Diabetic Foot Osteomyelitis
Objectives

• Recognize patients at risk for diabetic foot infections
• Design a diagnostic work-up for diabetic foot osteomyelitis
• State the principles of management of diabetic foot infections
Challenging Infections of Skin, Soft Tissue and Bone

- Cellulitis - management in the community MRSA era
- Furuncles, carbuncles, skin abscesses
- Recurrent skin abscesses
- Diabetic foot osteomyelitis
Disclosure

• Very few antibiotics have FDA approval for osteomyelitis

• Newer antibiotics often gain approval for skin and soft tissue infections
  – Amoxicillin-clavulanate
  – Daptomycin
  – Linezolid

• Older antibiotics often lack an FDA indication for skin and soft tissue infection
  – Nafcillin
  – TMP-SMX
A previously healthy 40 y/o woman presents with uncomplicated lower extremity cellulitis. Which of the following options is the best treatment?

A. Co-trimoxazole
B. Amoxicillin-clavulanate
C. Linezolid
D. Doxycycline
E. A and B
Skin and Soft Tissue Infections

Purulent
- Furuncle
- Carbuncle
- Abscess

Nonpurulent
- Cellulitis
- Erysipelas
- Necrotizing fasciitis

DL Stevens et al; www.idsociety.org
Purulent SSTIs

• Furuncles - purulent infection of a hair follicle extending through the dermis into the subcutaneous tissue

• Carbuncles - coalescent infection of multiple hair follicles, usually larger and deeper than furuncles

• Abscesses
Purulent SSTIs
Furuncles, Carbuncles, Abscesses

• Skin flora-may be polymicrobial
• *Staph aureus*, recently USA 300 MRSA
Purulent SSTIs
Furuncles, Carbuncles, Abscesses

• Incision and drainage is the cornerstone of management, and is more effective ultrasound guided needle aspiration in an RCT

• Packing may not be necessary for small, uncomplicated abscesses

GF O’Malley Acad Emerg Med 16:470, 2009
Packing versus simple I & D

- Abscess $\leq 5$ cm on trunk or extremities
- $\geq 18$ y/o
Open I & D versus Needle Aspiration

• Primary endpoint = treatment failure
  – Day 0 unable to fully aspirate pus
  – Day 2 residual abscess by US, increased symptoms
  – Day 7-antibiotics and/or continued symptoms or additional procedure

• Randomized by numbered packets-some packets disappeared!

• TMP-SMX DS 2 tabs bid recommended

Open I & D versus Needle Aspiration

101 patients enrolled

54 I & D

43/54 (80%) success

47 needle aspiration

12/47 (26%) success

## Microbiology

<table>
<thead>
<tr>
<th>Culture Result</th>
<th>Incision and Drainage (%)</th>
<th>Ultrasound Guided Needle Aspiration (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
<td>18 (35)</td>
<td>15 (38)</td>
<td>33 (36)</td>
</tr>
<tr>
<td>MSSA</td>
<td>20 (39)</td>
<td>11 (28)</td>
<td>31 (34)</td>
</tr>
<tr>
<td>Group A strep</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (6)</td>
<td>6 (15)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>No culture growth</td>
<td>4 (8)</td>
<td>2 (5)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Mixed growth</td>
<td>5 (10)</td>
<td>5 (13)</td>
<td>7 (11)</td>
</tr>
</tbody>
</table>
Open I & D versus Needle Aspiration

33 patients with MRSA enrolled

- 54 I & D: 11/18 (61%) success
- 13 needle aspiration: 1/13 (8%) success

Packing versus simple I & D

48 patients enrolled

23 I & D + packing
4/23 repeat procedure at 48 hours

25 simple I & D
5/25 repeat procedure at 48 hours

GF O’Malley Acad Emerg Med 16:470, 2009
Purulent SSTIs
Furuncles, Carbuncles, Abscesses

• Antibiotics-necessary only in selected cases
  – systemic signs (fever, tachycardia, tachypnea, leukocytosis)
  – Immunocompromised
  – Extremes of age
  – Recurrent infections
  – Failure after adequate I & D
TMP-SMX vs. placebo after I & D

• N=220
• Age > 16 y/o
• Intervention TMP-SMX DS 2 tabs BID
• Primary outcome: treatment failure at day 7
• Secondary outcome: relapse within 30 days

GR Schmitz; Ann Emerg Med, 56:283, 2010
Exclusions

• Immunocompromised
  – Diabetes, HIV, malignancy
• Fever or signs of systemic illness
• Pregnant or breast-feeding
• Sulfa allergy
• Antibiotics in previous week
• Hospitalized in previous month
## Bacteriology

<table>
<thead>
<tr>
<th></th>
<th>Placebo (%)</th>
<th>TMP-SMX (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
<td>47</td>
<td>60</td>
</tr>
<tr>
<td>MSSA</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Coag neg staph</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Viridans strep</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>No growth</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>other</td>
<td>8</td>
<td>12</td>
</tr>
</tbody>
</table>
Antibiotics After I & D

P = 0.12

Failure

Recurrence
## Management of Treatment Failures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Placebo N=27</th>
<th>TMP-SMX N=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admit-iv antibiotics</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>IV antibiotics in ED</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Repeat I &amp; D</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Sent home w antibiotic</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>I &amp; D plus home with antibiotics</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>
RCT-Antibiotics vs. Placebo After I & D

• N = 161
• 3 months to 18 y/o
• Excluded patients with fever
• TMP-SMX 10-12 mg/kg/day TMP component

Duong; Ann Emerg Med, 55:410, 2010
## Bacteriology

<table>
<thead>
<tr>
<th>Culture Results</th>
<th>Placebo (%)</th>
<th>Trimethoprim-Sulfamethoxazole (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA-MRSA</td>
<td>61 (81)</td>
<td>58 (79)</td>
<td>129 (80)</td>
</tr>
<tr>
<td>MSSA</td>
<td>6 (8)</td>
<td>7 (10)</td>
<td>14 (9)</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>4 (5)</td>
<td>2 (3)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>GAS</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>3 (4)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>No culture/growth</td>
<td>3 (4)</td>
<td>2 (3)</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>

Duong; Ann Emerg Med, 55:410, 2010
RCT-Antibiotics vs. Placebo
Non-inferiority Trial, margin 7%

Duong; Ann Emerg Med, 55:410, 2010
Recurrent Skin Abscesses

• Evaluate site for local cause
  – Inadequate drainage
  – Hidradenitis
  – Pilonidal cyst
  – Foreign body

• R/O neutrophil disorder if onset in early childhood

• Consider decolonization therapy
Decolonization Therapy

- Nasal mupirocin BID x 5 days
- Daily bathing
  - Chlorhexidine
  - Dilute bleach 1/4 to 1/2 cup bleach in tub
- Daily disinfection of clothing, towels, sheets, combs, razors, environmental surfaces
- Consider treating family simultaneously
Purulent SSTIs
Wrap Up

• Incision and drainage
• Packing not be essential for small abscesses
• Antibiotics not necessary for most cases
• Recurrences-look for local cause, consider decolonization strategies

GF O’Malley Acad Emerg Med 16:470, 2009
Figures 1A and 1B: Notice the integrity of the skin, the ill-described border of the lesion as well as the extension of erythema up medial aspect of the leg (figures courtesy of DermNetNZ.org).
Cellulitis

- Low burden of organisms
- Brisk inflammatory response
- Culture yield is low—not recommended for routine practice
- Punch biopsy cultures and serology confirm
  - Group A strep
  - Groups B, G, C, F strep
Cellulitis

• Select agent with good activity against streptococci
• If patient is improving at day 5, antimicrobial therapy may be discontinued
• Coverage for *S. aureus*, including MRSA, is recommended if there is
  – Penetrating trauma
  – Purulent drainage
  – Concurrent MRSA infection elsewhere
Cellulitis
Agents with good strep coverage

- Penicillin G 2-4 million units Q 4-6 h
- Clindamycin 600-900 mg Q 8 h
- Nafcillin 1-2 grams Q 4-6 h
- Cefazolin 1 gram Q 8 h
- Pen VK 250-500 mg po Q 6 h
- Cephalexin 500 mg po Q 6 h
- Doxycycline
- TMP-SMX
Duration of Therapy
Uncomplicated Cellulitis

121 subjects enrolled

87 eligible for randomization at day 5

43 received 5 more days of therapy

42/43 resolved at day 14 and relapse free at day 28

44 received 5 days of placebo

43/44 resolved at day 14 and relapse free at day 28

MJ Hepburn; Arch Intern Med, 164:1669, 2004
Recurrent cellulitis

- Annual recurrence rate 8%-20%

- Risk factors
  - Edema
  - Obesity
  - Eczema
  - Venous insufficiency
  - Tobacco use
  - Malignancy
  - Homelessness
  - Toe web abnormalities, e.g. tinea pedis
Recurrent Cellulitis
Antimicrobial Prophylaxis

- 40 patients
- > 2 episodes in previous 3 years
- Venous insufficiency or lymphatic congestion
- Daily pen VK
- Decreased recurrences P< 0.06

AC Sjoblom; Infection 21:390, 1993
Recurrent Cellulitis
Antimicrobial Prophylaxis

36 subjects enrolled

18 received erythromycin 250 mg bid
zero relapses over 18 months

18 received placebo
9 relapses

Cellulitis Wrap-Up

• Streptococci are the predominant pathogen
• No need to cover MRSA unless
  – Penetrating trauma
  – Purulent drainage
  – Concurrent MRSA infection elsewhere
• 5 days therapy is sufficient if symptoms improving on day 5
• Recurrence common
  – Address risk factors
  – Consider penicillin prophylaxis if recurrences are frequent
Image 4. Diabetic Foot Ulcer (image courtesy antimicrobe.org)
Burden of Disease

• 21 million adults with diabetes in the U.S.
• 2-3% annual incidence of foot ulcer
• 15-30% of patients with foot ulcer require amputation
• 68,000 amputations in 2009

Number of Nontraumatic Lower Extremity Amputations among Diabetics

http://www.cdc.gov/diabetes/statistics/lea/fig1.htm
Diabetic Foot Osteomyelitis

- Risk of amputation in a patient with a diabetic foot ulcer rises 3 to 4-fold when osteomyelitis is present

Ramsey SD; Diabetes Care, 22:382, 1999
Outcomes of Infected Diabetic Foot Ulcer With or Without Osteomyelitis

# Prevalence of Osteomyelitis in Diabetic Foot Ulcers

<table>
<thead>
<tr>
<th>Study</th>
<th>N DFUs</th>
<th>N OM</th>
<th>Prevalence OM</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aragon-Sanchez 2008(1)</td>
<td>498</td>
<td>292</td>
<td>37%</td>
<td>Referral center</td>
</tr>
<tr>
<td>Ramsey 1999(2)</td>
<td>471</td>
<td>79</td>
<td>17%</td>
<td>Single center HMO</td>
</tr>
<tr>
<td>Stockl 2004 (3)</td>
<td>2253</td>
<td>855</td>
<td>37.9%</td>
<td></td>
</tr>
</tbody>
</table>

Image 4. Diabetic Foot Ulcer (image courtesy antimicrobe.org)
Diagnostic Criteria
Definite: >90% specificity

• Bone sample with both:
  – Positive culture
  – Positive histology
• Purulence in bone at surgery
• Atraumatically detached bone fragment removed from ulcer
• Bone abscess on MRI

Diagnostic Criteria
Probable: 50-90% specificity

• Visible cancellous bone in ulcer
• MRI shows bone edema
• Bone culture positive
• Bone histology positive

Diagnostic Criteria-Probable
Any TWO of the following:

- Plain X-rays show cortical destruction
- MRI shows bone edema or cloaca
- Probe to bone positive
- Visible cortical bone
- ESR > 70 mm/hr with no other plausible explanation
- Non-healing wound despite adequate offloading and perfusion for > 6 weeks
- Ulcer of > 2 weeks duration with clinical evidence of infection
Approach to Patient

• History
  – Duration of ulcer
  – Trauma-penetration through tennis shoe?
  – Local care at home-Soaking?

• Exam
  – Rubor, dolor, calor
  – Visible bone
  – Probe to bone
  – Perfusion
  – Sensation
Approach to Patient

• Lab
  – CBC
  – ESR
  – HbA1c

• Imaging
  – Plain films
Approach to Patient

• Who should undergo an MRI?
  – Ulcer present > 2 weeks PLUS signs of inflammation
  – Ulcer not healed after 6 weeks, despite adequate perfusion and unloading
  – Probe to bone positive
  – Visible cortical bone
  – ESR > 70
  – Plain film with cortical destruction
Management

• Treat empirically with broad spectrum antibiotics if SIRS criteria present

• In the absence of SIRS
  – Debride as needed
  – Send bone for culture and histology

• Assess perfusion and re-perfuse if necessary

• Unload the ulcer

• Provide culture-directed antimicrobial therapy
Common Pathogens in DFO

- *Staphylococcus aureus*
- Streptococci
  - Group B strep
  - Group A, G, C strep
- Enterobacteriaceae
  - E. coli
  - Klebsiella
- *Pseudomonas aeruginosa*
- Anaerobes
Typical IV Empiric Regimen

• Vancomycin
  – MRSA
  – Streptococci

• Ertapenem
  – Broad coverage of enterobacteriaceae, including ESBL organisms, as well as anaerobes
  – Does not cover P. aeruginosa
When is therapy directed at *P. aeruginosa* indicated?

- Culture positive for *P. aeruginosa*
- High “cost of failure”
  - Sepsis syndrome
- High risk that *P. aeruginosa* is infecting pathogen
  - History of soaking the limb
  - Previous history of *P. aeruginosa* infection at the site
Intravenous agents for *P. aeruginosa*

- Cefepime
- Ceftazidime
- Imipenem-cilastatin
- Meropenem
- Doripenem
- Aztreonam
Intravenous Agents for MRSA Osteomyelitis

Vancomycin
- FDA approved for MRSA infection
- Decades of clinical experience
- Less costly
- Requires serum level monitoring
- Nephrotoxic at higher levels
- 2.5 fold increased risk of failure compared to beta lactams

Daptomycin
- FDA approved for bacteremia and soft tissue infections
- Higher drug acquisition cost
- Once daily dosing
- No serum level monitoring
- Good bone penetration
- Good outcomes in uncontrolled case series
## Cochrane Review

### Oral versus IV Therapy for DFO

<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>IV</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of treatment remission</td>
<td>70/80</td>
<td>58/70</td>
<td>1.04 (0.92-1.18)</td>
</tr>
<tr>
<td>12 month remission</td>
<td>49/64</td>
<td>44/54</td>
<td>0.94 (0.78-1.13)</td>
</tr>
<tr>
<td>Mild adverse events</td>
<td>11/64</td>
<td>8/54</td>
<td>1.08 (0.49-2.42)</td>
</tr>
<tr>
<td>Severe adverse events</td>
<td>3/49</td>
<td>4/42</td>
<td>0.69 (0.19-2.57)</td>
</tr>
</tbody>
</table>

Oral Empiric Regimen

- **TMP-SMX**
  - Active against 97.5% of *S. aureus*
- **Moxifloxacin**
  - 400 mg po daily

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Bactrim</th>
<th>Bactrim + FQ</th>
<th>FQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>72%</td>
<td>82%</td>
<td>75%</td>
</tr>
<tr>
<td>Klebsiella pneumonia</td>
<td>87%</td>
<td>90%</td>
<td>97%</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>88%</td>
<td>93%</td>
<td>98%</td>
</tr>
<tr>
<td>Staph. aureus</td>
<td>97.5%</td>
<td></td>
<td>54%</td>
</tr>
</tbody>
</table>
## TMP-SMX Dosing

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Cases</th>
<th>Dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saengnipanthkul(1)</td>
<td>66</td>
<td>Chronic OM</td>
<td>1 DS BID</td>
<td>45% cure</td>
</tr>
<tr>
<td>Sanchez(2)</td>
<td>25</td>
<td>S. aureus Debrided Rifampin added</td>
<td>7 mg/kg/day 9 months</td>
<td>100% cure</td>
</tr>
<tr>
<td>Nguyen(5)</td>
<td>28</td>
<td>Rifampin 10 mg/kg bid added</td>
<td>8 mg/kg/day</td>
<td>78% cure</td>
</tr>
<tr>
<td>De Barros(3) Portuguese</td>
<td>60</td>
<td></td>
<td>TMP 20 mg/kg/day</td>
<td>98%</td>
</tr>
<tr>
<td>Stein(4)</td>
<td>39</td>
<td>Orthopedic implants 8 subjects dropped out</td>
<td>TMP 20 mg/kg/day</td>
<td>67%</td>
</tr>
</tbody>
</table>

### Rifampin RCTs
#### Osteomyelitis in Non-diabetics

<table>
<thead>
<tr>
<th>Author</th>
<th>Monotherapy</th>
<th>Rifampin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norden, van der Auwera</td>
<td>12/21 (57%)</td>
<td>17/20 (85%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Zimmerli</td>
<td>7/12 (58%)</td>
<td>12/12 (100%)</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

Rifampin in Diabetic Foot Osteomyelitis
Retrospective Study

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy</th>
<th>Rifampin Regimen</th>
<th>P (Fisher)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>15/27 (55%)</td>
<td>17/23 (74%)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Senneville E, Diabetes Care 31:637–642, 2008
Antimicrobial Therapy for DFO

Wrap-Up

• If systemic signs absent, delay therapy until bone sample obtained for culture
• IV therapy still considered standard by many
• Oral therapy may be considered for mild to moderate disease
• Rifampin looks like a promising adjunct, but limited data, and not FDA approved for OM
## Extent of Debridement

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Design</th>
<th>Duration therapy</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bamberger 1987</td>
<td>51</td>
<td></td>
<td>&gt;10 weeks</td>
<td>53%</td>
</tr>
<tr>
<td>Nix 1987</td>
<td>24</td>
<td>Cipro + mtz</td>
<td>115 days</td>
<td>29%</td>
</tr>
<tr>
<td>Peterson 1989</td>
<td>29</td>
<td>Limited debridement</td>
<td>3 months</td>
<td>65%</td>
</tr>
<tr>
<td>Ha Van 1996</td>
<td>35</td>
<td>Limited debridement</td>
<td>Mean 246 days</td>
<td>57%</td>
</tr>
<tr>
<td>Venkatesan 1997</td>
<td>22</td>
<td>Limited debridement</td>
<td>Median 12 weeks</td>
<td>81%</td>
</tr>
<tr>
<td>Pittet 1999</td>
<td>50</td>
<td>Occasional debridement</td>
<td>IV 24 days + &gt; 6 weeks oral</td>
<td>70%</td>
</tr>
<tr>
<td>Eneroth 1999</td>
<td>112</td>
<td>I &amp; D or bone resection</td>
<td>IV 7 days + 17-18 weeks oral</td>
<td>45%</td>
</tr>
<tr>
<td>Senneville 2001</td>
<td>17</td>
<td>Rifampin + ofloxacin</td>
<td>IV 5.5 days</td>
<td>88%</td>
</tr>
<tr>
<td>Oral 6 months</td>
<td></td>
<td>IV mean 40 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yadlipalli 2001</td>
<td>58</td>
<td>“least resection possible”</td>
<td>IV mean 40 days</td>
<td>79%</td>
</tr>
</tbody>
</table>
Debridement
Goal of Initial Operation

• Removal of callus, fibrinous or other acellular debris, and any areas of obvious/irreversible necrosis.

• Draining any abscess cavities / joint space infections that are present

Neal Barshes, MD
Debridement
Objectives of First or Second Stage

• Resecting any remaining necrotic, non-viable or grossly-infected bone.
• Achieving soft tissue coverage over any remaining bone.
• Any further procedures needed to optimize subsequent foot function or surgical offloading (ex. Achilles tendon lengthening, completion transmetatarsal amputation)

Neal Barshes, MD
Standardization of Offloading

Piaggesi A, Diabetes Care: 586, 2007