# MSS LECTURE 6

**OSTEOMYELITIS**

- Osteomyelitis, an infection of bone that leads to tissue destruction and often to debility and formation of sequestra(dead necrotic bone).
- Caused by a wide variety of bacteria (including mycobacteria) but can also be caused by fungi and may be associated with viral infections.
- Management is tailored for each individual
- Tailored management depends on man factors that include:
  - **Causative organism**
  - Which **bone is involved**
  - **State of the vascular supply**
  - **State of nerve function**
  - **Presence of foreign bodies**
  - **Recent injury,**
  - The status of the **host and any associated comorbidities**.

- The spectrum of osteomyelitis can range from extensive (such as tibial or vertebral osteomyelitis) to localized (such as bone invasion following a tooth abscess).
- Due to the many factors mentioned so far, the syndrome is identified as a spectrum, and two major classification systems are used (mainly to making therapeutic decisions).
- 1) Lee and Waldvogel system: used three main criteria
  - **a) acute or chronic**
  - **b) hematogenous or contiguous**
  - **c) with or without vascular compromise.**

- 2)The Cierny and Mader system: used for long bone osteomyelitis takes into account the location and extent of infection (+other factors)

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**TABLE 23-1**

## MICROORGANISMS THAT CAUSE OSTEOMYELITIS

| ORGANISM | COMMENT |
|---|---|
| **Frequently Encountered Bacteria** | |
| *Staphylococcus aureus* | Most likely bacterial pathogen<br>Aggressive, invasive<br>Often metastatic foci with bacteremia<br>Consider surgery early |
| Staphylococci other than *S. aureus* (coagulase-negative) | Usually associated with foreign material or implants<br>Biofilm production |
| Streptococci | May spread rapidly through soft tissues |
| Enterobacteriaceae (*Escherichia coli*, *Klebsiella*, others) | Considerable variation in antibiotic susceptibility<br>Increasing antibiotic resistance with overuse<br>May become resistant to antibiotics during therapy |
| *Pseudomonas aeruginosa* | Increasingly resistant to antibiotics<br>Frequent successor to other bacteria when initial therapy fails<br>May be related to contamination |

| Unusual Organisms | |
|---|---|
| Anaerobic bacteria | Usually mixed with aerobic bacteria<br>May be synergistic<br>Survival dependent on devitalized tissue |
| *Bartonella henselae* | Associated with cat scratches and probably with fleas |
| *Brucella species* | Prominent in developing countries, especially with unpasteurized milk |
| Fungi | *Candida* the most likely genus<br>Considerable variation in susceptibility, depending on species<br>Surgery may be helpful if infection is invasive. |
| *Mycobacterium tuberculosis* | May involve any bone<br>Vertebral osteomyelitis common in some countries |
| Mycobacteria other than *M. tuberculosis* | Need special culture media to recover |
| Viruses | Associated with some viral infections, including varicella and variola |

# Osteomyelitis

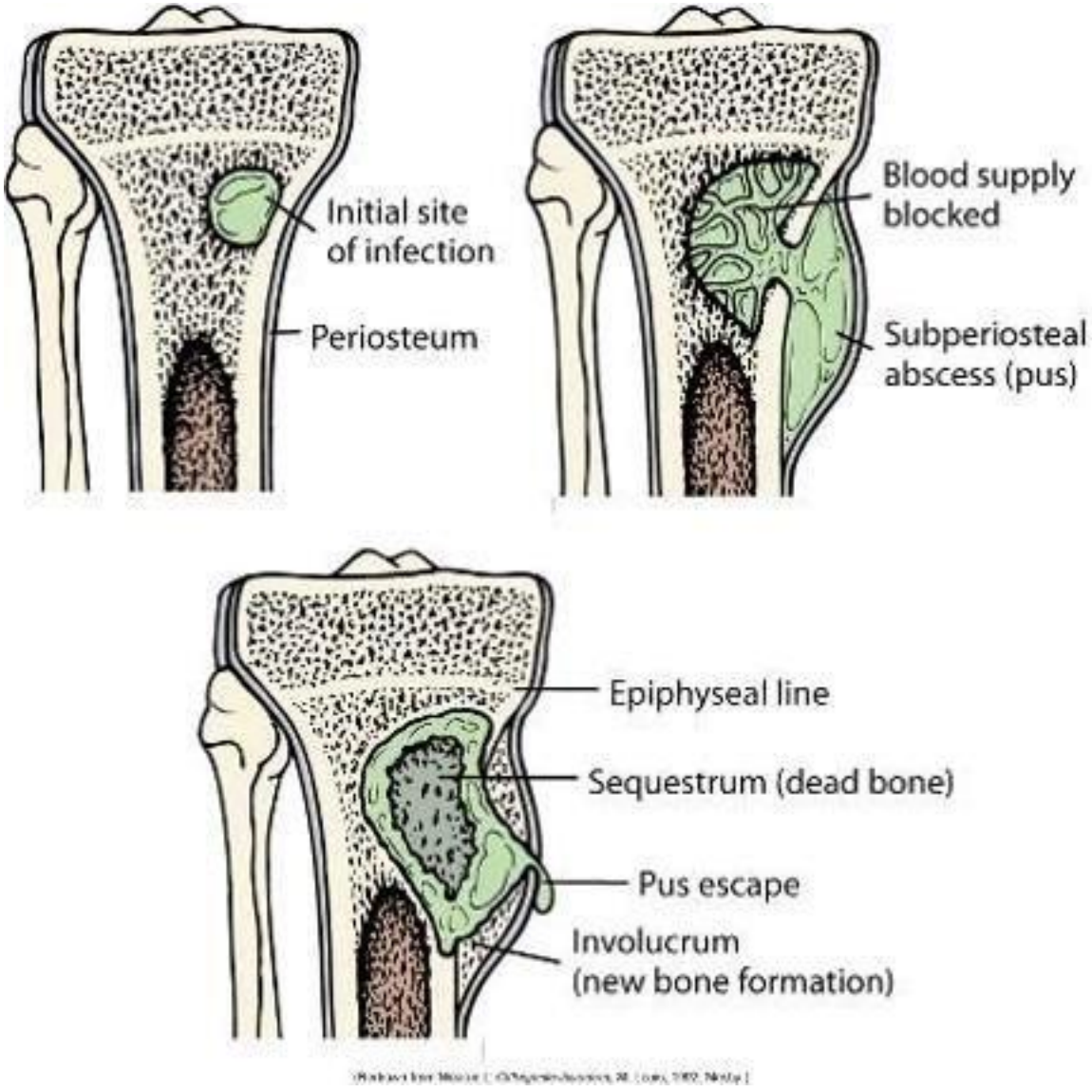
- Pathogenesis is usually due to three main routes:

A) Haematogenous seeding

B) Contiguous spread from adjacent infected tissues

C) Traumatic or surgical inoculation of microorganisms.

- Collection of inflammatory exudates in the bone marrow leads to increased medullary (bone medulla) pressure →extension of the exudate to bone cortex →rupture through the periosteum.
- If periosteal rupture occurs, the blood supply is interrupted →this leads to necrosis and separation of dead bone (sequestrum).
- The site of periosteal damage then becomes site for new bone formation (involucrum).


Initial site of infection
Periosteum
Blood supply blocked
Subperiosteal abscess (pus)
Epiphyseal line
Sequestrum (dead bone)
Pus escape
Involucrum (new bone formation)

# Classification

- • The Cierny–Mader system—is a functional classification, based on the affected portion of bone and physiological status of the host, and is useful in guiding therapy.
- There are four anatomical types:

stage 1 = **medullary osteomyelitis**,

stage 2 = superficial osteomyelitis,

stage 3 = localized osteomyelitis,

stage 4 = diffuse osteomyelitis.

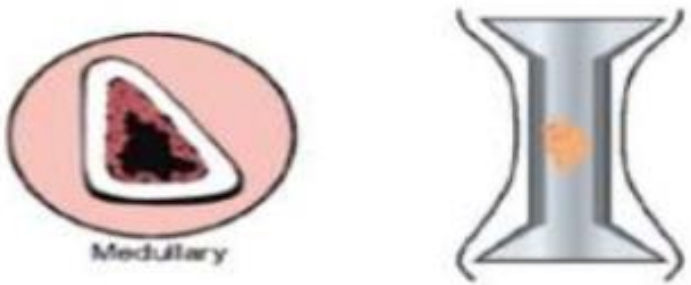
- →There are three physiological classes:

A = normal host

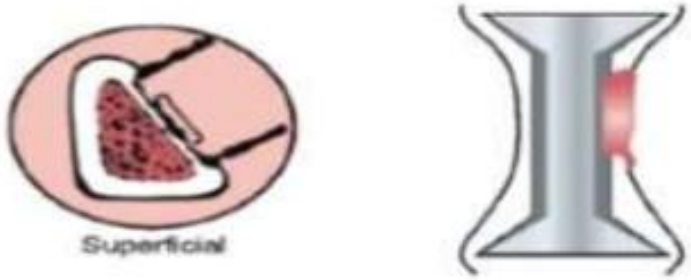
B = host with local (BL) or systemic (Bs) compromise

C = treatment worse than disease.

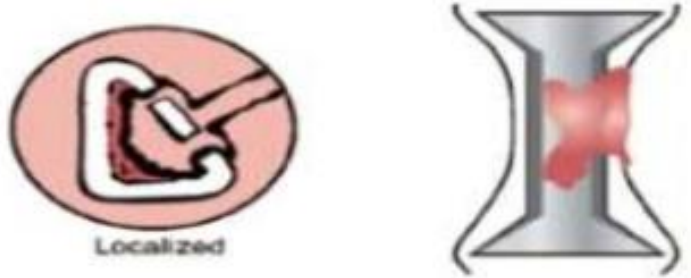
Type I: Medullary osteomyelitis




Type II: Superficial osteomyelitis




Type III: Localized osteomyelitis




Type IV: Diffuse osteomyelitis

# Etiology

- > Haematogenous osteomyelitis → usually monomicrobial
- > Contiguous osteomyelitis → monomicrobial or polymicrobial.
- In patients with sinuses, the superficial flora may not represent the true pathogen.

- •The most common bacteria (>50%) cause of osteomyelitis is Staphylococcus aureus and CoNS .

- Gram-ve organisms such as *Pseudomonas aeruginosa* and *Escherichia coli , enterococci, and propionibacteria* may also be found.

# Etiology cont.

- *Mycobacterium tuberculosis* is a common cause in countries with limited medical resources (other mycobacterial species that infect bone include *M. marinum , M. chelonei , and M. fortuitum*) .

- Fungi may include *Candida , Coccidioides , Histoplasma , and Aspergillus* species.

- The precipitating **factors** can vary according to route of infection:
- 1- Prosthetic joint implants and stabilization devices (all foreign objects) are being used more frequently in orthopedic surgery and are associated with complex infections.
- 2- Trauma if a wound is involved with trauma that leads to contamination of bone or surrounding tissue - with significant tissue damage or destruction.
- **Not necessary to have an open wound or a compound fracture**. In a similar fashion to what is seen in pyomyositis : → *damaged tissue and internal bleeds slows down the circulation which creates favorable condition for bacterial growth.*
- In these damaged tissues, bacteria from peripheral veins or lymphatic channel (low level bacteremia) maybe sufficient to cause infection – in otherwise situation, circulation would prevent that from occurring.

- Bacteremia—is a frequent cause of osteomyelitis, maybe arising from endocarditis or from seeding of other infection sites (abscess, boils..etc)
- A- Prosthetic joints and *S. aureus*: Studies show that *S. aureus* bacteremia cause a rate of metastatic osteomyelitis approaching 28% if there is a prosthetic joint in place. can be complicated by the involvement of methicillin-resistant strains (MRSA), which are **progressively replacing** strains that are more susceptible to antibiotics.
- B-Urinary tract circulation: The overlapping circulations of the urinary tract and the spine is suggested to be the source of vertebral osteomyelitis especially due to UTI causing pathogens (*E. coli* and *Klebsiella)*.
- C- Limited vascular supply: other predisposing factors →limited arterial and venous blood supply →limit perfusion to bone to the point of an inadequate response and poor healing.
- D-Diabetes and other host factors contribute significantly to the development of osteomyelitis through impaired immunity with hyperglycemia, loss of sensation, vascular disease, and renal failure.

# Epidemiology

- In the United States, acute osteomyelitis affects ~0.1–1.8% of the otherwise healthy adult population.
- After a foot puncture, 30–40% of adults with diabetes develop osteomyelitis.
- MRSA has been steadily replacing MSSA over the last few decades.
- The morbidity and economic burden is greater for MRSA osteomyelitis that that causes by MSSA.
- Is MRSA more aggressive because it can evade antimicrobials so has more time to cause damage? Or is it cause there bugs survive longer and get more virulence factors??

- Certain countries that have more aging population and / or populations with more DM and obesity all contribute to the frequency of osteomyelitis in these areas.

- Any type of instrumentation may lead to infection in a small proportion of cases.

- Richer countries have more orthopedic related Osteomyelitis , whereas poorer countries have more TB and brucella or significant wounds in the society (wars, accidents)→less healthcare service (micro labs, Abx..etc).

# Pathogenesis-can be applied to all pathogens mentioned in this module

- The most common predisposing factor for osteomyelitis is an area of bone ( or contiguous surrounding tissue) that is defective in in viability, blood supply, sensation.
- This damaged tissue suffers from reduced *oxygenated arterials supply* and **hindered venous and lymph out flow (less in , less out)**, these are prime factors that provide bacteria with optimal growth conditions ($O_2$, nutrients, less inflammatory cytokines and WBC..etc).
- Host factors such as poor nutrition and immunosuppression may also be relevant.
- As mentioned, Diabetes in adults poses the most significant risk (and further accentuates the above factors).

- Diabetic neuropathy makes progression of the disease much worse, as the patient would be unaware or any symptoms (pain sensation reduced)

- → makes DM a significant cause for many amputation due to OM.

- In a similar fashion, other causes of immunosuppression will predispose to serious and frequent infections and OM is no exception.

# Bacterial pathogenesis:

- Bacterial pathogens that cause OM perpetuate themselves (the maintain their presence)

- → they do this by secreting toxins that continually damages surrounding tissue.

- *S. aureus* is especially strong in this respect, where it colonizes the nasal area in about one-third of healthy populace and can produce a variety of cytokines, enzymes, and toxins that destroy tissue and **affect neutrophil response**.

- Certain strains of *S. aureus* can survive uptake into the phagocytic vacuoles of macrophages, this enables them to keep causing tissue damage by consistently evading host defenses

- Basically → two populations of *S. aureus,* intra and extra cellular, where intra cellular keeps replenishing the extra cellular pathogens.

- *S. aureus* has the capacity to remain dormant (sometimes called NCBV-viable but not culturable form)
- → these are resistant forms that hibernate and remain inactive for decades before infection erupts at sites of old injuries (especially penetrating wounds, shrapnel…)

- Although CoNS are typically less virulent than *S. aureus* but they have been found to persist by producing a biofilm that protects them from the host and is thought to be the mechanism that allows them to persist for many years on especially prosthetic joints, with minimal symptoms.

- In CoNS it is not uncommon for prosthetic joints to show no symptoms and suddenly show infection a year or even more later.

- How much other organisms use their biofilm to their advantage is not fully understood, but biofilm production probably plays an important role in osteomyelitis, especially in chronic forms.

- Multiple bacteria may be recovered from cultures, especially when there is an entry wound.
- This makes the decision which one to target in antibiotic therapy difficult.
- At this point → Typically common skin flora and colonizing bacteria are not targeted (if they are , it might make them more aggressive and resistant).
- Anaerobic bacteria can often be recovered and can play synergistic role with other pathogens → these are usually targeted with specific therapy.

# Clinical features

- • Acute osteomyelitis presentation usually in pediatric patients and due to hemtogenous spread
- Whereas: subacute to chronic usually in adults
- Onset of pain around the affected site.
- Local and systemic signs of inflammation such as swelling, tenderness, warmth, and erythema may or may NOT be present! (especially in vertebra, hip or pelvis-not long bones)
- •

- Chronic osteomyelitis presentation may begin local signs of inflammation and/or presence of a sinus tract, or even fracture).
- 
- If skin ulcers are present that are prolonged that fail to heal with antibiotic therapy may indicate **underlying osteomyelitis.**
- In such case, if bone is felt when palpating an ulcer can be sufficient to diagnose osteomyelitis

# Diagnosis 1

- Usually based on clinical suspicion and then confirmed by a radiology, microbiology and pathology.

- • Blood tests—
- White cell count may be raised but can be normal.
- Inflammatory markers (ESR and CRP) are usually high

→ CRP changes occur earlier in bacterial infection.

However, ESR and CRP are not specific and can be elevated in other conditions other than osteomyelitis

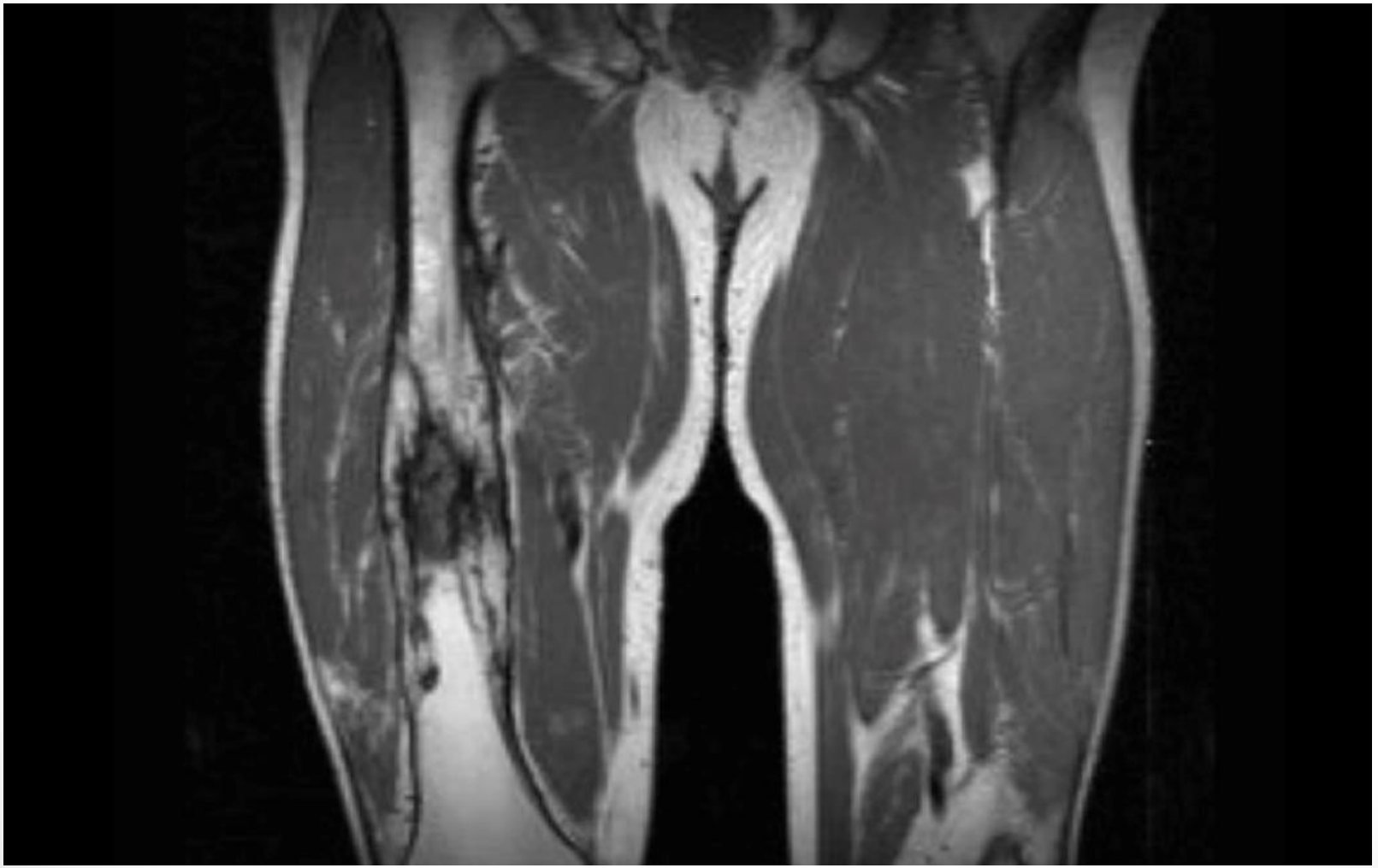
- Blood cultures are more likely positive in vertebral infection and in haematogenous spread (clavicle, pubis).

# Dx 2

- • Radiology—plain X-ray may show changes after 1-2 weeks.
- may eliminate the need for further imaging studies.
- Bone loss, sequestra, periosteal elevation or swelling (which can develop early on), and shadows around foreign bodies are hallmarks of bone infection.

- CT or MRI scans are the investigations of choice (MRI is both specific and sensitive).

- MRI may be contraindicated in patients with metalware; these may also cause artefacts on CT.



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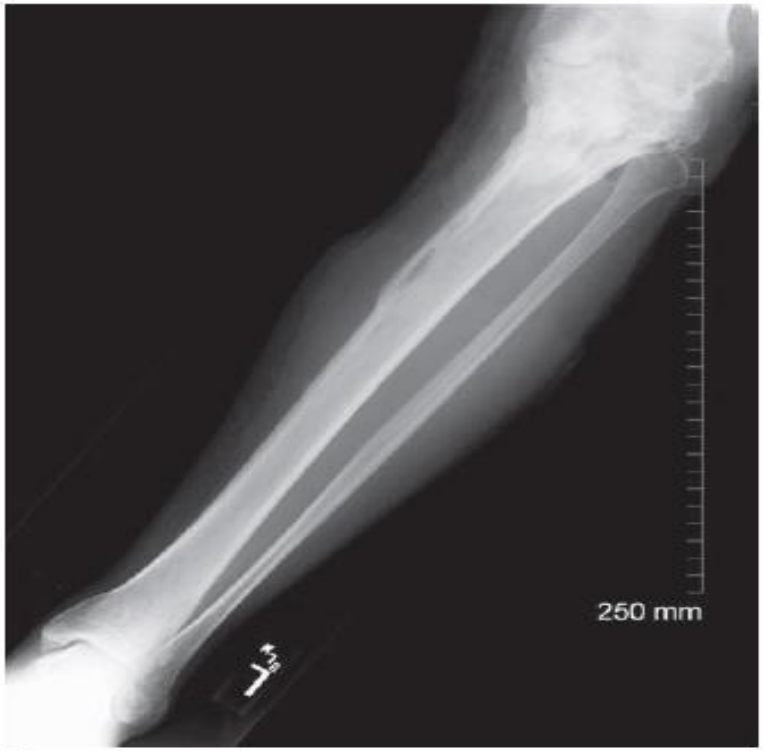


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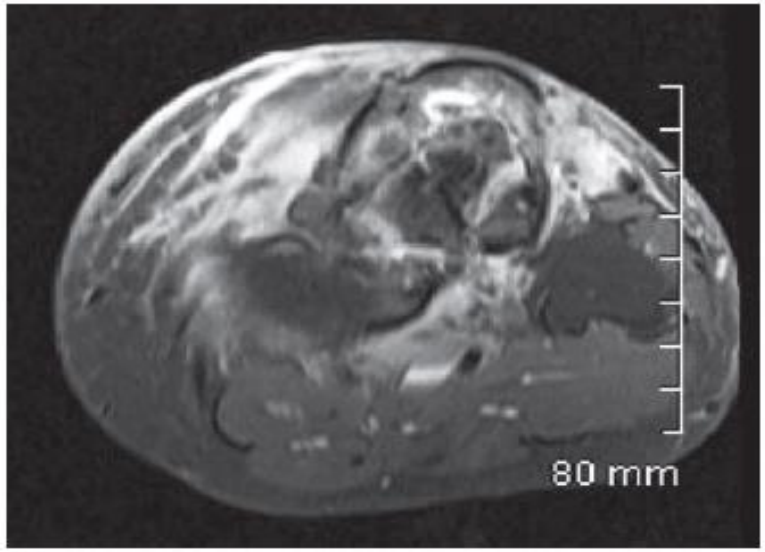


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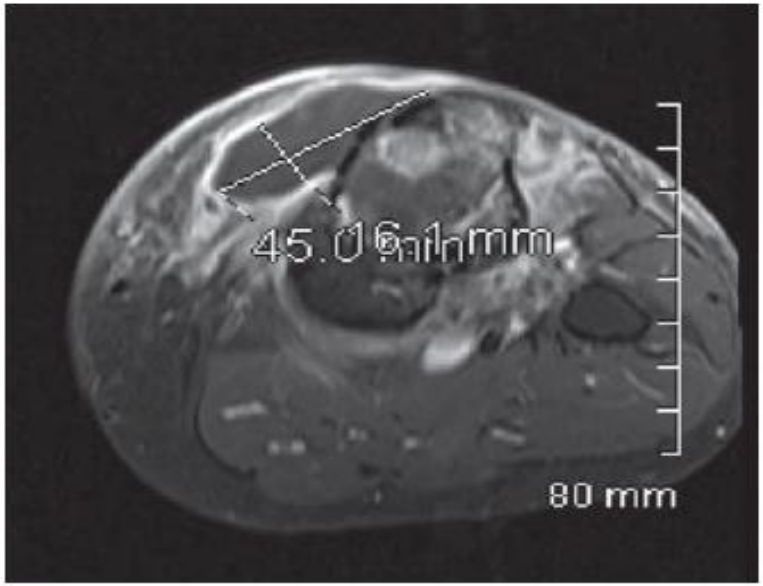


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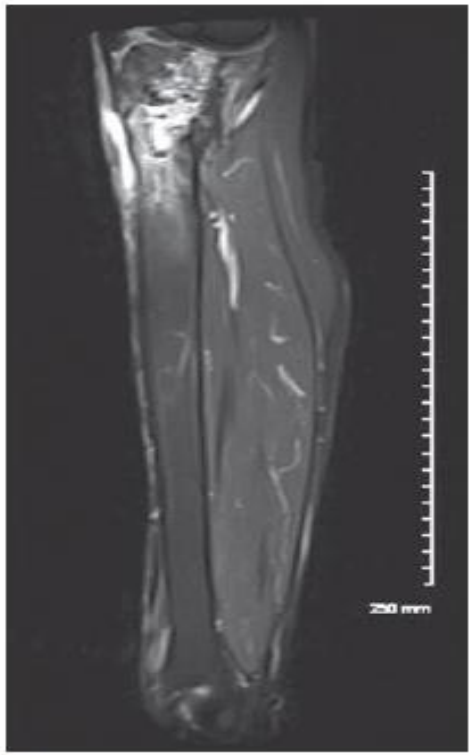

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# Dx 3

- • Biopsy—an open or percutaneous bone biopsy should be taken and sent to microbiology and histology labs.
- Needle aspiration of pus collection is both Rx and Dx for the pathogen
- Biopsy can be taken in open surgery with debridment of all necrotic tissue, which is again both Rx and Dx.
- antibiotics should be stopped 48-72 hours prior to biopsy to improve the yield of culture.
- Swabs from sinus tracts are of questionable value, and may often just be presenting the local flora.

- PCR, and sequencing technologies are becoming more standard Dx to detect and identify specific organisms
- (even their sensitivity to Abx) within hours instead of days or weeks.

# Management

- • General principles—

- The aim of treatment is to eradicate the causative agent and restore ( or at least preserve) function of the bone.
- OM in adults is usually treated with a combination of surgical debridement and antibiotic therapy.

- • Surgery—the principles of surgical therapy are debridement of infected tissue, removal of metalware, management of dead space (using a flap), wound closure, and stabilization of infected fractures.

# Antimicrobial therapy

- Choice of ABx therapy is based on culture and sensitivity results. duration, however, duration is unknown and most experts treat for 4-6 weeks IV therapy!

- The addition of rifampicin to β-lactams was shown to be effective in certain staphylococcal OM animal models is often used in infections, particularly those involving prosthetic material.

- Patients are usually discharged once they are clinically stable and treated as outpatient with an IV antimicrobial catheter.

- Hyperbaric oxygen has been shown to be effective in animal studies (no data in humans) and can be used as adjunctive therapy.

- Negative pressure wound therapy (vacuum-assisted closure) is being increasingly used and may accelerate wound healing in complex wounds and in diabetic patients.

**TABLE 23-2**

## ANTIBIOTICS FOR THE TREATMENT OF OSTEOMYELITIS

| ORGANISM | ANTIMICROBIAL AGENT | DOSING | COMMENTS |
|---|---|---|---|
| Methicillin-susceptible *Staphylococcus aureus* | Oxacillin or nafcillin | 2 g IV q6h | May be more active than cephalosporins<br>More difficult than cephalosporins to administer for long periods |
| | Cephalosporins | Cefazolin: 2 g IV q8h<br>Ceftriaxone: 1–2 g IV q24h | Ceftriaxone advantageous with OPAT |
| | Clindamycin[a] | 600–900 mg IV q8h | Not well studied for osteomyelitis<br>Oral form possible (300–600 mg q8h)<br>Resistance significant and increasing<br>Toxicity different from that of β-lactam antibiotics |
| Methicillin-resistant *S. aureus* | Vancomycin | 15 mg/kg IV q12h | Strains with an MIC of ≥2 μg/mL may not respond well. |
| | Daptomycin[a] | 4–6 mg/kg IV q24h | Promising, but concern about adverse effects with prolonged therapy |
| | Linezolid[a] | 600 mg IV or PO q12h | Effectiveness and adverse effects with prolonged therapy unclear<br>Bacteriostatic |
| Streptococci | Penicillin | 5 mU IV q6h or 20 mU/d by continuous infusion | Not all streptococci are susceptible.<br>Ceftriaxone (1 g/d IV or IM) and ampicillin (12 g/d IV) are alternatives. |
| Enterococci | Penicillin plus gentamicin | As above<br>5 mg/kg daily IV | If strain is susceptible |
| | Vancomycin | As above | If strain is susceptible |
| Enterobacteriaceae (*E. coli*, *Klebsiella*, other) | Ceftriaxone or another cephalosporin | As above | If strain is susceptible |
| | Ciprofloxacin | 400 mg IV q8–12h | 500–750 mg q8–12h if strain is susceptible |
| *Pseudomonas aeruginosa* | Ciprofloxacin | As above | Resistance may develop during therapy; if strain is resistant, drugs to consider include cefepime and ceftazidime. |

[a]Not approved for use in osteomyelitis by the U.S. Food and Drug Administration.
***Abbreviations:*** MIC, minimal inhibitory concentration; OPAT, outpatient parenteral antimicrobial therapy.

- There is still controversy about the optimal route and duration of therapy.
- However a 4- to 6-week course of IV therapy remains the standard and is the usual recommended minimum.
- Although in pediatric population, some studies are suggestive adequate treatment with somewhat shorter duration + oral therapy.

- Because some of the active agents reach comparable levels when given by mouth, a switch from the recommended IV administration to oral therapy may be appropriate in some situations.

- Duration is increased for more extensive disease or with patients with additional comorbidity (see previous classification-Cierny Mader) + vertebral OM.

# Complications

- • Sinus tract formation.
- • Pathological fractures, as the sequestra make that specific area of bone less able to bear weight and is prone to fracture.
- • Haematogenous spread and sepsis, especially in aggressive disease.
- • Tumours in patients with long-standing (4–5 years)
- In rare instances, chronic inflammation and infection may lead to malignant transformation into squamous cell carcinoma or sarcoma
- Osteomyelitis, e.g. squamous cell carcinoma (commonest), fibrosarcoma, myeloma, lymphoma, plasmacytoma, angiosarcoma, rhabdomyosarcoma, and malignant fibrous histiocytoma

# Prognosis

- Varies, on all the factors that are included in the classfication systems.
- Veretbral - immunecompromised-late Dx..etc → poorer prognosis
- Mandible following tooth extraction, early proper treatment→ better prognosis.

# Prevention

- Osteomyelitis can be prevented with better preopertive infection and prevention measures.
- Agents such as mupirocin and chlorhexidine have been shown to be successful in preventing operative infections (which are a common cause in prosthetic joins OM).
- Early Dx and treatment of other infection routes (abscess, bactermia, boil…etc).
- Early surgical treatment of wounds (esp extensive ones) have better outcome.
- Sacral ulcers, can be often a point of infection –bed ridden patients- and easily overlooked.

# Septic Arthritis

Defined as : An **inflammatory reaction** of the joint space caused by an infectious agent.

→ Usually caused by bacteria but may be caused by mycobacteria or fungi.

→ Very common and hard to treat due to use of prosthetic joints (2-10% of all prosthetic joints!)

→ Also common among immune compromised and eldery (45% of ppl with Septic arthritis are above 65 years and 56% are male)

# Etiology:

- • *S. aureus* : commonest cause overall, especially in acute cases, the increase in incidence here matches that of increase use of Prosthetic joints.
- • Streptococci → groups A, B, C, and G streptococci, + *S. pneumoniae* and viridans groups (20%) of all cases.
- • CoNS.
- • *E. coli*.
- • *H. influenzae.*
- • *N. gonorrhoeae* (the commonest cause in sexually active young adults)
- • *N. meningitidis*.
- • *P. aeruginosa*.(sternoclavicular joints, sacroilliac joints)
- • *Salmonella* spp.
- + other causes, brucella, polymicrobial.

# Prosthetic join infection

- According to presentation:

- Acute (*S. aureus*) within 3 months
- Subacute within 3-24 months
- Chronic >24 months

- Overall *S.aureus*, but CoNS and G-ve aerobes cause the delayed cases more

# Epidemiology

- The reported incidence of septic arthritis varies from two to five cases per 100000 population or 8–27% of adults presenting with painful joints (20,000 cases /year in US)

- Risk factors for septic arthritis include
- Age >80 years,
- Diabetes mellitus
- Rheumatoid arthritis
- Prosthetic joint
- Recent joint surgery
- Skin infection/ulcers
- Intra-articular corticosteroid infection

injection drug use, and alcoholism.

# Pathogenesis

- Septic arthritis usually occurs after haematogenous seeding of pathogenic bacteria- this is the most common route.
- But like osteomyelitis contiguous spread or direct inoculation can also be causes.
- Healthy synovial cells have phagocytic activity and normally able to clear any seeding from outside sources.
- Any weakness to immune system (SLE, Rhuematoic arthritis..etc) increases risk (hence old age!)

- Previously damaged joints are most susceptible to infection (arthritis)
- These joints show neovascularization and and adhesion factors, which promote bacteremia and consequent infection.
- *S. aureus* especially, binds to articular sialoprotein, collagen, elastic and prosthetic materials visa tissue adhesion factors that they possess.
- Infection typically damages the cartilage (chondrocyte proteases of *S. aureus* , the inflammation in turn causes further damage to the cartilage)
- Gonococcal arthritis exhibits much less influx of WBC into the joint, which explains why it is **not as destructive** to joints as other bacteria.

# Clinical features

- • Children and adults with acute septic arthritis usually present with fever (60–80%) and monoarticular involvement (90%).
- • The knee is the most commonly affected joint, followed by the hip.
- Clinical features include pain, swelling, and reduced mobility in the joint.
- • Polyarticular infections occur in 10–20% of patients, especially those with rheumatoid arthritis and viral causes.
- • Infections with mycobacteria or fungi usually have an insidious onset.

# Diagnosis

- Laboratory investigations frequently show a raised WCC and inflammatory markers.
- Joint aspiration shows purulent synovial fluid, with an elevated WCC (50 000–100 000 cells/mm3), mostly neutrophils.
- Gram stain is positive in 29–50%, and culture is positive in 80–90% of cases (synovial fluids in blood culture bottles may improve yield)
- Samples should also be sent for microscopy for crystals. BCs are positive in 75% of cases.

# Imaging

- Radiographs of the affected joint may be normal at presentation.
- Typical changes are periarticular soft tissue swelling, fat pad edema, periarticular osteoporosis, loss of joint space, periosteal reactions, erosions, and loss of subchondral bone.
- Ultrasound can be used to confirm an effusion and guide aspiration.
- CT and MRI are highly sensitive for imaging early septic arthritis. CT is better for imaging bone lesions.
- MRI may not distinguish septic arthritis from inflammatory arthropathies.

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## CLINICAL HISTORY

*43-year-old female with a history of lupus treated with steroids, presents with developing left knee pain, swelling, and fevers.*

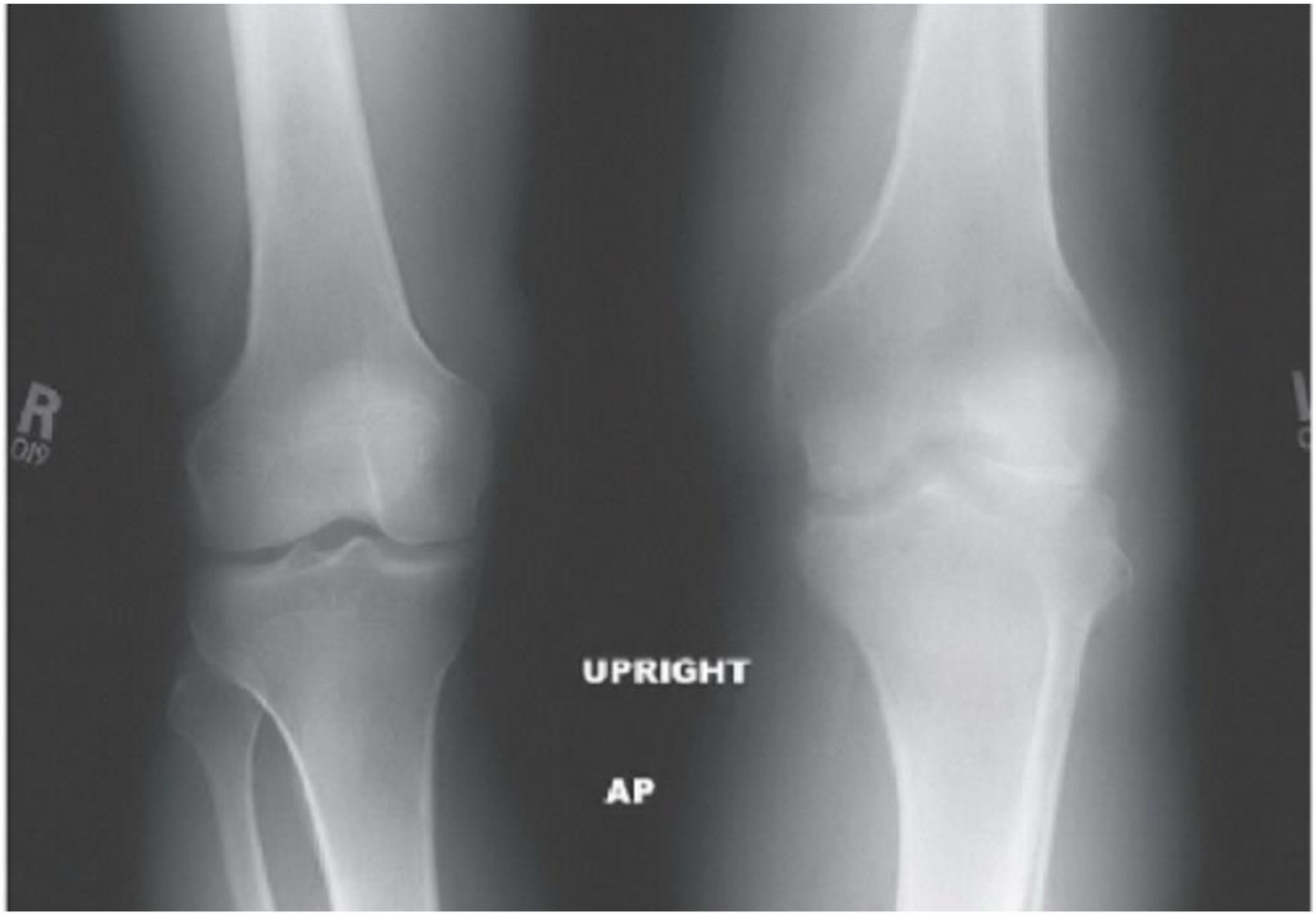


FIGURE 88A

# Management

- • Drainage of the joint, either by closed aspiration or arthroscopic washout, should be performed **urgently.**
- Open drainage may be required either when repeated drainage has failed to control the infection or for drainage of hip joints.
- Prosthetic joint infections often require removal of the prosthesis.

# Antimicrobial therapy

According to the initial Gram stain findings.

Empirically - IV piperacillin–tazobactam ± vancomycin.

- Definitive therapy is tailored to culture and sensitivity results
- • Adjunctive therapy with a short-course systemic corticosteroid treatment has been shown to be of benefit in children with haematogenous bacterial arthritis.

# End