Nuclear Medicine & Diabetic Foot Infections

Christopher J. Palestro, M.D.
Professor & Chief
Nuclear Medicine & Molecular Imaging
North Shore Long Island Jewish Health System
Manhasset & New Hyde Park, New York
Diabetes Mellitus

Total prevalence in USA: ~ 23-24 million (7% of population)
  17 million diagnosed
  > 6 million undiagnosed

60%-70% of diabetics have mild to severe nervous system damage
  30% of diabetics ≥ 40 yrs. old have impaired sensation in the feet

Severe forms of diabetic neuropathy major contributing cause of LE amputations
  In 2002, 60% (~ 82,000) of all nontraumatic lower limb amputations performed on diabetics
The Foot

26 bones
  7 tarsals
  5 metatarsals
  14 phalanges
Numerous joint articulations
2 dorsal muscles
4 layers of plantar muscles
Intricate network of vessels & nerves
The Foot

• Hind foot
  Proximal row of tarsal bones (talus, calcaneus, & navicular)
  Distal tibia
  Distal fibula

• Mid foot
  Distal row of tarsal bones (cuboid + 3 cuneiform bones)

• Forefoot
  5 metatarsals
  14 phalanges
The Foot

HIND FOOT

MID FOOT

FORE FOOT

HINDFOOT  MIDFOOT  FOREFOOT

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The Diabetic Forefoot

Pedal trophic (mal perforans) ulcer
Most common complication
Usually underlies distal metatarsal/phalanx
Multifactorial etiology
  Unperceived, repeated injury & altered
  weight bearing $\rightarrow$ bony deformity,
callus formation, skin fissuring &
cracking $\rightarrow$ frank ulcer formation
The Diabetic Forefoot

Pedal ulcers
Directly underlie > 90% of osteomyelitis cases
Present in most infection-related amputations
The Diabetic Mid/Hind Foot

Neuropathic (Charcot) joint
Most common complication
35% of diabetics develop neuropathy
5% develop neuropathic joint
5th – 7th decades of life
≥ 15 year h/o diabetes
Neuropathic Joint

Pathophysiology
Diminished pain sensation
Repetitive stress on an insensitive foot
→ bone/joint disruption, varus/valgus deformities, joint instability, degeneration & destruction
Endless cycle of injury, destruction, incomplete healing, partial repair
→ grossly deformed foot
Neuropathic Joint

• Clinical Presentation
  Swelling (often massive)
  Crepitis ($2^0$ to bony destruction)
  Palpable loose bodies
  Large osteophytes
  Synovial effusions
    Noninflammatory/hemorrhagic
    Predominantly mononuclear cells
  Often painless
  Ulcers over hypoesthetic
  weight bearing areas
Diabetic Pedal Osteomyelitis*

Patients frequently present without systemic illness and lack signs and symptoms (except the ulcer). Imaging studies are often used to confirm the diagnosis.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N= (%)</td>
<td>N= (%)</td>
<td>N= (%)</td>
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<tr>
<td>Clinical judgment</td>
<td>9/28 (32)</td>
<td>13/13 (100)</td>
<td>22/41 (54)</td>
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<tr>
<td>Ulcer area &gt;2cm</td>
<td>15/27 (56)</td>
<td>12/13 (92)</td>
<td>27/40 (68)</td>
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<tr>
<td>Ulcer inflammation</td>
<td>10/28 (36)</td>
<td>10/13 (77)</td>
<td>20/41 (49)</td>
</tr>
<tr>
<td>Bone exposure</td>
<td>9/28 (32)</td>
<td>13/13 (100)</td>
<td>22/41 (54)</td>
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<tr>
<td>ESR &gt;70mm/hr</td>
<td>5/18 (28)</td>
<td>10/10 (100)</td>
<td>15/28 (54)</td>
</tr>
<tr>
<td>noninflamed ulcers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 100 mm/hr all ulcers</td>
<td>6/26 (23)</td>
<td>13/13 (100)</td>
<td>19/39 (49)</td>
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</tbody>
</table>

Diabetic Pedal Osteomyelitis

Morphologic imaging
- X-ray
- CT
- MR

Functional imaging
- Bone scintigraphy
- Gallium scintigraphy
- Labeled leukocyte imaging
  - $^{111}$In-oxine
  - $^{99m}$Tc-exametazime
  - $^{18}$F-FDG
3 Phase Bone Scan in Diabetic Foot Infections

Osteomyelitis Rt. Great Toe
3 Phase Bone Scan in Diabetic Foot Infections

Reactive Bone Rt. Great Toe

Flow          Blood Pool          Bone

Osteomyelitis Rt. Great Toe
3 Phase Bone Scan in Diabetic Foot Infections

Neuropathic Joint

Flow  Blood pool  Bone
3 Phase Bone Scan in Diabetic Foot Infections

Bilateral Neuropathic Joints

Flow  Blood pool  Bone
## Bone Scintigraphy

<table>
<thead>
<tr>
<th>Series</th>
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<td>Seldin JNM 1985</td>
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<tr>
<td>Maurer Radiology 1986</td>
<td>13</td>
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<td>Shults Am J Surg 1989</td>
<td>25</td>
<td>67%</td>
<td>43%</td>
</tr>
<tr>
<td>Keenan Arch Int Med 1989</td>
<td>77</td>
<td>100%</td>
<td>38%</td>
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<tr>
<td>Larcos AJR 1991</td>
<td>51</td>
<td>93%</td>
<td>43%</td>
</tr>
<tr>
<td>Newman JAMA 1991</td>
<td>41</td>
<td>69%</td>
<td>39%</td>
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<tr>
<td>Harvey JFAS 1997*</td>
<td>31</td>
<td>91%</td>
<td>40%</td>
</tr>
<tr>
<td>Blume JFAS 1997*</td>
<td>27</td>
<td>75%</td>
<td>29%</td>
</tr>
<tr>
<td>Palestro JFAS 2003*</td>
<td>25</td>
<td>90%</td>
<td>27%</td>
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</tbody>
</table>
Labeled Leukocyte Imaging in Diabetic Foot Infections

Right Great Toe Osteomyelitis

Dorsal

Plantar
Labeled Leukocyte Imaging in Diabetic Foot Infections

Labeled leukocytes *do* accumulate in the uninfected neuropathic joint. Activity on leukocyte images *cannot* automatically be equated with infection.
Labeled Leukocyte Imaging in Diabetic Foot Infections

- Labeled leukocyte uptake in uninfecte
  neuropathic joint attributed to:

  Inflammation
  Fracture
  Reparative processes
  Bone marrow
Neuropathic Joint
Hematopoietically Active Marrow

• ? Part of the inflammatory process
• ? Fracture repair
cartilage formation → blood vessel proliferation → marrow precursors → bone & bone marrow
Neuropathic Joint
Leukocyte/Marrow Imaging*

17 patients (13 women, 4 men)
20 sites of labeled leukocyte accumulation in mid/hind foot
  Unilateral in 14 patients
  Bilateral in 3 patients
Radiographic evidence of neuropathic joint in all 20 sites
Osteomyelitis in 4/20 sites

*Palestro et al., JNM 1998
# Neuropathic Joint Leukocyte/Marrow Imaging*

(n=20)

<table>
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<tr>
<th></th>
<th>WBC/Marrow (+)</th>
<th>WBC/Marrow (-)</th>
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</thead>
<tbody>
<tr>
<td>Osteomyelitis (+)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Osteomyelitis (-)</td>
<td>1</td>
<td>16</td>
</tr>
</tbody>
</table>

sensitivity: 3/3; specificity: 16/17; accuracy: 19/20 (0.95)

*Palestro et al., JNM 1998*
Leukocyte/Marrow Imaging

Neuropathic Joint

111In-WBC  99mTc-SC
Leukocyte/Marrow Imaging

Neuropathic Joint + Osteomyelitis
$^{111}$InWBC or $^{99m}$Tc-WBC?
## $^{99m}$TcWBC vs. $^{111}$InWBC

<table>
<thead>
<tr>
<th></th>
<th>$^{99m}$Tc-WBC</th>
<th>$^{111}$In-WBC</th>
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<tbody>
<tr>
<td>Resolution</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Label stability</td>
<td>++</td>
<td>++++</td>
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<tr>
<td>Delayed imaging</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Dual isotope imaging</td>
<td>+</td>
<td>++++</td>
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<tr>
<td>SPECT</td>
<td>++++</td>
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*Slides are not to be reproduced without permission of author.*
### Table: 111In-WBC Scintigraphy

<table>
<thead>
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<th>Series</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
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<td>78%</td>
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<tr>
<td>Larcos</td>
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<td>79%</td>
<td>78%</td>
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<tr>
<td>AJR 1991</td>
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<tr>
<td>Newman</td>
<td>41</td>
<td>89%</td>
<td>69%</td>
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<tr>
<td>JAMA 1991</td>
<td></td>
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</tr>
<tr>
<td>Palestro</td>
<td>25</td>
<td>80%</td>
<td>67%</td>
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*Ankle Surg 2003*
### 99mTc-WBC Scintigraphy

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<td>Johnson</td>
<td>22</td>
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<td>Foot Ankle Int 1996</td>
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<tr>
<td>Harvey</td>
<td>52</td>
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<tr>
<td>J Foot &amp; Ankle Surg 1997</td>
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<td>Blume</td>
<td>27</td>
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<td>86%</td>
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<td>J Foot &amp; Ankle Surg 1997</td>
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<td></td>
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<td>Devillers</td>
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<tr>
<td>Love</td>
<td>14</td>
<td>80%</td>
<td>89%</td>
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<td>EANM 2008</td>
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### $^{111}$In-WBC vs $^{99m}$Tc-WBC

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<td>$^{99m}$Tc-WBC</td>
<td>14</td>
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<td>100%</td>
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<td>(4 hrs)</td>
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<td>$^{99m}$Tc-WBC</td>
<td>14</td>
<td>80%</td>
<td>100%</td>
<td>93%</td>
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<tr>
<td>(24 hrs)</td>
<td></td>
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<tr>
<td>$^{99m}$Tc-WBC</td>
<td>14</td>
<td>40%</td>
<td>100%</td>
<td>79%</td>
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<tr>
<td>(4 + 24 hrs)</td>
<td></td>
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<tr>
<td>$^{111}$In-WBC</td>
<td>14</td>
<td>80%</td>
<td>89%</td>
<td>86%</td>
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<tr>
<td>(24 hrs)</td>
<td></td>
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</table>

* Love, EANM 2008
$^{111}$In-WBC vs $^{99m}$Tc-WBC*

Osteomyelitis left 1st & 3rd Metatarsals
(M. Morgagni)

Tc-WBC
4 hrs

Tc-WBC
24 hrs

In-WBC
24 hrs
$^{111}\text{In-WBC}$ vs $^{99m}\text{Tc-WBC}^*$

Osteomyelitis Rt. Great Toe
(E. Faecalis & Staph coagulase (-))

Tc-WBC
4 hrs

Tc-WBC
24 hrs

In-WBC
24 hrs
$^{111}$In-WBC vs $^{99m}$Tc-WBC*

Reactive Bone Left 5\textsuperscript{th} Metatarsal
WBC & Bone Scintigraphy

Bone scintigraphy as a screening test

Bone + labeled leukocyte imaging
# Bone Scan as Screening Test

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<thead>
<tr>
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<th>WBC</th>
<th>3PBo*</th>
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<tbody>
<tr>
<td><strong>Sens</strong></td>
<td>8/10</td>
<td>9/10</td>
</tr>
<tr>
<td></td>
<td>(80%)</td>
<td>(90%)</td>
</tr>
<tr>
<td><strong>Spec</strong></td>
<td>10/15</td>
<td>4/15</td>
</tr>
<tr>
<td></td>
<td>(67%)</td>
<td>(27%)</td>
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</table>

*Palestro et al. J Foot Ankle Surg; 2003*

- WBC only: 25 scans (72% accuracy)
- WBC (25) + bone (25): 50 scans (80% accuracy)
- +Bone (20) + WBC (25): 45 scans (80% accuracy)
## WBC + Bone Scintigraphy

<table>
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<tr>
<th></th>
<th>Bone</th>
<th>WBC</th>
<th>WBC + Bone</th>
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<tr>
<td>Keenan</td>
<td>63%</td>
<td>87%</td>
<td>87%</td>
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<tr>
<td>Arch Int Med 1989</td>
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<tr>
<td>Johnson</td>
<td>—</td>
<td>86%</td>
<td>91%</td>
</tr>
<tr>
<td>Foot Ankle Int 1996</td>
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<td></td>
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<tr>
<td>Palestro</td>
<td>52%</td>
<td>72%</td>
<td>80%</td>
</tr>
<tr>
<td>J Foot &amp; Ankle Surg 2003</td>
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WBC + Bone Scintigraphy

<table>
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<tr>
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<th>WBC/Bo</th>
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<td>Sens</td>
<td>8/10</td>
<td>9/10</td>
<td>8/10</td>
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<td></td>
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<tr>
<td>Spec</td>
<td>10/15</td>
<td>4/15</td>
<td>12/15</td>
</tr>
<tr>
<td></td>
<td>(67%)</td>
<td>(27%)</td>
<td>(75%)</td>
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<tr>
<td>Acc</td>
<td>18/25</td>
<td>13/25</td>
<td>20/25</td>
</tr>
<tr>
<td></td>
<td>(72%)</td>
<td>(52%)</td>
<td>(80%)</td>
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Paiset al. J Foot Ankle Surg; 2003
Osteomyelitis Rt. Great Toe

$^{111}$In WBC

$^{99m}$Tc MDP
Reactive Bone Right Great Toe

$^{111}$In WBC

$^{99m}$Tc MDP

BLOOD FLOW  BLOOD POOL  DELAYED IMAGE
Gangrene

$^{111}$In WBC

$^{99m}$Tc MDP

BLOOD FLOW, BLOOD POOL, DELAYED IMAGE
SPECT CT

Improved diagnostic accuracy
Facilitates differentiation of soft tissue versus bone uptake
Poor resolution of $^{111}$In-WBC
Size of structures being evaluated
Osteomyelitis Rt. 5th Metatarsal

\(^{\text{111}}\text{In WBC}\)

Dorsal

Plantar
Osteomyelitis Rt. 5th Metatarsal

Dorsal

Plantar
Reactive Bone Rt. 5th Metatarsal

Dorsal

Plantar
FDG-PET/CT
FDG-PET & The Diabetic Foot

Schwegler et al. (Journal of Internal Medicine, 2008)

20 diabetic patients
All with pedal ulcers for at least 8 weeks
Low index of suspicion for osteomyelitis
No previous antibiotic treatment
Compared FDG-PET, $^{99m}$Tc-MoAb, & MRI

Results
7/20 pts. had osteomyelitis
FDG-PET & The Diabetic Foot*

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>MRI</td>
<td>86% (6/7)</td>
<td>92% (12/13)</td>
<td>90% (18/20)</td>
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<tr>
<td>FDG-PET</td>
<td>29% (2/7)</td>
<td>92% (12/13)</td>
<td>70% (14/20)</td>
</tr>
<tr>
<td>$^{99m}$TcMoAb</td>
<td>29% (2/7)</td>
<td>85% (11/13)</td>
<td>65% (13/20)</td>
</tr>
</tbody>
</table>

*Schwegler et al. J of Internal Medicine, 2008
FDG-PET & The Diabetic Foot

Schwegler et al. Observations/Conclusions
1. MRI superior to FDG-PET & $^{99m}$Tc MoAB in this series
2. Possible explanations for FDG-PET results
   a. Population with low degree of inflammation
   b. Insulin resistance (Bone uptake of FDG may be insulin dependent)
   c. Motion artifacts/limited spatial resolution
FDG-PET/CT & The Diabetic Foot

Keidar et al. (JNM, 2005)

14 diabetic pts. 18 sites
  7 forefoot
  11 mid/hindfoot
7 with non healing wounds/ulcers

Results

PET: identified 14 sites, but could not separate bone from soft tissue
PET/CT: localized uptake to bone in 8 sites, to soft tissue in 5 sites, & to osteoarthropathy in 1 site.
FDG-PET/CT & The Diabetic Foot

Keidar et al. Observations/conclusions

1. Blood glucose
   84-330 mg/dL (7 > 200 mg/dL)
   Did not affect PET/CT results

2. SUV max: 5.7 (1.7-11.1)

3. FDG-PET/CT allows precise diagnosis of osteomyelitis vs soft tissue infection.
FDG-PET & The Neuropathic Joint

Hopfner et al. (Foot & Ankle Intl, 2004)
Compared Hybrid PET, Ring PET & MRI in 16 diabetic patients

Surgical results: 39 neuropathic lesions
29 osseous: 0 osteomyelitis
15 soft tissue: 0 infection

Imaging results
Hybrid PET: 30/39 (77%)
Ring PET: 37/39 (95%)
MRI: 31/39 (79%)
FDG-PET & The Neuropathic Joint

Hopfner et al. Observations/Conclusions

1. Image quality better in pts. with blood glucose 80-120 mg/dL compared to pts. with blood glucose > 200 mg/dL (no impact on sensitivity)
2. Mean lesion SUV: 1.8 (0.5-4.1)
3. Ring PET & MRI comparable except in presence of metallic hardware, where PET is better
4. PET can differentiate neuropathic joint from osteomyelitis based on SUV
FDG-PET & The Neuropathic Joint

Basu et al. (Nucl Med Commun; 2007)
Evaluated ability of FDG-PET to differentiate neuropathic joint from osteomyelitis and soft tissue infection.

- 63 patients (Blood glucose levels < 200 mg/dL in 62 pts.)
- 17 neuropathic joints (1 osteomyelitis)
- 21 uncomplicated diabetic feet
- 20 normal nondiabetic feet
- 5 complicated diabetic feet with osteomyelitis
FDG-PET & The Neuropathic Joint

Basu et al. Observations/Conclusions
1. SUV max in normals/uncomplicated diabetic feet: 0.42 (0.2-0.7)
2. SUV max in neuropathic joint: 1.3 (0.7-2.4)
3. SUV max in neuropathic joint + osteomyelitis: 6.5
4. SUV max in pedal osteomyelitis: 4.38 (2.9-6.2)
5. FDG-PET useful in differentiating neuropathic joint & osteomyelitis & better than MRI in this series
## Diagnosing Pedal Osteomyelitis*

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>Radiographs</td>
<td>54%</td>
<td>80%</td>
</tr>
<tr>
<td>3-Phase Bone</td>
<td>91%</td>
<td>46%</td>
</tr>
<tr>
<td>Labeled Leukocytes</td>
<td>88%</td>
<td>82%</td>
</tr>
<tr>
<td>MRI</td>
<td>92%</td>
<td>84%</td>
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</table>

Diabetic Pedal Osteomyelitis

Radiographs

Initial imaging test
Relatively inexpensive
Readily available
Provide anatomic overview of the ROI
Identify pre-existing conditions that influence selection & interpretation of subsequent tests

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Diabetic Pedal Osteomyelitis

Labeled leukocyte imaging
Radionuclide procedure of choice

$^{111}$In or $^{99m}$Tc

Most useful
Early, unsuspected, osteomyelitis
Monitoring response to medical therapy
Neuropathic joint (WBC/marrow)

Bone scan
Questionable value
Diabetic Pedal Osteomyelitis

**SPECT/CT**
- Likely useful in mid/hind foot
- ? forefoot

**PET/CT**
- ? $^{18}$F-FDG
- ? Other PET tracers