

Diabetic Foot Ulcers & Osteomyelitis

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Objectives

- Describe pathogenesis & clinical characteristics of diabetic foot ulcers and osteomyelitis
- Identify most likely etiologic organism
- Suggest appropriate drug therapy

Diabetic foot ulcers



Diabetic Foot Ulcers

- Leading cause of hospitalization in diabetic patients
- Typically occur in patients with peripheral neuropathy and arterial vascular insufficiency
- Cellulitis, soft tissue necrosis, osteomyelitis or sepsis
- 85% of lower extremity amputations are preceded by foot ulcers

Diabetic Foot Ulcers: Pathogenesis

- Sensory neuropathy → loss of appreciation of pain/temperature/injury
- Peripheral artery dz → decreased blood flow
- Hyperglycemia → impair neutrophil fxn
- Trauma → ulceration → progressive necrosis, poor wound healing, avenue for infection

Classification of Infection

- Mild
 - Superficial ulceration, no systemic toxicity
 - Purulent drainage, erythema, minimal/absent cellulitis
 - Therapy: oral abx, local podiatry care
- Moderate
 - Ulceration/necrosis of deep tissues +/- involvement of muscle, tendon, joint, bone
 - No fever, chills, tachycardia, hypotension, ect.
 - Therapy: IV abx, surgical drainage
- Severe
 - Ulceration deep tissues + systemic toxicity
 - Fever, chills, tachycardia, hypotension, confusion, ect.
 - Therapy: IV abx, surgical debridement

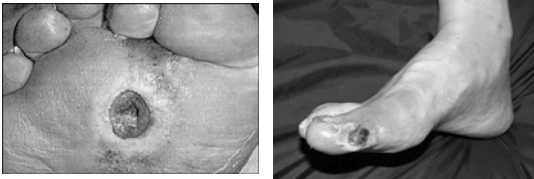
Microbiology

- Polymicrobial:
 - 3 to 9 organisms per infection in hospitalized patients
 - Aerobes:
 - Gram + (80% of cases): Staphylococci, Streptococcus, Enterococcus
 - Gram – (50% of cases): *Enterobacter* spp., *Pseudomonas*
 - Anaerobes (50% of cases):
 - Gram + cocci, *Prevotella*, *Bacteriodes*

Microbiology

<u>Gram Negative</u>	<u>Gram positive</u>	<u>Anaerobes</u>
<i>Proteus</i> spp.	<i>S. aureus</i>	<i>Fingoldia magna</i>
<i>E. coli</i>	<i>S. epidermidis</i>	<i>Clostridium</i> spp.
<i>Klebsiella pneumoniae</i>	<i>Streptococci</i> spp.	<i>Bacteroides</i> spp.
<i>P. aeruginosa</i>	<i>Enterococcus</i> spp.	<i>Prevotella</i> spp.
<i>Enterobacter</i> spp.		<i>Porphyromonas</i> spp.

Diabetic Foot Ulcers



Typical diabetic foot ulcer caused by high plantar pressures at the second metatarsal head

Case 1

- CC: 78 y/o F presents with ulceration on the bottom of her L foot that appears infected
- PMH: uncontrolled DM2x20yrs, peripheral neuropathy, retinopathy, HTN, high cholesterol
- Meds: glucotrol XL 10 mg bid, amlodipine 5 mg qd, simvastatin 10 mg qhs
- PE: erythema+swelling of L foot, no apparent involvement beyond superficial tissue
- Labs/vitals: Scr 1.3, BP 132/76, HR 71, afebrile
- Pharmacy is consulted for empiric abx therapy!

Case 1, cont.

1. Stage
 - a) Mild
 - b) Moderate
 - c) Severe
2. Organisms most likely involved
 - a) *S. pneumoniae*, *N. meningitidis*, *Enterococcus faecium*
 - b) *Candida* spp., *H. pylori*, *Bacteriodes* spp.
 - c) *S. aureus*, *P. aeruginosa*, *B. fragilis*
3. Your empiric abx treatment recommendation:
 - a) TMP/SMX PO + levofloxacin PO x 10d
 - b) Imipenem/Cilastatin IV + daptomycin IV x 2-4 wks
 - c) Penicillin VK + metronidazole PO x 14d

Case 1, cont.

- 1) Stage
 - a) *Mild: based on sx and no systemic/deep tissue involvement
 - b) Moderate: no signs of deep tissue involvement
 - c) Severe: no fever, tachycardia, hypotension, systemic toxicity
- 2) Organisms most likely involved:
 - a) *S. pneumoniae*, *N. meningitidis*, *Enterococcus faecium*
 - b) *Candida* spp., *H. pylori*, *Bacteriodes*
 - c) **S. aureus*, *P. aeruginosa*, *B. fragilis*
- 3) Your empiric abx treatment recommendation:
 - a) *TMP/SMX PO + levofloxacin PO x 10d: covers MRSA/gram +, gram –, and anaerobes for empiric therapy
 - b) Imipenem/Cilastatin IV + daptomycin IV x 2-4 wks: IV therapy not indicated at this time
 - c) Penicillin VK + metronidazole PO x 14d: no gram – coverage

Empiric Tx:
Mild Infections (oral tx)

- If no recent abx use, can direct towards gram +’s:
 - CA-MRSA: TMP/SMX, clindamycin
 - MSSA: dicloxacillin, 2nd gen. ceph, fluoroquinolone
- If recent abx use, add gram – coverage:
 - MRSA: from above if sensitive; or consider linezolid
 - Gram –’s: add FQ (cipro, levo, moxi)
- Tx for 1-2 weeks if improvement
- Longer duration or IV tx if no improvement

Empiric Tx:
Moderate Infections (IV)

- Direct tx towards gram +, gram -, anaerobes until cultures available
 - Ciprofloxacin + clindamycin, ampicillin/sulbactam, piperacillin/tazobactam
- Suspicion of resistant organisms:
 - Gram + (MRSA): vanco, linezolid, or daptomycin
 - Gram -: ceftazidime, aztreonam, or cipro
 - Anaerobes: metronidazole
- Tx for 2-4 weeks, switch to PO if good response

Empiric Tx:
Severe Infections (IV)

- Mono or combo tx until cultures available
- Monotherapy
 - piperacillin/tazobactam OR imipenem
 - Consider coverage for MRSA
- Combo therapy
 - vanco, linezolid, OR daptomycin
 - PLUS:
 - ceftazidime, aztreonam, OR ciprofloxacin
- Anaerobes: metronidazole, imipenem
- Tx for 2-4 weeks based on clinical response

Case 2

- Same patient from Case 1 presents 1 week later, c/o of leg pain, erythema of lower leg, swelling, fever x 2 days
- Pt. admits to not completing full course of abx prescribed at last visit
- Labs/PE: Scr 1.2 mg/dl, WBC 16000 cells/mm³, BP: 106/57 mmHg, HR 103 bpm, Temp 101.4 °F
- Pharmacy is called for recommendations!

Case 2, cont.

- 1) Empiric abx therapy you recommend:
 - a) Repeat course of TMP/SMX PO + Levofloxacin PO x14 days; persisting infection likely due to lack of adherence
 - b) Linezolid PO + moxifloxacin PO x 28d; change abx combination in case of organism resistance to recent abx exposure
 - c) Daptomycin IV + Imipenem/cilastatin IV x 28d based on clinical response
 - d) Vancomycin IV + ceftazidime IV x 28d based on clinical response

Case 2, cont.

- 1) Empiric abx therapy you recommend
 - a) Repeat course of TMP/SMX PO + Levofloxacin PO x14 days; persisting infection likely due to lack of adherence: no, pt requires hospital admission & IV tx
 - b) Linezolid PO + moxifloxacin PO x 28d; change abx combination in case of organism resistance to recent abx exposure: no, pt requires IV tx
 - c) *Daptomycin IV + Imipenem/cilastatin IV x 28d based on clinical response: IV tx covers gram +, gram -, and anaerobes
 - d) Vancomycin IV + ceftazidime IV x 28d based on clinical response: no, no anaerobic coverage

Special Considerations

- *Enterococcus* spp. (not common pathogen)
 - NO enterococcal coverage: clindamycin, cephalosporins, ticarcillin
 - Consider: penicillin, ampicillin, piperacillin, imipenem/cilastatin, vancomycin
- *Pseudomonas aeruginosa*
 - piperacillin, ceftazidime, imipenem/cilastatin, quinolone, amikacin
 - Increasing resistance to cipro, tobra
- MRSA
 - vancomycin; linezolid; daptomycin; synergid; tigecycline

Factors Affecting Abx Selection

- Vascular impairment - penetration of abx
- Impaired renal funct. - caution aminoglycosides
- Autonomic neuropathy/gastroparesis
 - decreased absorption of oral abx
- Abx resistance patterns, previous abx exposure
- Drug allergies (PCN, Sulfa)
- Linezolid: myelosuppression (up to 45% of pts)
- Severe infections more likely polymicrobial

Treatment: Wound Care

- Apligraf®: living/biological dressing made from neonatal foreskin
 - approved for adjunct treatment of mild diabetic foot ulcers
- Becaplermin (Regranex®) Gel 0.01%: topical recombinant human platelet-derived growth factor (rhPDGF)
 - Limited effects due to elevated proteases in ulcers
- Promogran®: collagen & oxidized regenerated cellulose, sterile & freeze dried matrix sheet binds/inactivates proteases, protects growth factors
 - Indicated for use in exuding wounds
- Vacuum Assisted Closure®: negative pressure wound therapy through sterile, latex-free foam dressing

Treatment, cont.

- Adequate perfusion: promotes healing
- Debridement: removal of dead tissue, foreign materials and particulate matter
 - Generally first step in wound care
- Pressure mitigation: reduce pressure at site of ulcer
 - Bedrest, wheelchair, removable cast walker (“moon boot”)

Osteomyelitis

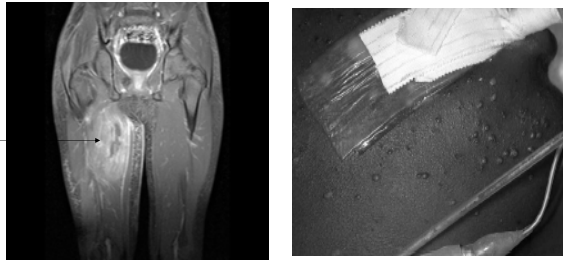
Case

- 15 yr old boy, injury to R thigh during foot ball game
- Pain intense, left game..pain subsided
- During night: chills and 103°F fever
- Next day: lower R thigh hot, swollen, tender
- Knee joint full range of motion
- Small boils on neck and chest..
- X-ray right femur showed soft tissue swelling

Severe CA-MRSA (USA300) Sepsis in Adolescents (n=14)

93% bone and joint infection

50% had vesicles/pustules

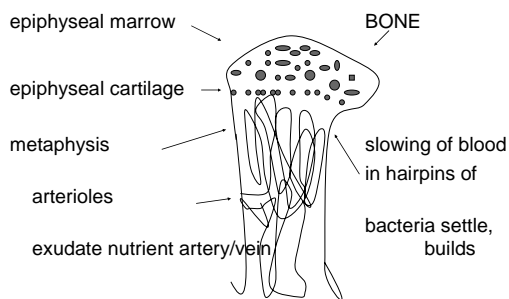


Gonzalez BE et al. *Pediatrics* 2005;115:642-648

Definition & Classification

- Infection of bone, progressive, results in inflammatory destruction of bone
- Based on route infecting organism reaches bone
 - Contiguous-direct inoculation (trauma, prosthetic)
 - 47% of infections
 - Hematogenous-spread through blood stream
 - 20% of infections
 - Typically, patients < 16 years of age
 - Other- due to peripheral vascular disease, DM

Pathogenesis-Hematogenous



Clinical Signs and Symptoms

- Hematogenous:
 - Abrupt onset involving metaphysis of long bones
- Contiguous:
 - Fever, swelling, erythema (soft tissue infection)
 - Open fractures, following hip fracture replacement
- Vascular insufficiency:
 - patients 50 to 70 yrs with diabetes, toes/small bones of feet affected
 - fever, swelling, erythema, septicemia(uncommon)
- Vertebral Osteomyelitis:
 - following trauma/surgery, hematogenous, surgical drainage necessary, paralysis

Disease Course

- Acute Osteomyelitis: (develops days to weeks)
 - treated within 1 weeks responds well to therapy, if delayed may progress to chronic
- Chronic Osteomyelitis: (develops weeks to months)
 - prolonged course of therapy (4 to 6 weeks)
 - relapse common, amputation often necessary in vascular insufficiency
 - multiple courses of abx therapy often required

Microbiology

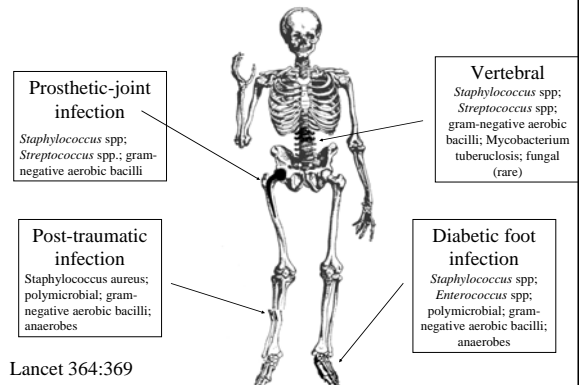
- Hematogenous:
 - 95% single organism
 - *S. aureus*: 50% of isolates
 - Streptococcus, *H. influenzae*, other Gram negatives less common (*E. coli*: vertebral)
 - Pseudomonas/Serratia infections: IVDA
 - Unusual (immunocompromised):
 - Candida, Cryptococcus, Aspergillus, Pneumocystis

Microbiology

■ Contiguous:

- Polymicrobial: *S. aureus* (most common), *Pseudomonas aeruginosa*, *Proteus*, *Streptococcus*, *E. coli*, *S. epidermidis*, anaerobes
- Orthopedic implants: *S. epidermidis*, *S. aureus*
 - 0.5-1% hip, 0.5-2% knee, <1% shoulder
- Puncture wounds of feet: *P. aeruginosa*

Microbiology of Osteomyelitis

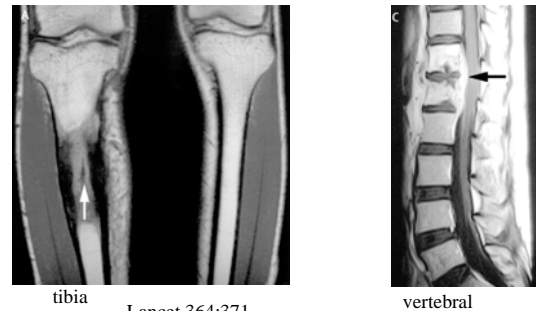


Diagnosis

■ Early diagnosis Critical

- Technetium-99: taken up into areas of increased blood supply, look for changes, 81% sensitivity
- MRI/CT scan
- Blood cultures, biopsy or ulcer swabs
- Synovial fluid aspirate (elevated neutrophils, leukocytes)
- CRP or ESR: non-specific

MRI in Chronic Osteomyelitis



Empiric Treatment: Hematogenous Osteomyelitis

- Cover *S. aureus*, Streptococci, GNB (rare)
 - MRSA: vancomycin, linezolid, daptomycin
 - MSSA: nafcillin, oxacillin, cefazolin, TMP/SMX if allergy
 - GNB: ceftazidime (*Pseudomonas*), cefotaxime, ceftriaxone

Empiric Therapy: Contiguous Osteomyelitis

- Cover *S. aureus*, Streptococci, *Pseudomonas*, GNB, anaerobes
 - vancomycin or linezolid
 - Plus:
 - ceftazidime or cefepime
 - Consider aminoglycoside for GNBs, carbapenem for broad coverage (no *Pseudomonas* coverage with ertapenem)
 - metronidazole or clindamycin for anaerobes

Treatment Basics

- Administer therapy 4 to 6 weeks
- Surgical debridement often required
- IV to PO switch (outpatient treatment)

- Hematogenous:
 - 14 days of IV abx, followed by oral therapy

Prophylaxis in Bone Surgery

- 30 min prior to surgery (hip replacement), continue for 24 hrs following surgery
- Closed fractures:
 - penicillins/nafticillin, cefazolin, ampicillin/sulbactam, vancomycin (PCN allergy)
- Complex fractures:
 - 2nd, 3rd generation cephalosporin, ampicillin/sulbactam, +/- aminoglycoside, fluoroquinolone

Conclusions

- Treat most likely causative organism
 - *Staphylococcus*, Gram negatives, anaerobes
- Adjust therapy based on cultures & sensitivities
- Appropriate duration of therapy
 - IV to PO switch
- Patient considerations
 - Allergies, renal dysfunction, immunosuppression

References

- Wu SC, Driver VR, Wrobel JS, Armstrong DG. Foot Ulcers in the Diabetic Patient: Prevention and Treatment. *Vascular Health and Risk Management*. 2007; 3(1):65-76.
- Citron DM, Goldstein EJC, Merriam CV, Lipsky BA, Abramson MA. 2007. Bacteriology of Moderate-to-Severe Diabetic Foot Infections and In Vitro Activity of Antimicrobial Agents. *Journal of Clinical Microbiology*. 2007; 45(9):2819-2828.
- Lockhart SR, Abramson MA, Beekmann SE, Gallagher G, Riedel S, Diekema DJ, Quinn JP, Doern GV. *Journal of Clinical Microbiology*. 2007; 45(10):3352-3359.
- UpToDate®. Management of Diabetic Foot Ulcers. Accessed 3/10/2008.
- Gilbert DN, Moellering RC, Eliopoulos GM, Sande MA. *The Sanford Guide to Antimicrobial Therapy*, 37th Ed. 2007.
- IDSA Guidelines. Diagnosis and Treatment of Diabetic Foot Infections. Available at: <http://www.journals.uchicago.edu/doi/pdf/10.1086/424846?cookieSet=1>.