Infections in the Diabetic Patient
Richard A. Jacobs, M.D.,PhD.

Overview
- Pathophysiology
- Generalizations about infections in the diabetic patient
- Case presentations

Pathophysiology
- Adaptive immunity
  - T-cell function and humoral immunity
  - Minimal effect
  - Normal immunoglobulins and response to vaccinations
Pathophysiology

- Defects in host defense thought to be mediated by hyperglycemia
  - Innate immunity
    - Complement
    - Pro-inflammatory cytokines—TNF, IL-6
  - Cell mediated immunity—PMNs
    - Chemotaxis & phagocytosis
    - Oxidative burst
    - Intracellular killing

Basal levels of cytosolic calcium, phagocytosis, and adenosine triphosphate (ATP) content in polymorphonuclear leukocytes (PMNLs) from controls and patients with non-insulin-dependent diabetes mellitus

The relation between cytosolic calcium ([Ca^{2+}]_i) levels in polymorphonuclear leukocytes (PMNLs) and serum glucose levels (top), between phagocytosis and serum glucose levels (middle), and between phagocytosis and [Ca^{2+}]_i levels (bottom) in PMNLs in patients with non-insulin-dependent diabetes mellitus
In patients with non-insulin-dependent diabetes mellitus, the effect of 3 months of treatment with glyburide on cytosolic calcium levels, adenosine triphosphate (ATP) content, and the phagocytic activity of PMNLs

Clinical Correlations

- Glucose control and surgical site infections in cardiothoracic surgery (Infect Control and Hosp Epidemiol 2001;22:607)
  - Glucose ≥ 200 mg/dL 48 hours before or after surgery associated with increased risk of SSI (OR 2.02, P = .007)
  - CMS now using this as a key indicator for patient safety and extending it to other types of surgery.

Clinical Correlations of Hyperglycemia

- Outcomes in patients receiving parenteral nutrition (Diabetes Care 2005;10:2367)
  - Increased risk of cardiac complications, infection, systemic sepsis
- Outcomes in trauma patients (J of Trauma 2004;56:1058)
  - Early (first 2 days) hyperglycemia (> 220 mg/dL) associated with increased infection and mortality
Clinical Correlations of Hyperglycemia

- Diabetics undergoing elective surgery (J of Parenteral and Enteral Nutrition 1998;22:77)
  - Early (1 day) hyperglycemia (> 220 mg/dL) associated with 5.7 fold increased risk of serious infection
  - Glucose < 150mg/dL associated with lower infection rate and mortality
  - Glucose of > 200 mg/dL associated with increased risk of SSI

CONCLUSION

• HYPERGLYCEMIA NOT GOOD

Infections in Diabetics—General Principles

- Expect the worst and be pleased by anything better
  - Severe & complicated infections common
  - PNA—>increased risk of bacteremia and death
  - Cholecystitis—>emphysematous cholecystitis
  - Pyelonephritis—>perinephric abscess, emphysematous pyelonephritis, papillary necrosis
  - Be aggressive—treat early
  - Be vigilant—follow carefully
Infections in Diabetics—General Principles

- Two types of infections
  - Those that occur with increased frequency in diabetics, but also occur in other hosts
  - Those seen predominantly in diabetics (>50%)

Infections in Diabetics

- Increased incidence in diabetics, but occur in other hosts
  - **Head and Neck**
    - Oral and esophageal candidiasis
    - Periodontal disease
  - **Pneumonia**
    - Unusual pathogens
      - S. aureus, klebsiella, TB (+ PPD = 10 mm)
      - S. pneumoniae
    - Increased morbidity and mortality
    - Remember pneumovax

- **Abdominal**
  - Cholecystitis —> c/b emphysematous cholecystitis
  - Salmonella, campylobacter—> due to decreased mobility

- **Urinary tract**
  - Cystitis—>
    - Colonization upper tract in 40%—> thus treat for 7 days, NOT 3 days
  - Pyelonephritis—>
    - 5 X more common
    - Increased risk of complications—> renal/perinephric abscess, renal papillary necrosis
Infections in Diabetics

- Increased incidence in diabetics, but occur in other hosts
  - Skin and Soft Tissue
    - Surgical wound infections
    - Foot infections/osteomyelitis

Infections in Diabetics

- Infections seen predominantly in diabetics
  - Head and neck
    - Rhinocerebral mucormycosis
    - Malignant (invasive) otitis externa
  - Urinary tract
    - Emphysematous cystitis/pyelitis/pyelonephritis
  - Skin and soft tissue
    - Necrotizing fasciitis
    - Fournier’s gangrene

Case Presentation

- A 56 year old diabetic presents with an ulcer on the metatarsal–phalangeal area of the plantar aspect of the foot. There is surrounding cellulitis with a necrotic base to the ulcer, but no purulent material can be expressed and bone is not showing. He has no F/C.
International Working Group on the Diabetic Foot proposed “PEDIS” classification:
- P—perfusion
- E—extent/size
- D—depth/tissue loss
- I—infection
- S—sensation
PEDIS Clinical Classification of Diabetic Foot Ulcers

- PEDIS Grade:
  - I—clean w/o infection
  - II—mild—≥ 2 of the following: purulence, erythema, pain, tenderness, warmth, induration; cellulitis < 2 cm; skin / superficial subcut tissue
  - III—as above + one of the following: > 2 cm cellulitis, lymphangitis, necrosis, bone/joint/muscle involvement
  - IV—Ill = metabolic instability or systemic toxicity

Purpose of Classification

- Assist the clinician in assessing severity of disease
  - Grade I & II—less complicated and able to treat as outpatient
  - Grade III & IV—more extensive tissue involvement and/or metabolic alterations—require hospitalization, parenteral antibiotics and surgical intervention
- Validation
  - Higher the score greater likelihood of amputation and higher anatomic level of amputation
What is the bacteriology?

1. S aureus
2. Gp A strep
3. Staph + gp A strep
4. Polymicrobial--gpc, gnr, anaerobes

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Bacteriology

(J Clin Microbiol 2007;45:2819)

- Multicenter study of 433 patients with pretreatment cultures
  - Aspiration, curettage, or biopsy of tissue
- Results
  - 48% aerobes
  - 44% aerobes and anaerobes
  - 1% anaerobes
  - Average 2.7 aerobes and 2.3 anaerobes per culture

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Bacteriology

- Aerobes
  - 80% gram–positive
    - Staphylococcus
    - Streptococcus
    - Enterococcus
  - 20% gram–negative
    - Enterobacteriaceae
    - Pseudomonas
- Anaerobes
  - Gram–positive cocci
  - Bacteroides fragilis group
  - Prevotella
  - Porphyromonas
Outcomes of Therapy - Diabetic Foot Infections

<table>
<thead>
<tr>
<th>Wound Healing</th>
<th>Clindamycin (n=25)</th>
<th>Cephalexin (n=27)</th>
<th>Total (n=52)</th>
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<tbody>
<tr>
<td>Healed</td>
<td>10 (40%)</td>
<td>9 (33%)</td>
<td>19 (37%)</td>
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<tr>
<td>Improved</td>
<td>14 (56%)</td>
<td>18 (67%)</td>
<td>32 (62%)</td>
</tr>
<tr>
<td>Unimproved</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
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Role of MRSA in DFI

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<tr>
<th>(Diabet Med 2003:48:406)</th>
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<tr>
<th>Total number of isolates</th>
<th>1998</th>
<th>2001</th>
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<tbody>
<tr>
<td>Total number of organisms</td>
<td>1.4</td>
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<tr>
<td>Staphylococcus aureus</td>
<td>13 (67)</td>
<td>17 (81)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>1 (5.3)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Enterococci</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other species</td>
<td>2 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Total number of organisms</td>
<td>203</td>
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What is the treatment of choice?

1. Keflex
2. Clindamycin
3. Keflex + clindamycin
4. Levofloxacin
5. Septra/Bactrim

100%
Therapeutic Considerations

- **THE WAY IT WAS**
  - Gp A strep + MSSA = dicloxacillin or cephalexin (Keflex®)
- **THE WAY IT IS**
  - Gp A strep + ?? MRSA

Therapeutic Considerations

- **TMP-SMX (95–100%); doxy/minocycline (90–95%); clindamycin (85–95%) are active against CA-MRSA**
- **TMP-SMX and doxy/mino +/− against gp A strep**
  - If use these must add ß-lactam [PCN, Amox, 1st gen ceph (Keflex®)]
- **Clinda active against gp A strep**

What is the treatment of choice?

1. Keflex
2. Clindamycin
3. Keflex + clindamycin
4. Levofoxacin
5. Septra/Bactrim
What is the best way to make the diagnosis of osteomyelitis?

1. Bone biopsy
2. Tc bone scan
3. Indium WBC scan
4. Probing to bone
5. MRI

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<tr>
<th>Procedure</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>Probe to bone test</td>
<td>66%</td>
<td>85%</td>
</tr>
<tr>
<td>Tc Bone scan</td>
<td>68-100%</td>
<td>18-79%</td>
</tr>
<tr>
<td>Indium WBC scan</td>
<td>80-100%</td>
<td>70-90%</td>
</tr>
<tr>
<td>MRI</td>
<td>98%</td>
<td>89%</td>
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Gold Standard is bone biopsy with culture and histology

"The Diabetic Foot"
Outpatient diagnosis of osteomyelitis

(+ ) MRI—what is best way to define bacteriology?

1. Culture wound?
2. Bone biopsy?
Defining Bacteriology of Osteomyelitis in Diabetics
(Senneville E et al. Clin Infect Dis 2006;42:57)

- 81 episodes of osteomyelitis, off abx at least 4 wks
  - Pathogens in bone bx found in swab only 30% of time
  - Concordance in 17%
    - S. aureus—42.8%
    - Gram-negative bacilli—28.5%
    - Streptococci—22.5%

Does Defining Bacteriology Improve Outcome?
(Lombart AM et al. 43rd Annual Meeting of IDSA #337)

- 50 patients with osteomyelitis
  - 24 Rx’d with empirical abxs
  - 26 treated based on bone bx
- Successful therapy—healing, major/minor amputations/recurrences
  - 76.9% of those with bone bx v. 45.8% of those treated empirically

Bacteriology of Diabetic Foot Infections

- Cellulitis or ulcer with cellulitis
  - E. hemolytic strep and S. aureus
  - Duration—10–14 days
- Chronic ulcer or previously treated
  - E. hemolytic strep, S. aureus, and GNRs
    - If low prevalence of MRSA—Augmentin®, levofloxacin or moxifloxacin
    - If MRSA prevalent—Clindamycin + fluoroquinolone or ertapenem
  - Duration—2–4 weeks
- "Fetid foot": necrosis or gangrene
  - E. hemolytic strep, S. aureus, enterococcus GNRs, nonfermenting GNRs, anaerobes—often MRSA organism
    - Vancomycin + Zosyn® or vancomycin + ertapenem or vancomycin + cefazolin (cefazolin) + metronidazole
  - Duration—6 weeks
Adjunctive Therapy

- Growth factors
  - G-CSF (granulocyte), PDGF (platelet-derived), EGF (epidermal)
  - Insufficient data to support routine use
- HBO (Hyperbaric oxygen)
  - One small double-blinded study showed benefit (Eur J Vasc Endovasc Surg 2003;25:513)
  - Need more and larger controlled studies
  - If it is available (and you are a “believer”) it is used

Etiology and Classification

- Etiology
  - Dermatophytes—80%
    - Trichophyton rubrum
    - Trichophyton mentagrophytes
    - Non-dermatophytes
    - Candida spp.
    - Molds
      - Acremonium
      - Aspergillus
      - Fusarium
Therapy of Onychomycosis

- **Topical**—Penlac® (Ciclopirox olamine 8% lacquer)
  - Daily X 48 wks—30% mycologic cure & 7% clinical cure
- **Oral therapy**
  - Griseofulvin is less effective than azoles (fluc/itra) or terbinafine (Lamisil®)
  - Terbinafine 250/day for 12 weeks is mycologically superior, clinically comparable and better tolerated than azole regimens

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Therapy of Onychomycosis
Arch Dermatol 2002;138:353

<table>
<thead>
<tr>
<th>Continuous terbinafine</th>
<th>Pulse terbinafine</th>
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<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>8</td>
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<table>
<thead>
<tr>
<th>Weeks of treatment</th>
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<tr>
<td>Terbinafine: 250 mg qid</td>
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**Table 2. Mycologic and Clinical Cure Rates**

<table>
<thead>
<tr>
<th></th>
<th>Monthly cure (%)</th>
<th>Complete cure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naftifine (n = 11)</td>
<td>56 (50)</td>
<td>35 (30)</td>
</tr>
<tr>
<td>Itraconazole (n = 11)</td>
<td>50 (46)</td>
<td>30 (25)</td>
</tr>
<tr>
<td>Fluconazole (n = 11)</td>
<td>35 (31)</td>
<td>25 (21)</td>
</tr>
<tr>
<td>Terbinafine (n = 11)</td>
<td>36 (32)</td>
<td>24 (21)</td>
</tr>
<tr>
<td>Complete cure (%)</td>
<td>23 (20)</td>
<td>15 (14)</td>
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</table>

*These data pertain to number percentages of patients.

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UTIs in Diabetics

- Bacteriology same as in non-diabetics
- Because of colonization of upper tract and high recurrence rate with 3 days of Rx, 7 days recommended
- TMP–SMX or FQ recommended
- **REMEMBER**
  - Complications common
  - If no response in 72 hours—look for them
  - Don’t be fooled by normal UA—obstruction present in 30%–40% with complications
A 50 year old female diabetic presents requesting a physical and referral for colonoscopy. As part of the evaluation, at the request of the patient, a UA with culture is obtained—concern about increased risk of infection despite being asymptomatic.

Culture grows $10^5$ E. coli

1. Yes
2. No

Asymptomatic Bacteriuria in DM

- 55 received 14 D TMP-SMX; 50 placebo
- At 4 weeks, 78% of placebo group and 20% of antibiotic group had bacteriuria
- BUT in 27 months of follow-up:
  - 40% placebo and 42% Rx—>symptomatic UTI
  - Time to first symptomatic episode the same
  - Pyelonephritis and hospitalizations for UTIs the same
- CONCLUSION: no need to screen for or RX asymptomatic bacteriuria in diabetics
Case Presentation

- A 50 year old female diabetic presents with dysuria, urgency and frequency and LGF. Exam shows R CVA tenderness.
- UA + leukocyte esterase
- Culture eventually grows a sensitive E coli
- 4 days into a course of TMP-SMX (Septra/Bactrim), she calls and says fevers higher and she has continued N & V

What would you do?

1. Repeat urine C&S
2. Change to cipro
3. Obtain a CT
4. Admit for IV therapy
5. All of the above
Case Presentation

- A 42 y/o diabetic presents with a 5 day h/o sinus congestion w/o preceding viral URI. A diagnosis of acute sinusitis is made and he is treated with amoxicillin. He fails to improve and 4 days later presents with ptosis and proptosis.
Mucormycosis (Zygomycosis)

- Caused by saprophytic fungi of order Mucorales—rhizopus, absidia, mucor, rhizomucor
- Predilection for vascular invasion (like aspergillus) and direct tissue invasion
- Predisposing factor
  - DM—rhinocerebral
  - Neutropenia—rhinocerebral/pulmonary
  - Iron overload states

Rhinocerebral Mucormycosis

- Early—facial or ocular pain; Sxs of sinusitis
- Late—orbital cellulitis, ptosis, proptosis, loss of EOM
- Palatal/nasal necrosis or eschar very suggestive
- REMEMBER:
  - Diabetics/neutopenic pts with new onset face or eye pain should have imaging of sinus/orbits

Case Presentation

- A 65 y/o diabetic man was visiting his son in Marin. They frequently used the hot tub. About 10 days later, both the father and son developed painful, red, swollen external ears. They were treated with topical antibiotic/hydrocortisone. The son improved rapidly, but the father failed to improve despite 3 courses of Rx.
Almost exclusively seen in elderly diabetics
Almost always Psuedomonas (rarely S aureus)
Invasion through fissure of Santorini at bone-cartilage junction
Severe pain hallmark: painful, red, swollen external ear with granulation/debris in canal
Facial palsy common
Rx = 6–8 weeks abx with monitoring by MRI/radionuclide scans; Otolaryngologists reluctant to do surgery

Basilar Skull Osteomyelitis (Malignant Otitis Externa)
References


References