If we need to distinguish infection from inflammation we must use labeled leukocytes

• If we want evaluate the response to therapy we can use both labelled leukocytes or $^{18}$F-FDG PET (and 67 or 68-Gallium)

• Hybrid systems (PET/CT and SPECT/CT) add a great value in accuracy for both PET and SPECT imaging of bone infection

n.prandini@ospfe.it