ID of Diabetic Foot

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DISCLOSURES

• Relevant Financial Relationship(s)
  • Travel and Wellness LLC

• Off Label Usage
  • None
OBJECTIVES

• Identify the best methods to make the diagnosis of diabetic foot infection (DFI)
• Describe the classification of DFI
• Understand the microbiology of DFI
• Explain the principles of DFI management
Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

9.3% of US population or 29.1 million people have diabetes

Obesity (BMI ≥30 kg/m²)

1994

2000

2014

Diabetes

1994

2000

2014

CDC's Division of Diabetes Translation. United States Surveillance System available at http://www.cdc.gov/diabetes/data
Diabetes complications

- 15% lifetime risk of developing foot ulcers
- 66% of open ulcers → result in infection
- Osteomyelitis prevalence in diabetic foot ulcers ~ 10-20%
- In 2010, ~73,000 non-traumatic lower-limb amputations (adults)

http://www.cdc.gov/diabetes
Pathogenesis of diabetic foot infection

Neuropathy

Sensory Neuropathy
Decreased pain sensation
Clawing of toes
Decreased proprioception

Autonomic Neuropathy
Reduced sweating
Fissures / callus formation
Altered blood flow

Motor Neuropathy
Abnormal foot mechanics
Increased foot pressure

Vascular Insufficiency

Infection
Diabetic foot infection and osteomyelitis

**Host immune response**
- Reduced neutrophilic/macrophage response

**Host glycemic control**

**Colonization**

**Bacterial burden**

**Bacterial virulence**

**Infection**
When should infection be suspected in patients with diabetic foot ulcers?

- Clinical signs of infection
  - Local:
    - **Usual signs**: Erythema, swelling, purulent secretions
    - **Atypical signs**: non-purulent secretions, friable or discolored granulation tissue, undermining of the wound edges, or foul odor
  - Systemic signs of infection
- Presence of risk factors
- Classify diabetic foot ulcers / infection
  - Clinical classification
Risk factors for DFI

- Previous lower extremity amputation [OR 19.9]
- Probe-to-bone is positive [OR 6.7]
- Ulceration present for >30 days [OR 4.7]
- Peripheral neuropathy [OR 3.4]
- History of recurrent foot ulcers [OR 2.4]
- Traumatic foot wound [OR 2.4]
- Peripheral vascular disease [OR 1.9]
- Renal insufficiency
- Barefoot walking
Classification of DFI is helpful in management

• Why classify diabetic foot ulcers?
  • Assist in
    – Antimicrobial choice
    – Urgency of evaluation and management
    – Assessing need for involvement of other specialties
    – Prognosis and predict outcomes

• Many classification systems in literature

• Most user friendly and validated
  • Infectious Diseases Society of America (2012)
  • International Working Group on the Diabetic Foot (IWGDF) developed PEDIS (Perfusion, Extent/size, Depth/tissue loss, Infection, Sensation)

### IDSA and PEDIS DFI Classification

<table>
<thead>
<tr>
<th>Clinical Manifestation of Infection</th>
<th>PEDIS Grade</th>
<th>IDSA Infection Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms or signs of infection</td>
<td>1</td>
<td>Uninfected</td>
</tr>
<tr>
<td>Infection defined by the presence of at least 2 of following:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Local swelling or induration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Erythema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Local tenderness or pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Local warmth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Purulent discharge (thick, opaque to white or sanguineous secretion)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Lipsky, B et al. *CID* 2012;54(12):132–173
Hospitalization and amputation based on the Infectious Diseases Society of America and the International Working Group on the Diabetic Foot infection severity classification.

Figure 1. Hospitalization and amputation based on the Infectious Diseases Society of America and the International Working Group on the Diabetic Foot foot infection severity classification.

PEDIS stage 2 or mild infection
PEDIS stage 3 or moderate infection

- Deeper structure involvement
  - Tendons
  - Fascia
  - Joints
  - Bone
How do I assess a patient with DFI?

• Assess the person as a whole for
  • Signs of sepsis
  • Metabolic status
  • Cognitive and social function status

• …then the foot/limb – for biomechanics, neurological, vascular status
  • Charcot foot neuroarthropathy
  • Claw foot
  • Calluses etc

• …then the ulcer – for infection
### Initial assessment

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

#### 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 odor, friable or discolored granulation tissue, undermining, purulent or non-purulent secretions)
5. Probe-to-bone or not
Key initial questions

• Need for hospitalization?
  • All severe
  • Some moderate
  • Social or cognitive limitations

• Need for urgent or emergent surgery?
  • Necrotizing fasciitis
  • Gangrene
  • Critical ischemia

• What grade DFI is it?
Diagnosing infection in the diabetic foot

• Clinical symptoms and signs

• Laboratory testing
  • CBC, Sed rate and CRP – not very helpful
    – Leukocytosis → present in 50% of patients with osteo
    – Normal CBC does not preclude osteomyelitis diagnosis
  • Procalcitonin
    – Jury is still out.
    – *May* help in diagnosing DFI or diabetic foot osteomyelitis
  • Not helpful:
    – Interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor alpha (TNFα), monocyte chemotactic protein-1 (MCP-1) and macrophage inflammatory protein-1 alpha (MIP1α)

When to suspect osteomyelitis?

• Chronic ulcer > 4 weeks
• Deep ulcer > 3 mm
• Intermittently healing and draining wound
• Bone visible or probe-to-bone positive
• Sausage toe ➔
• Osteomyelitis present
  • 10-20% of moderate infections
  • 50-60% of severe infections
Diagnosis of Osteomyelitis in DFI

• Plain radiographs

• Radionuclide bone scans
  • Technetium-99 bone scan: more sensitive than X-rays, but non-specific

• Radionuclide white blood cell scans
  • Slightly less sensitive than bone scan, specificity is typically higher
  • Generally done when MRI unavailable

• Magnetic resonance imaging (MRI)
  • Most useful imaging study for diagnosing DFO and for evaluation of extent of both bone and soft-tissue involvement and surgery planning

• Positron emission tomography (PET)
  • May be helpful but not that well studied and more expensive

• Bone biopsy
  • For culture and histological examination of bone to both confirm the diagnosis and potentially identify the pathogen(s)
Diagnosing osteomyelitis in the diabetic foot
Using ESR, CRP and Procalcitonin

<table>
<thead>
<tr>
<th></th>
<th>ESR (mm/hr)</th>
<th>CRP mg/l</th>
<th>PCT (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No osteomyelitis (n 34)</td>
<td>66</td>
<td>8.7</td>
<td>0.71</td>
</tr>
<tr>
<td>Osteomyelitis (n 27)</td>
<td>76</td>
<td>25</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Gold standard comparator: probe to bone + imaging

Diagnosing osteomyelitis in the diabetic foot
Using ulcer size, ESR or both

Gold standard comparator: MRI imaging or histopath

Diagnosing osteomyelitis in the diabetic foot
Meta-analysis - 9 cohort trials
Using x-ray, MRI, Bone scan and probe to bone

Gold standard comparator: histopath or bone cultures

Diagnosing osteomyelitis in the diabetic foot
Meta-analysis - 21 cohort trials
Using ulcer size, x-ray, ESR and probe to bone

Gold standard comparator: bone biopsy

### International Working Group on the Diabetic Foot → Osteomyelitis Diagnostic Criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Post-test probability of osteomyelitis</th>
<th>Management advice</th>
<th>Criteria Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite (‘beyond reasonable doubt’)</td>
<td>&gt;90%</td>
<td>Treat for osteomyelitis</td>
<td>Bone sample with positive culture AND positive histology OR Purulence in bone found at surgery OR Atraumatically detached bone fragment removed from ulcer by podiatrist/surgeon OR Intraosseous abscess found on MRI OR Any two probable criteria OR one probable and two possible criteria OR, any four possible criteria below</td>
</tr>
<tr>
<td>Probable (‘more likely than not’)</td>
<td>51–90%</td>
<td>Consider treating, but further investigation may be needed</td>
<td>Visible cancellous bone in ulcer OR MRI showing bone edema with other signs of osteomyelitis OR Bone sample with positive culture but negative or absent histology OR Bone sample with positive histology but negative or absent culture OR Any two possible criteria below</td>
</tr>
<tr>
<td>Possible (but on balance, less rather than more likely)</td>
<td>10–50%</td>
<td>Treatment may be justifiable, but further investigation usually advised</td>
<td>Plain X-rays show cortical destruction OR MRI shows bone edema OR cloaca, OR Probe to bone positive OR, Visible cortical bone OR ESR &gt;70mm/h with no other plausible explanation OR Non-healing wound despite adequate offloading and perfusion for &gt;6 weeks OR ulcer of &gt;2 weeks duration with clinical evidence of infection</td>
</tr>
<tr>
<td>Unlikely</td>
<td>&lt;10%</td>
<td>Usually no need for further investigation or treatment</td>
<td>No signs or symptoms of inflammation AND normal X-rays AND ulcer present for &lt;2 weeks or absent AND any ulcer present is superficial OR Normal MRI OR Normal bone scan</td>
</tr>
</tbody>
</table>

## Initial Clinical assessment

<table>
<thead>
<tr>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visible cancellous bone in ulcer</td>
<td>2</td>
</tr>
<tr>
<td>Positive PTB test or visible cortical bone in ulcer</td>
<td>1</td>
</tr>
<tr>
<td>ESR &gt;70 with no other plausible explanation</td>
<td>1</td>
</tr>
<tr>
<td>Cortical destruction on initial plain radiograph</td>
<td>1</td>
</tr>
<tr>
<td>Ulcer size more than 2 square cm</td>
<td>1</td>
</tr>
<tr>
<td>Clinical gestalt: nonhealing wound for &gt;6 weeks despite perfusion or ulcer &gt;2 weeks duration with evidence of Infection</td>
<td>1</td>
</tr>
</tbody>
</table>

### Radiology Scores: (add if initial score less than 4)

<table>
<thead>
<tr>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive MRI scan:</td>
<td>+2</td>
</tr>
<tr>
<td>Interval change (minimum 2 weeks) on plain radiograph:</td>
<td>+1</td>
</tr>
<tr>
<td>Positive leukocyte scan:</td>
<td>+1</td>
</tr>
<tr>
<td>Negative MRI scan:</td>
<td>−2</td>
</tr>
<tr>
<td>Negative bone scan:</td>
<td>−2</td>
</tr>
</tbody>
</table>

- **≥ 4**
  - Osteomyelitis
  - High probability
- **< 4**
  - Low probability of osteomyelitis. Treat as SSTI. Reassess.

PEDIS stage 3 or moderate infection

right fifth ray amputation
MSSA bloodstream infection
### Table 5. Recommendations for Collection of Specimens for Culture From Diabetic Foot Wounds

<table>
<thead>
<tr>
<th>Do</th>
<th>Deeper tissue or bone cultures should be obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain an appropriate specimen for culture from almost all infected wounds</td>
<td>Lipsky, B et al. <em>Clin Infect Dis</em> 2012;54(12):132–173</td>
</tr>
<tr>
<td>Cleanse and debride the wound before obtaining specimen(s) for culture</td>
<td></td>
</tr>
<tr>
<td>Obtain a tissue specimen for culture by scraping with a sterile scalpel or dermal curette (curettage) or biopsy from the base of a debrided ulcer</td>
<td></td>
</tr>
<tr>
<td>Aspirate any purulent secretions using a sterile needle and syringe</td>
<td></td>
</tr>
<tr>
<td>Promptly send specimens, in a sterile container or appropriate transport media, for aerobic and anaerobic culture (and Gram stain, if possible)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Do not</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture a clinically uninfected lesion, unless for specific epidemiological purposes</td>
</tr>
<tr>
<td>Obtain a specimen for culture without first cleansing or debriding the wound</td>
</tr>
<tr>
<td>Obtain a specimen for culture by swabbing the wound or wound drainage</td>
</tr>
</tbody>
</table>
How do the cultures help?

• Aim for continued clinical response with the narrowest spectrum antimicrobial covering organisms isolated

• If clinically responding
  • Select the narrowest spectrum based on cultures
  • Not all organisms always need to be covered e.g. MRSA isolated but patient clinically responding to cephalexin

• If not responding
  • Broaden treatment to cover organisms not being covered based on cultures
  • Consider missed diagnosis – un-drained abscess, gout, underlying osteomyelitis, etc
  • Consider need for surgical intervention
**Microbiology of DFI**

- **Ulcer**
  - Polymicrobial colonization
  - Mostly aerobic gram-positive cocci such as *S. aureus*, *S. agalactiae* (GBS), *S. pyogenes*, and coagulase-negative staphylococci

- **Infection**
  - *Staph aureus*
    - Beta-hemolytic strep such as *S. agalactiae* (GBS), *S. pyogenes*
    - Gram-negatives
    - In chronic or severe wounds → Anaerobes (~40%)

- **Infection with prior antibiotic use**
  - *Staph aureus* MRSA (10-30%)
  - *Enterococcus* spp
  - Gram-negatives
    - ESBL GNB
  - *Pseudomonas* (<10%)
  - Anaerobes
  - **Osteomyelitis**
    - *S. aureus* most common

---

Use culture data to refine antimicrobial treatment
Antimicrobial selection

- **Mild**
  - Start narrow and broaden if no response
  - Oral preferred, topical may help in very mild
  - Aimed at aerobic Gram-positive organisms mainly

- **Moderate**
  - Start narrow and broaden if no response
  - Oral preferred but on occasion IV may be needed
  - Aimed at aerobic Gram-positive organisms and anaerobes
  - Hold antibiotics if underlying osteomyelitis but no cellulitis or systemic toxicity

- **Severe**
  - Start broad and then narrow
  - Parenteral treatment
MRSA antimicrobial coverage if

• Patient known to have MRSA infection or colonization within the past year

• Local MRSA prevalence is high
  • For mild infections: cover MRSA if local prevalence 50%
  • For moderate infections: cover MRSA if local prevalence 30%

• Severe infection
Complexity of antimicrobial choice

**Patient factors**
- Allergies
- Renal function
- GI absorption
- Immune status

**Infection**
- Severity
- Recent Abx
- Osteomyelitis
- Vascular status

**Microbiology**
- Organisms present
- Resistance

**Antibiotics**
- Safety
- Spectrum
- Efficacy
- Cost
### Specific antimicrobial choices

Mild (usually treated with oral agent[s])

<table>
<thead>
<tr>
<th>Probable Pathogen(s)</th>
<th>Antibiotic Agent</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococcus aureus (MSSA); Streptococcus spp</strong></td>
<td>Dicloxacillin</td>
<td>Requires QID dosing; narrow spectrum; inexpensive</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin-clavulanate</td>
<td>Relatively broad-spectrum oral agent that includes anaerobic coverage</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>Check for inducible resistance in MRSA by confirming negative “D-test” in Microbiology susceptibilities testing</td>
</tr>
<tr>
<td></td>
<td>Cephalexin</td>
<td>Requires QID dosing; inexpensive</td>
</tr>
<tr>
<td>Methicillin-resistant S. aureus (MRSA)</td>
<td>Levofloxacin</td>
<td>Once-daily dosing; suboptimal against S. aureus</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>Active against many MRSA &amp; some gram-negatives; not good against streptococcus species</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim/sulfamethoxazole</td>
<td>Active against many MRSA &amp; some gram-negatives; not good against streptococcus species</td>
</tr>
</tbody>
</table>

## Specific antimicrobial choices
### Moderate to severe infections

<table>
<thead>
<tr>
<th>Probable Pathogen(s)</th>
<th>Antibiotic Agent</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA; Streptococcus spp; Enterobacteriaceae; obligate anaerobes</td>
<td><strong>Ceftriaxone</strong></td>
<td>Once-daily dosing, third-generation cephalosporin but not active against <em>P. aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td><strong>Ampicillin-sulbactam</strong></td>
<td>Adequate for mild to moderate infections</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin</td>
<td>Once-daily dosing; suboptimal against <em>S. aureus</em></td>
</tr>
<tr>
<td></td>
<td>Levofloxacin or ciprofloxacin with clindamycin or metronidazole</td>
<td>Limited evidence supporting clindamycin for severe <em>S. aureus</em> infections; PO &amp; IV formulations for both drugs</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>Once-daily oral dosing. Relatively broad-spectrum, including most obligate anaerobic organisms. Expensive.</td>
</tr>
<tr>
<td></td>
<td>Ertapenem</td>
<td>Once-daily dosing. Expensive. Relatively broad spectrum including anaerobes, not active <em>P. aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td>Very broad-spectrum (but not against MRSA); use only when this is required. Consider when ESBL producing pathogens suspected</td>
</tr>
</tbody>
</table>

## Specific antimicrobial choices
### Moderate to severe infections

<table>
<thead>
<tr>
<th>Probable Pathogen(s)</th>
<th>Antibiotic Agent</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MRSA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>Nephrotoxicity risk</td>
</tr>
<tr>
<td></td>
<td>Ceftaroline</td>
<td>BID dosing. Expensive.</td>
</tr>
<tr>
<td></td>
<td>Daptomycin</td>
<td>Once-daily. Expensive. Requires CPK monitoring</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>Expensive; increased toxicities when used &gt;2 wk</td>
</tr>
<tr>
<td></td>
<td>Dalbavancin</td>
<td>Expensive, 2 doses. Not studied for osteomyelitis</td>
</tr>
<tr>
<td></td>
<td>Oritavancin</td>
<td>Expensive, 1 dose. Not studied for osteomyelitis</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa</strong></td>
<td>Cefepime</td>
<td>Adequate for <em>Pseudomonas aeruginosa</em> and other common pathogens. <em>P. aeruginosa</em> is an uncommon pathogen in diabetic foot infections except in special circumstances</td>
</tr>
<tr>
<td></td>
<td>Piperacillin-tazobactam</td>
<td>QID dosing. Useful for broad spectrum coverage.</td>
</tr>
<tr>
<td><strong>Mixed infections: MRSA, Enterobacteriaceae, Pseudomonas, and obligate anaerobes</strong></td>
<td>Vancomycin plus one of the following: ceftazidime, cefepime, piperacillin/tazobactam, aztreonam or a carbapenem</td>
<td>Very broad-spectrum coverage; usually only used for empiric therapy of severe infection. Consider addition of anaerobic coverage with metronidazole if not using piperacillin/tazobactam or carbapenem.</td>
</tr>
</tbody>
</table>
Multidisciplinary Diabetic Foot Care Team

And more…. Nurses, social workers, pharmacists…. 
Which patients should undergo surgery?

- All severe infections posing risk to limb or life
- Necrotizing fasciitis
  - Suspected in severe deep pain in a previously insensate foot
- Necrosis, abscesses, gas gangrene
- Osteomyelitis
- Compartment syndrome
- Ischemia
Duration of antibiotics for DFI and osteomyelitis

**Bone/joint infection**
- Duration depends on extent of surgery and residual infection
- No residual infected tissue → 2 – 5 days
- Residual infected soft tissue → 14 – 28 days
- Residual infected (debrided) bone → 28 – 42 days
- No surgery or residual dead bone → ? months

**Soft tissue infection only**
- Mild → 7 - 14 days
- Moderate → 14 – 28 days
- Severe → 14 – 28 days

Vascular status may impact duration

Division of Infectious Diseases
Mayo Clinic, Rochester, MN

Thank you!
Questions?