Diagnosis & Treatment of skin, soft tissue and bone infections (incl. diabetic foot infections)

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Items to cover

- Increasing resistance to antibiotics
  - more targeted use of antibiotics
  - target patients who really need swabs
  - take specimens in a way that gives meaningful results
- Bacteria in culture report
  - avoid knee-jerk reactions to culture results
- Which bacteria are “pathogens”?
  - skin and soft tissue infections (e.g. cellulitis)
  - “skin ulcers” (pressure sore, venous, diabetic foot)
  - osteomyelitis
- Diagnosis of diabetic foot osteomyelitis
- Antibiotic treatment options
- Role of antimicrobial dressings
Concerns about increasing antibiotic resistance

- World Health Organisation website: “a post-antibiotic era – in which common infections and minor injuries can kill – far from being an apocalyptic fantasy, is instead a very real possibility for the 21st Century.”

- Prime Minister David Cameron stated on 02/07/2014 that the world could soon be "cast back into the dark ages of medicine" unless action is taken to tackle the growing threat of resistance to antibiotics.
Resistance in Gram-positives less of an issue nowadays
- Declining MRSA infection numbers
- More antibiotic options for MRSA than 15 years ago

Resistance in Gram-negatives is now main problem
- Increasing
- Fewer treatment options
- Sometimes virtually untreatable
- We need to reduce unnecessary antibiotic usage particularly for antibiotics with Gram-negative coverage
MEROPENEM is the most powerful antibiotic with activity against Gram-negatives.

In the UK resistance to meropenem was rare before 2005 → significant increase in resistance in past few years.
Diabetic foot ulcer

• No erythema/cellulitis
• No pus
• Not healing!
• Swab: S. aureus
• Does this result help?
Take skin ulcer swabs only if infected

Infection is present if
EITHER purulent secretions
OR >= 2 following criteria are met
- Erythema
- Pain/tenderness
- Local warmth
- Local swelling or induration

2012 Infectious Diseases Society of America Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infections
*Clinical Infectious Diseases* 2012;54(12):132–173
Diabetic foot infections: **how to take microbiology samples**

*IDSA guideline for the Diagnosis & Treatment of diabetic foot infection*

_Clin Infect Dis 2012: 54 (12): 132-172_

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**Table 5. Recommendations for Collection of Specimens for Culture From Diabetic Foot Wounds**

<table>
<thead>
<tr>
<th>Do</th>
<th>Do not</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain an appropriate specimen for culture from almost all infected wounds</td>
<td></td>
</tr>
<tr>
<td><strong>Cleanse and debride</strong> the wound before obtaining specimen(s) for culture</td>
<td></td>
</tr>
<tr>
<td><strong>Obtain a tissue specimen</strong> 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>
<tr>
<td>Culture a clinically uninfected lesion, unless for specific epidemiological purposes</td>
<td></td>
</tr>
<tr>
<td>Obtain a specimen for culture without first cleansing or debriding the wound</td>
<td></td>
</tr>
<tr>
<td>Obtain a specimen for culture by swabbing the wound or wound drainage</td>
<td></td>
</tr>
</tbody>
</table>
• After either DEBRIDEMENT or CLEANSING
• These procedures aim at reducing superficial “colonising” bacteria so that bacteria at deeper levels (more likely to be the cause of infection – if infection criteria are met)
• cleansing of the ulcer with **sterile physiologic glucose solution** by using a **sterile compress gauze** passed over the ulcer surface to reduce the amount of contaminating bacteria → swab from the bottom of the ulcer
Unfavourable outcomes

• Chronic non-healing ulcer
• Osteomyelitis
• Amputation

Treatment strategies

• Glycemic control
• Arterial revascularisation
• Mechanical load relief
• Debridement
• Antimicrobial dressings
• Antibiotics
Group A/C/G streptococcus (S. aureus)

Group A/C/G streptococcus or S. aureus

Group A/C/G streptococcus or S. aureus or anaerobes or coliforms (can be polymicrobial)

Erysipelas

Cellulitis

Necrotizing fasciitis

Myositis
Chronic skin ulcers are often colonised by:

- coliforms
- Pseudomonas aeruginosa
- Anaerobes

⇒ Cellulitis arising from skin ulcers may occasionally be caused by the above organisms
Bacteria in skin ulcers

3 scenarios
- colonization
- critical colonization (no signs of infection but high bacterial load or the presence of certain “pathogens” might result in failure to heal)
- infection (purulent discharge or surrounding cellulitis)


treatments options
- supportive care & appropriate dressings
- dressings with antiseptics (e.g. silver, iodine, honey)
- Sharp debridement or maggot therapy
- systemic antibiotics
Planktonic bacteria or biofilm?

BIOFILM = community of microorganisms attached to a surface and producing extracellular polymeric substances
The BIOFILM may confer various advantages to the bacteria

- Protection from macrophages & immune system
- Limited penetration of antibiotics
- Decreased susceptibility to antibiotics

More difficult to treat infections!

When foreign body involved (pace-maker, prosthetic heart valve, central line, urinary catheter) removal is often required
Biofilms in chronic wounds/ulcers

- No foreign body/material surface
- Bacterial growth along the wound or ulcer surface may be associated with the production of extra cellular polymeric substances → mimics behaviour of bacteria in biofilms over foreign bodies/substrates

The consequences of biofilm formation in wounds & ulcers:
- delayed wound healing
- ineffective immune response
- reduced response to antibiotics and antiseptics
- bacteria, esp. Pseudomonas, may not be culturable using conventional culture methods with short incubation
- In experimental model medical grade honey may inhibit or disrupt biofilm ??? does it happen in vivo
Treatment strategies for non-healing ulcers (suspected biofilm formation)

- Very limited evidence basis to make firm recommendations !!!

- Strategies that have been recommended include:
  - Cleansing
  - Debridement (sharp or autolytic)
  - Larval therapy
  - Antimicrobial dressings

*J Wound Care 2014;23:137-142*

*Clin Infect Dis 2012; 54:132-173*
Most common types of osteomyelitis in adults

“direct inoculation” (exposure during surgery) + “contiguous” (if superficial infection)

- metalwork used for fixation facilitates infection caused by low-pathogenicity bacteria

“contiguous”: bone infected from infected/colonised adjacent soft tissues (chronic ulcers, ischemic toes)
What bacteria are associated with these 4 types of osteomyelitis?

Picture copied & modified from Lancet 2004; 364 p369-79 fig 2
Calcaneal osteomyelitis

Jonathan D Evans foundation year 1 trainee, Adrian M Jennings consultant physician

Department of Diabetes and Endocrinology, Queen Elizabeth Hospital, King’s Lynn PE30 4ET, UK

that did not respond to oral antibiotics. The radiograph clearly shows extensive subcutaneous emphysema of the foot. There is also a curvilinear luency in the calcaneum extending to the cortex, with thinning of the cortex adjacent to the ulcer site. The bony changes were deemed to be secondary to osteomyelitis affecting the calcaneum.

Patient consent obtained.

Cite this as: BMJ 2013;346:f1527

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This plain radiograph shows the right foot of a 69 year old man with type 2 diabetes, who presented with an infected heel ulcer
Microbiology samples for suspected osteomyelitis
Clinical Infectious Diseases 2006; 42:57–62

ULCER SWABS: “obtained after brief cleansing of the ulcer with sterile physiologic glucose solution by using a sterile compress gauze passed over the ulcer surface to reduce the amount of contaminating bacteria → swab from the bottom of the ulcer

BEST NON-INVASIVE PROCEDURE

PERCUTANEOUS BONE BIOPSY: in the surgical room, under fluoroscopic guidance, through intact skin at least 2 cm from the ulcer

GOLD STANDARD
Pathogens associated with diabetic foot osteomyelitis

*Clinical Infectious Diseases 2006; 42:57–62*

<table>
<thead>
<tr>
<th></th>
<th>SWAB</th>
<th>BONE BIOPSY</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of samples</td>
<td>69</td>
<td>76</td>
</tr>
<tr>
<td>Mean no of isolates</td>
<td>1.58</td>
<td>1.54</td>
</tr>
<tr>
<td>Staphylococci</td>
<td>41</td>
<td>65</td>
</tr>
<tr>
<td>Streptococci</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Enterococci</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Other aerobic gram-pos.</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>ALL AEROBIC GRAM-POS.</td>
<td>78</td>
<td><strong>96</strong></td>
</tr>
<tr>
<td>ALL AEROBIC GRAM-NEG (incl. coliforms, Pseudomonas)</td>
<td>28</td>
<td><strong>23</strong></td>
</tr>
<tr>
<td>ANAEROBES</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>total</td>
<td>109</td>
<td>125</td>
</tr>
</tbody>
</table>
Patients with diabetes of lower extremity infections have 10-fold greater risk of osteomyelitis.

Osteomyelitis may complicate as many as 20% of diabetic foot ulcers.

**Diagnosing osteomyelitis is critical to deliver effective treatment**: a much longer course of high-dose antibiotics is required.

Bone exposed or you can probe to bone: could be osteomyelitis.

Plain radiography is often negative during the early stages of osteomyelitis.

MRI most sensitive radiological investigation!
Which antibiotics for cellulitis or osteomyelitis?

- Usually treat as presumptive Gram-positive infection:
  - Flucloxacillin (not allergic to penicillin, no history of MRSA)
  - Doxycycline/teicoplanin (penicillin-allergy or suspected MRSA)
  - Severe sepsis: daptomycin or linezolid + assess need for broader antibiotic coverage

- Broader antibiotic coverage (gram-negatives & anaerobes)
  - In necrotizing fasciitis (pending culture results)
  - In patients with chronic ulcers with severe sepsis OR not responding to gram-positive coverage (pending culture results)

- Assess clinical response
- Reassess on the basis of the culture results, if appropriately taken specimen and esp. in patients not responding to Gram-positive coverage
# Antibiotic options for Gram-positive infections (cellulitis, osteomyelitis)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>IV or oral</th>
<th>MRSA cover</th>
<th>Use in penicillin-allergy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flucloxacillin</td>
<td>both</td>
<td>NO</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>both</td>
<td>NO</td>
<td>YES</td>
<td>High risk for C. diff !!!</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>oral</td>
<td>YES</td>
<td>YES</td>
<td>Weak as monotherapy</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>IV</td>
<td>YES</td>
<td>YES</td>
<td>Higher dose in bone</td>
</tr>
<tr>
<td>(Vancomycin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>IV</td>
<td>YES</td>
<td>YES</td>
<td>Monitor CK</td>
</tr>
<tr>
<td>Linezolid</td>
<td>both</td>
<td>YES</td>
<td>YES</td>
<td>Bone-marrow tox if &gt;2w</td>
</tr>
<tr>
<td>Medication</td>
<td>Cost per day</td>
<td>Cost per day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------</td>
<td>--------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ORAL</td>
<td>IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>flucloxacillin</td>
<td>£ 0.4</td>
<td>£ 39.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>clindamycin</td>
<td>£ 6.86</td>
<td>£ 49.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>doxycycline</td>
<td>£ 0.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>teicoplanin</td>
<td></td>
<td>£ 9.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>daptomycin</td>
<td></td>
<td>£ 62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>linezolid</td>
<td>£ 89</td>
<td>£ 89</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Linezolid versus Vancomycin in Treatment of Complicated Skin and Soft Tissue Infections

randomised multicenter trial: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2005, p. 2260–2266

<table>
<thead>
<tr>
<th></th>
<th>Linezolid</th>
<th>Vancomycin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall clinical cure</td>
<td>92.2%</td>
<td>88.5%</td>
<td>0.057</td>
</tr>
<tr>
<td>Clinical cure in MRSA infections</td>
<td>71%</td>
<td>55.1%</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Daptomycin Versus Other Antimicrobial Agents for the Treatment of Skin and Soft Tissue Infections: A Meta-Analysis

Ann Pharmacother January 2010 vol. 44 no. 1 97-106

- 4 studies comparing with vancomycin (3 were randomised-controlled trials)
- No statistically significant difference in clinical success!
- 2 studies reported shorter treatment and faster clinical cure with daptomycin
When Gram-positive cover is not good enough

- Patient with cellulitis or osteomyelitis AND severe sepsis (pending cultures)
- Necrotising fasciitis
- When sterile fluids (blood cultures) or tissues (bone biopsy) grow gram negatives or anaerobes
- Patients with cellulitis/osteomyelitis not responding to Gram-positive coverage ESPECIALLY if chronic ulcers present with gram-negatives/anaerobes colonisation

Options for further antibiotic treatment
- Metronidazole (esp. if ischemia/necrosis)
- Antibiotics with Gram-negative cover
OPAT (Outpatient Parenteral Antibiotic Therapy) regimens

- Recent review by Ann Chapman in BMJ 2013;346:f1585
- Frequently used for:
  - Cellulitis: to treat without admission
  - Bone & joint infections: to allow early discharge
- Suitable for clinically stable patients
- Delivered through EITHER ambulatory care centre OR community nurse
- Formal OPAT service is SAFER (to identify non-responders & deal with side-effects of treatment)
  - OPAT specialist nurse
  - Pharmacist support
  - Doctor support including infection specialist
Suitable antibiotics for OPAT

Convenience in dosing & administration is key consideration → antibiotics which can be given no more than once-daily!

- **Teicoplanin**
  - OD: 6-12 mg/kg (reduced in renal impairment)
  - Three times weekly: 12-15 mg/kg e.g. Mon-Wed-Fri (no experience myself)

- **Daptomycin OD**

- **Ceftriaxone OD** un-necessary

Gram-negative coverage
Antimicrobial dressings

- Iodine: topical products + dressings
- Chlorhexidine dressing
- Silver-releasing agents (incl. Cadexomer iodine)**
- Medical grade honey
- Polyhexanide
- “Flaminal” (glucose oxidase & lactoperoxidase)

- Some early products may have been toxic to both human cells as well as bacteria → delayed healing
- Many newer or improved formulations

** Cadexomer iodine gave improved healing in venous leg ulcers when compared with «standard care» (Cochrane Database Syst Rev. 2014 Antibiotics and antiseptics for venous leg ulcers)
I am not an expert on antimicrobial dressings!

I have sometimes suggested to consider antimicrobial dressings in 2 scenarios:
- Non-infected ulcers that you would expect should heal but is not healing (esp. If heavy bacterial load or potential pathogens (e.g. S. Aureus or Pseudomonas))
- Chronic osteomyelitis in patients with non-healing ulcers
Despite the widespread use of dressings and topical agents containing silver for the treatment of diabetic foot ulcers, no randomised trials or controlled clinical trials exist that evaluate their clinical effectiveness. Trials are needed to determine clinical and cost-effectiveness and long term outcomes including adverse events.
Topical silver for treating infected wounds.

- Only three trials with a short follow-up duration were found
- silver-containing foam dressings did not significantly increase complete ulcer healing as compared with standard foam dressings
- although a greater reduction of ulcer size was observed with the silver-containing foam.
- “insufficient evidence” of benefit

CASE SERIES: 60 patients, some with suspected Osteomyelitis.

STUDY CONCLUSIONS
We can conclude from our pilot study that honey ointment may be a promising, safe conservative local treatment.
However, further double-blind randomised controlled studies are needed to confirm this.
Take away messages

Resistance to antibiotics is a major problem esp. with Gram-negatives:
- targeted antibiotic use (only for proven infections)
- selective Gram-positive coverage is usually preferable in most skin & bone infections

Skin ulcer swabs do NOT tell you whether there is infection: they always grow bacteria !!!

Take skin ulcer swabs ONLY if you have diagnosed infection and AFTER cleansing or debridement

Importance of diagnosing osteomyelitis

PERCUTANEOUS BONE BIOPSY is the gold standard for osteomyelitis
Take away messages

- Treatment outside hospital is always cheapest option: IV parenteral antibiotics can be used in OPAT (teicoplanin, daptomycin)

- Review antibiotic treatment on the basis of both the clinical response and the culture results (beware of limitations of swab culture results)

- “biofilms” may develop in chronic wounds/ulcers and may account for delayed healing → consider debridement + antimicrobial dressings

- Role for antimicrobial dressings INSTEAD OF antibiotics OR TOGETHER with antibiotics
2012 Infectious Diseases Society of America Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infections


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Foot infections are a common and serious problem in persons with diabetes. Diabetic foot infections (DFIs) typically begin in a wound, most often a neuropathic ulceration. While all wounds are colonized with microorganisms, the presence of infection is defined by ≥2 classic findings of inflammation or purulence. Infections are then classified into mild (superficial and limited in size and depth), moderate (deeper or more extensive), or severe (accompanied by systemic signs or metabolic perturbations). This classification system, along with a vascular assessment, helps determine which patients should be hospitalized, which may require special imaging procedures or surgical interventions, and which will require amputation. Most DFIs are polymicrobial, with aerobic gram-positive cocci (GPC), and especially staphylococci, the most common causative organisms. Aerobic gram-negative bacilli are frequently copathogens in infections that are chronic or follow antibiotic treatment, and obligate anaerobes may be copathogens in ischemic or necrotic wounds. Wounds without evidence of soft tissue or bone infection do not require antibiotic therapy. For infected wounds, obtain a post-debridement specimen (preferably of tissue) for aerobic and anaerobic culture. Empiric antibiotic therapy can be narrowly targeted at GPC in many acutely infected patients, but those at risk for infection with antibiotic-resistant organisms or with chronic, previously treated, or severe infections usually require broader spectrum regimens. Imaging is helpful in most DFIs; plain radiographs may be sufficient, but magnetic resonance imaging is far more sensitive and specific. Osteomyelitis occurs in many diabetic patients with a foot wound and can be difficult to diagnose (optimally defined by bone culture and histology) and treat (often requiring surgical debridement or resection, and/or prolonged antibiotic therapy). Most DFIs require some surgical intervention, ranging from minor (debridement) to major (resection, amputation). Wounds must also be properly dressed and off-loaded of pressure, and patients need regular follow-up. An ischemic foot may require revascularization, and some nonresponding patients may benefit from selected adjunctive measures. Employing multidisciplinary foot teams improves outcomes. Clinicians and healthcare organizations should attempt to monitor, and thereby improve, their outcomes and processes in caring for DFIs.