Απεικονιστική διερεύνηση διαβητικού ποδιού

Γ. Αρσος, Γ΄ Εργ. Πυρηνικής Ιατρικής ΑΠΘ - ΓΝ "Παπαγεωργίου"
Complications of DM

- no diabetic brain
- no diabetic eye
- no diabetic ear
- no diabetic heart
- no diabetic kidney
- no diabetic penis

...but, THE diabetic foot!
Definition of diabetic foot

“The foot of diabetic patients with:

- ulceration
- infection
- and/or destruction of the deep tissues

associated with:

- neurological abnormalities
- and various degrees of peripheral vascular disease in the lower limb”

WHO & International Working Group on the Diabetic Foot, 1999
● Approximately 60-70% of DM patients:
  mild - severe diabetic neuropathy

● Rate of amputation for people with DM:
  X 10 than for people without DM (NHS: X15)

● After an amputation:
  chance of another amputation within 3-5 yrs ≥ 50%
Relative 5-year mortality (%)

DFU: Diabetic foot ulcer

Armstrong DG et al, Int Wound J 2007
“Every 30 seconds a lower limb is lost somewhere in the world as a consequence of diabetes.”

See Review page 1719
Number and rate of hospitalizations among adults aged ≥18 years with diagnosed diabetes for selected causes, United States, 2014

<table>
<thead>
<tr>
<th>Cause of hospitalization</th>
<th>No. in thousands</th>
<th>Crude rate per 1,000 persons with diabetes (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes as any listed diagnosis</td>
<td>7,155</td>
<td>327.2 (311.3–343.1)</td>
</tr>
<tr>
<td>Major cardiovascular disease</td>
<td>1,539</td>
<td>70.4 (66.8–73.9)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>400</td>
<td>18.3 (17.3–19.3)</td>
</tr>
<tr>
<td>Stroke</td>
<td>251</td>
<td>11.5 (10.9–12.1)</td>
</tr>
<tr>
<td>Lower-extremity amputation</td>
<td>108</td>
<td>5.0 (4.7–5.2)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>168</td>
<td>7.7 (7.3–8.1)</td>
</tr>
</tbody>
</table>
The system of care for the diabetic foot: objectives, outcomes, and opportunities

Barsches NR et al, Diabetic Foot & Ankle 2013

Lancet, 2005
The system of care for the diabetic foot: objectives, outcomes, and opportunities

Barshes NR et al, Diabetic Foot & Ankle 2013

Lancet, 2005
Ulcer-OM relationships in the DF

- in > 90% of OM cases: a pre-existing ulcer is the gate of infection
- pre-existing ulcer in 85% of DF amputations

The system of care for the diabetic foot: objectives, outcomes, and opportunities

Barshees NR et al, Diabetic Foot & Ankle 2013
Diabetic neuropathy
Charcot arthropathy
ULCER
Soft tissue infection
OSTEOMYELITIS
AMPUTATION
the diagnostic dilemmas

DFU, diabetic foot ulcer; STI, soft tissue infection
OM, osteomyelitis; aCA, acute Charcot Arthropathy

treatment - duration
Treating Foot Infections in Diabetic Patients: A Randomized, Multicenter, Open-Label Trial of Linezolid versus Ampicillin-Sulbactam/Amoxicillin-Clavulanate

Ulcer: 4
Soft Tissue Infection: 3
Osteomyelitis: 1

![Bar Chart]

- **Linezolid**
- **Ampic/Clav**

Lipsky BA, Clin Inf Dis 2004
<table>
<thead>
<tr>
<th>Severity / Extent</th>
<th>Route</th>
<th>Setting</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOFT TISSUE ONLY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Topical- P.O.</td>
<td>Outp</td>
<td>1-2 w</td>
</tr>
<tr>
<td>Moderate</td>
<td>I.V. → P.O.</td>
<td>Outp (Inp)</td>
<td>1-3 w</td>
</tr>
<tr>
<td>Severe</td>
<td>I.V. → P.O.</td>
<td>Inp → Outp</td>
<td>2-4 w</td>
</tr>
<tr>
<td><strong>BONE or JOINT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No residual infected tissue</td>
<td>I.V. → P.O.</td>
<td>Inp → Outp</td>
<td>2-5 d</td>
</tr>
<tr>
<td>Residual infected soft tissue (not bone)</td>
<td>I.V. / P.O.</td>
<td>Inp → Outp</td>
<td>1-3 w</td>
</tr>
<tr>
<td>Residual infected (but viable) bone</td>
<td>I.V. → P.O.</td>
<td>Inp → Outp</td>
<td>4-6 wk</td>
</tr>
<tr>
<td>No surgery / residual dead bone postop.</td>
<td>I.V. → P.O.</td>
<td>Inp → Outp</td>
<td>≥3 mo</td>
</tr>
</tbody>
</table>

Lipsky AB et al, ISDA Guidelines 2012
“General inspection

A careful inspection of the feet in a well-lit room should always be carried out after the patient has removed shoes and socks.”...
Table 1 Summary of potentially useful clinical findings in diagnosing diabetic foot infection

A. History
1. Long duration (> 4 weeks) of foot wound
2. Previous infection at the same or a nearby site
3. Presence of new pain in the wound (especially in a previously insensate foot)
4. Presence of immunosuppressive condition (beyond that related to diabetes)

B. Physical examination
1. Large wound (> 2 cm²)
2. Deep wound (> 3 mm)
3. Classic signs of inflammation (tenderness, pain, redness, warmth, induration)
4. Secondary signs of infection (foul odour, friable or discoloured granulation tissue, rim undermining, purulent or non-purulent secretions)

Impact of OM likelihood on Probe-to-Bone test performance

- PPV
- NPV

<table>
<thead>
<tr>
<th>% OM</th>
<th>65.8</th>
<th>12.1 ALL</th>
<th>12.1 INF</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>76 Inf Ulcers</td>
<td>247 Ulcers - 199 Inf Ulcers</td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>66 Se</td>
<td>87 Se</td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td>85 Sp</td>
<td>91 Sp</td>
<td></td>
</tr>
</tbody>
</table>

Grayson ML et al, JAMA 1995
Lavery LA et al., Diabetes Care 2007
The Performance of Serum Inflammatory Markers for the Diagnosis and Follow-up of Patients With Osteomyelitis

OM = 44.3%

Cutoffs:
- CRP >14 mg/L
- ESR >67 mm/h
- WBC >14 × 10⁹/L
- PCT >0.30 ng/mL

Sensitivity and Specificity

bone biopsy: sensitivity 88-100% (7 studies)*

- histology
- culture
- sensitivity?
- no significant sequelae
  - 15g trocar
  - not contiguous to ulcer

- sampling error
- bone biopsy expertise
- significant peripheral vascular disease?

*Diagnosing pedal osteomyelitis: testing choices and their consequences
Mushlin AI et al., J Gen Int 1994
Needle Puncture vs Transcutaneous Bone Biopsy

31 patients

Needle Puncture and Transcutaneous Bone Biopsy Cultures Are Inconsistent in Patients with Diabetes and Suspected Osteomyelitis of the Foot.

Senneville E et al., Clin Infect Dis 2009

13 patients with positive Needle Puncture cultures
20 patients with positive Biopsy cultures

+50%
hindfoot
midfoot
forefoot
RADIOLOGY

- Ro
- US
- CT
- MRI

NUCLEAR MEDICINE

- Bone scan: 99mTc-MDP
- Ga-67-citrate
- Tc-99m-IgG
- Tc-99m-ciprofloxacin
- In-111-WBC
- Tc-99m-HMPAO-WBC
- Tc-99m-Ab-WBC
- F-18-FDG (PET)

HYBRID TECHNIQUES: PET/CT, SPECT/CT
3 very good reasons for plain Rx in diabetic foot!
Plain Rx in diabetic foot

Early OM - focal lucency
- loss of trabecular pattern
- cortical destruction

Late abnormalities - periosteal reaction
- sclerosis
- new bone formation

Se ~ 60%  Sp ~ 80%

changes visible with demineralization of > 30–50% / 2–4 weeks
suboptimal for detecting soft tissue infection
dif. infection from co-existing neuro-osteoarthropathy ??

serial radiographs /2 weeks
changes characteristic of osteomyelitis over time

likelihood of OM very high or low
sufficient to confirm the clinical suspicion
Short Report: Complications

Diagnosing diabetic foot osteomyelitis: is the combination of probe-to-bone test and plain radiography sufficient for high-risk inpatients?

J. Aragón-Sánchez, Benjamin A. Lipsky*† and J. L. Lázaro-Martínez‡


OM = 72.4%

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probe-to-bone test</td>
<td>0.95 (0.89–0.96)</td>
<td>0.93 (0.86–0.97)</td>
<td>0.97 (0.95–0.99)</td>
<td>0.83 (0.72–0.94)</td>
</tr>
<tr>
<td>Plain X-ray</td>
<td>0.82 (0.77–0.87)</td>
<td>0.93 (0.86–0.97)</td>
<td>0.97 (0.95–0.99)</td>
<td>0.65 (0.47–0.83)</td>
</tr>
<tr>
<td>Combined*</td>
<td>0.97 (0.95–0.99)</td>
<td>0.92 (0.84–0.96)</td>
<td>0.97 (0.95–0.99)</td>
<td>0.93 (0.88–0.98)</td>
</tr>
</tbody>
</table>
MRI of the diabetic foot: differentiation of infection from neuropathic change

<table>
<thead>
<tr>
<th>MRI findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Bone marrow signal change</td>
</tr>
<tr>
<td>2 Bone marrow oedema pattern</td>
</tr>
<tr>
<td>3 Distribution</td>
</tr>
<tr>
<td>4 Typical location</td>
</tr>
<tr>
<td>5 Deformity</td>
</tr>
<tr>
<td>6 Soft tissue changes</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td><strong>BM signal change</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>BM oedema pattern</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
</tr>
<tr>
<td><strong>Typical location</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td><strong>Deformity</strong></td>
</tr>
<tr>
<td><strong>ST changes</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
</tbody>
</table>
MRI findings
13 DM patients
15 MR examinations before surgery

MR - histologic correlations in 57 bones
T2-weighted, STIR

18 bones with increased signal: edema of the marrow, not OM

Se = 90%, Sp = 71%

“Marrow edema cannot be reliably distinguished from osteomyelitis with MR imaging…….”
Main radionuclide imaging

A) 3-phase bone scan : $^{99m}$Tc-MDP
Sensitive, not specific (+ in uninfected Charcot !)

B) Radionuclide labelled WBC scan

Labelled WBCs migrate to sites of infection (chemotaxy)
Not in sites of increased bone metabolism !
Specificity > bone scan

1) $^{111}$In-WBC
2) $^{99m}$Tc-HMPAO-WBC
3) $^{99m}$Tc-Antibodies-WBC
improved spatial resolution
lower radiation dose
complete in a single day
99mTc Phosphate

polyphosphate
Subramanian and McAfee, 1971

pyrophosphate

diphosphonate
Making the diagnosis of osteomyelitis. The role of prevalence

Σ. Γεώργα Διαφορική διάγνωση της οστεομυελίτιδας στους άκρους πόδες διαβητικών ασθενών με ραδιοϊσοτοπικές μεθόδους. Διδ. Διατριβή, Θεσσαλονίκη 2007

Σ. Γεώργα Διαφορική διάγνωση της οστεομυελίτιδας στους άκρους πόδες διαβητικών ασθενών με ραδιοϊσοτοπικές μεθόδους. Διδ. Διατριβή, Θεσσαλονίκη 2007
Infected right foot plantar ulcer without OM

- 66-yr-old woman with NIDDM
- bilateral Charcot joints
- presented with a right midfoot deep plantar ulcer (Wagner 2)

Focal intense leucocyte uptake limited to the ulcer, incongruent with BS uptake

99mTc-MDP bone scan
- dynamic phase
- blood pool phase
- delayed images

99mTc-HMPAO-LS

Σ. Γεώργιο, Εργ. Πυρηνικής Ιατρικής ΑΠΘ, ΓΝΘ Ιπποκράτειο
Σ. Γεώργα, Εργ. Πυρηνικής Ιατρικής ΑΠΘ, ΓΝΘ Ιπποκράτειο
clinical presentation of Charcot arthropathy

- warmth
- redness
- swelling
- pedal ulcer in 50%

also present in osteomyelitis

pain often absent

joint instability
foot deformity

Osteomyelitis may be clinically indistinguishable from an acute Charcot joint and both may occur simultaneously
69-yr-old woman
20-yr history of DM type 2

Presentation: warm & swollen right foot, no pain

Rö: findings indicative of Charcot arthropathy
no findings of Osteomyelitis

MRI: bone marrow edema, compatible with Osteomyelitis
**Diagnosis:**

Acute Charcot arthropathy, without OM

**Outcome:**

Resolution of signs and symptoms after 4-months off-loading of the foot, without antibiotic treatment
SPECT/CT

GE Optima, NM/CT 640

Dept of Nuclear Medicine, AUTH, “Papageorgiou” Gen. Hospital
FDG tumor model

Normal cell

- Glucose 6-phosphatase
- Glycolysis
- Hexokinase
- G6P
- Glucose 6-phosphatase
- FDG6P
- FDG

Tumour cell

- Glucose 6-phosphatase
- Glycol. (inflammatory cells)
- Hexokinase
- G6P
- Glucose 6-phosphatase
- FDG6P
- FDG

FDG6P
G
G6P
GE Discovery 710 PET/CT - Time of Flight (TOF)

Dept of Nuclear Medicine, AUTH, “Papageorgiou” Gen. Hospital
Keidar Z et al. The Diabetic Foot: Initial Experience with 18F-FDG PET/CT
J Nucl Med 2005
RESEARCH ARTICLE

Diagnostic Performance of FDG-PET, MRI, and Plain Film Radiography (PFR) for the Diagnosis of Osteomyelitis in the Diabetic Foot

Asad Nawaz, Drew A. Torigian, Evan S. Siegelman, Sandip Basu, Timothy Chryssikos, Abass Alavi

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>Number of patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>110</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Range, 29–85</td>
<td></td>
</tr>
<tr>
<td>Mean, 59.3</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>76</td>
</tr>
<tr>
<td>Female</td>
<td>34</td>
</tr>
<tr>
<td>Diagnosis of osteomyelitis</td>
<td>27</td>
</tr>
<tr>
<td>Number of patients confirmed by bone culture and histology</td>
<td>37</td>
</tr>
<tr>
<td>Number of patients confirmed by clinical evaluation</td>
<td>73</td>
</tr>
</tbody>
</table>
Diagnostic Performance of FDG-PET, MRI, and Plain Film Radiography (PFR) for the Diagnosis of Osteomyelitis in the Diabetic Foot

Asad Nawaz, Drew A. Torigian, Evan S. Siegelman, Sandip Basu, Timothy Chryssikos, Abass Alavi

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFR</td>
<td>63</td>
<td>87</td>
<td>60</td>
<td>88</td>
<td>81</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>81</td>
<td>93</td>
<td>78</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>MRI</td>
<td>91</td>
<td>78</td>
<td>56</td>
<td>97</td>
<td>81</td>
</tr>
</tbody>
</table>
### Table: ACR Appropriateness Criteria 2008

<table>
<thead>
<tr>
<th>Clinical Condition:</th>
<th>Suspected Osteomyelitis of the Foot in Patients with Diabetes Mellitus Neuropathy without ulcer.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variant 4:</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiologic Procedure</th>
<th>Rating</th>
<th>Comments</th>
<th>RRL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray foot</td>
<td>9</td>
<td>Initial study. Radiographs and MRI are complementary. Both are indicated.</td>
<td>Min</td>
</tr>
<tr>
<td>MRI foot with contrast</td>
<td>9</td>
<td>Radiographs and MRI are complementary. Both are indicated. See statement regarding contrast in text under “Anticipated Exceptions.”</td>
<td>None</td>
</tr>
<tr>
<td>MRI foot without contrast</td>
<td>9</td>
<td>Radiographs and MRI are complementary. Both are indicated.</td>
<td>None</td>
</tr>
<tr>
<td>CT foot without contrast</td>
<td>5</td>
<td>For neuropathy or if MRI contraindicated.</td>
<td>Min</td>
</tr>
<tr>
<td>Tc-99m 3-phase bone scan foot</td>
<td>5</td>
<td>Useful for pre-radiographic findings of neuropathy. Also if MRI contraindicated.</td>
<td>Med</td>
</tr>
<tr>
<td>Tc-99m 3-phase bone scan and In-111 WBC scan foot</td>
<td>2</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>In-111 WBC scan and Tc-99m sulfur colloid marrow scan foot</td>
<td>1</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Tc-99m 3-phase bone scan and In-111 WBC scan and Tc-99m sulfur colloid marrow scan foot</td>
<td>1</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>US foot</td>
<td>1</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>FDG-PET foot</td>
<td>1</td>
<td></td>
<td>High</td>
</tr>
</tbody>
</table>

**Rating Scale:** 1=Least appropriate, 9=Most appropriate

*Relative Radiation Level*
ACR Appropriateness Criteria 2012: learning... but still inappropriate

<table>
<thead>
<tr>
<th>Clinical Condition:</th>
<th>Suspected Osteomyelitis of the Foot in Patients with Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variant 2:</td>
<td>Soft-tissue swelling with neuropathic arthropathy without ulcer.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiologic Procedure</th>
<th>Rating</th>
<th>Comments</th>
<th>RRI.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray foot</td>
<td>9</td>
<td>Initial study. Radiographs and MRI are complementary, and both are indicated. The results of initial x-ray examination do not preclude the necessity for additional studies.</td>
<td></td>
</tr>
<tr>
<td>MRI foot without and with contrast</td>
<td>9</td>
<td>Radiographs and MRI are complementary, and both are indicated. MRI is useful preoperatively to identify the extent of involvement and to map devitalized areas. See statement regarding contrast in text under “Anticipated Exceptions.”</td>
<td>O</td>
</tr>
<tr>
<td>MRI foot without contrast</td>
<td>9</td>
<td>Radiographs and MRI are complementary, and both are indicated.</td>
<td>O</td>
</tr>
<tr>
<td>CT foot without contrast</td>
<td>5</td>
<td>For neuropathy or if MRI contraindicated.</td>
<td>O</td>
</tr>
<tr>
<td>Labeled leukocyte scan foot (In-111 or Tc-99m)</td>
<td>3</td>
<td>May be appropriate in certain circumstances such as if MRI is contraindicated or unavailable.</td>
<td>O</td>
</tr>
<tr>
<td>Labeled leukocyte scan foot (In-111 or Tc-99m) and Tc-99m sulfur colloid marrow scan foot</td>
<td>3</td>
<td>May be appropriate in selected clinical circumstances.</td>
<td>O</td>
</tr>
<tr>
<td>CT foot without and with contrast</td>
<td>1</td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>CT foot with contrast</td>
<td>1</td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>Tc-99m 3-phase bone scan foot</td>
<td>1</td>
<td></td>
<td>O</td>
</tr>
</tbody>
</table>

5, four yrs ago

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

*Relative Radiation Level
DFI imaging recommendations

Ro: All with DFI

MRI: Abcess, OM uncertain

Radionuclide imaging: Alternative to MRI

DFI, Diabetic foot infection

Lipsky BA et al, Clin Inf Dis 2012
Radionucleotide Scans

Four radionucleotide studies are discussed here:

- technetium Tc-99m (99mTc)-labeled diphosphonate bone scanning;
- indium In-111 white blood cell (WBC);
- non-specific human immunoglobulin (HIG) labeled with Tc-99; and
- 18-flourodeoxyglucose positron emission tomography (18-FDG-PET).
“The various modalities have similar sensitivity, but 18F-FDG-PET and 99mTc-HMPAO-labeled WBC scintigraphy offer the highest specificity”
Σχήμα 14.2.1 Αλγόριθμος απεικονιστικής διερεύνησης οστεομελίτιδας.
### Personal point of view

| Ro       | • initial imaging / serial  
|          | • all with DFI   |
| MRI      | • forefoot  
|          | • wide soft tissue infection  
|          | • possible surgical intervention   |
| Nuclear imaging | • specific infection imaging  
|          | - $^{99m}$Tc-HMPAO-WBC (not Ab-labelled!)  
|          | - hybrid imaging (SPECT/CT)   
|          | • mid-hidefoot : dif. aCA vs OM, > MRI  
|          | • response : unique   
|          | • bone scan : of limited value   
|          | • 18F-FDG PET/CT : expensive   
|          | • MRI alternative : on contraindications   |

Local expertise : indispensable
thank you for your attention!