MSS

Musculoskeletal System

Doctor 2019 | Medicine | JU

6 Microbiology

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Osteomyelitis

An infection of the bone 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

Management is tailored for each individual, why?

We know that all the cells in our bodies cover by a matrix (including bone cells; osteoblast and osteocytes), so the penetration of medication into the bone cells not always successful, and the pharmacodynamics is more difficult than other cells thus, each case of Osteomyelitis need different management.

Tailored management depends on many factors that include:

- Causative organism; if we know the organism this would give us indication which antibiotics to use and then from these antibiotics try to see which ones have a good penetration to the bone.
- Which bone is involved; usually it's linked to a causative organism.
- State of the vascular supply.
- State of nerve function; a good nerve helps the immune function as well as will probably aid in the treatment.
- Recent injury; if your patient has a recent injury, you may have to wait for healing and ensure the state of the nerve and the vascular function.
- The status of the host and any associated comorbidities; the medical history of the patient (diabetic, peripheral vascular disease, or immunosuppression) and the surrounding factors.

- Presence of foreign bodies; some kinds of bacteria like *Coagulase-negative staff* are likely to form **biofilms**, so the management must include removal of the foreign body.

Most foreign bodies that are done in bones are either in **orthopedic surgery** (joint replacement), **dental surgery** (tooth implant), or **the fracture that required the use of plates and screws** to stabilize the bone so, if you have a lapse in the aseptic technique at any level this provides an opportunity for bacteria to form biofilms which can't be managed by antibiotics. instead, you have to take the foreign body away then wait for healing, so the body can accept the new implant, joint.

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).

I. **Lee and Waldvogel system:** used three main criteria
   - acute or chronic.
   - hematogenous or contiguous; the infection spread through the blood or directly through the skin or the lumen.
   - with or without vascular compromise; vascular compromise result in poor prognosis.

II. **The Cierny and Mader system:** used for long bone osteomyelitis, takes into account the location (which site in the bone) and extent of infection (how far deep the infection inside the bone) +other factors.

The microorganisms that cause osteomyelitis

- ***Staphylococcus aureus;*** the most likely bacterial pathogen, it is very aggressive, invasive, and often metastatic with bacteremia, which means if it gains access to blood vessels it can spread from one side to another within the bone.
  Staph likes to nest, especially where are a lot of matrices, less immune defense, and fewer competitors such as the bone tissue, it's the most places where staph will be successful in an infection.
  The staph would behave like cancer, it would keep destroying the tissue which will continue to become revitalized so, you want to consider surgery early.
- ***Coagulase-negative;*** usually associated with **foreign body material** or **implants** ›› biofilm production so you have to remove the foreign body.
- ***Streptococci;*** spread rapidly through the **soft tissues**.
- ***Enterobacteriaceae;*** they have considerable variation in antibiotic susceptibility, increasing antibiotic resistance with overuse, may become resistant to antibiotic **during therapy** because of suboptimal doses of antimicrobials or suboptimal doses of antibiotic from the dietary protein
  Enterobacteriaceae gain access to the bone through the lumen.
- ***Pseudomonas;*** increasingly resistant to antibiotics, a frequent successor to other bacteria when initial therapy fails. thus, when you haven't able to treat up the patient and you have introduced him to the hospital Pseudomonas will be acquired in a hospital setting.

Unusual organisms

- ***Anaerobic bacteria;*** usually mixed with aerobic bacteria or facultative anaerobes to destruct the area for anaerobes to come, it's maybe synergistic, survival depends on the devitalized tissue.
- ***Bartonella hesneselae;*** associated with cat scratches and probably with fleas.

- ***Brucella species;*** is a **zoonotic** illness (transmitted from animals to humans), prominent in developing countries, it's usually coming from **unpasteurized milk**, it can spread everywhere and it is really hard to treat, it's like multi-tissue cancer!
- ***Fungi;*** yeast candida probably the most likely genus, it has considerable variation in susceptibility and depending on the species surgery, it's may be helpful if the infection is invasive.
- ***Mycobacterium tuberculosis;*** may involve any bone, but **vertebral** osteomyelitis is very common in some countries (underdeveloped countries).
- ***Mycobacterium other than tuberculosis;*** needs special culture media.
- ***Viruses;*** associated with some viral infections, including **Varicella** and **variola**.

You can skip these tables, We have already studied everything in :)

TABLE 23-1

MICROORGANISMS THAT CAUSE OSTEOMYELITIS

ORGANISM	COMMENT
Frequently Encountered Bacteria	
Staphylococcus aureus	Most likely bacterial pathogen Aggressive, invasive Often metastatic foci with bacteremia Consider surgery early
Staphylococci other than *S. aureus* (coagulase-negative)	Usually associated with foreign material or implants Biofilm production
Streptococci	May spread rapidly through soft tissues
Enterobacteriaceae (*Escherichia coli*, *Klebsiella*, others)	Considerable variation in antibiotic susceptibility Increasing antibiotic resistance with overuse May become resistant to antibiotics during therapy
Pseudomonas aeruginosa	Increasingly resistant to antibiotics Frequent successor to other bacteria when initial therapy fails May be related to contamination
Unusual Organisms	
Anaerobic bacteria	Usually mixed with aerobic bacteria May be synergistic 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 Considerable variation in susceptibility, depending on species Surgery may be helpful if infection is invasive.
Mycobacterium tuberculosis	May involve any bone 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:

→ **Hematogenous seeding;** happened because of the speed of the blood flow; the blood flow as fast as larger vessels and the smaller vessels have the slowest flow which going through the bone, this would be ideal for bacteria to get off themselves into the bone.

→ **Contiguous spread from adjacent infected tissues.**

→ **Traumatic or surgical inoculation of microorganisms;** the patient is more likely to be a healthy patient, but it had a trauma or surgery which has introduced unusual amount of microorganisms that overwhelm his buffer.

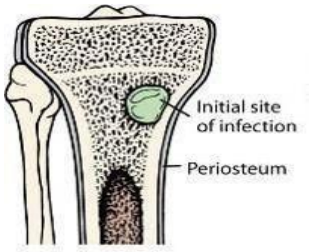
NB. Hematogenous and Contiguous spread happened because of pathological causes; e.g.(hematitis →inability to fight bacteria →Hematogenous seeding) OR (insufficient healing → contiguous spread)

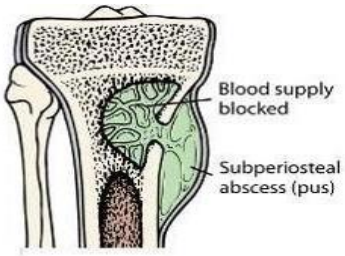
Remember: the healthy patient can deal with a specific number of bacteria particles, 50 or 100 for example but in the case of the trauma he will introduce millions or thousands of bacteria, this will overwhelm his buffer and then he will have infection no matter how healthy that patient is.

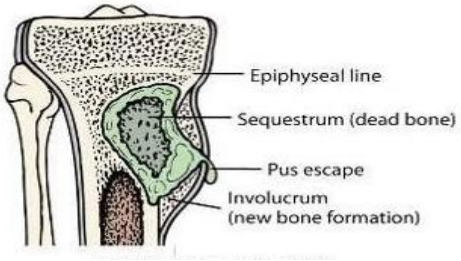
Once an infection happens, inflammation will ensue and the collection of inflammatory exudates in the bone marrow. the bone marrow is not malleable as the soft tissue so it won't swell thus, the pressure will increase inside the medulla of the bone and it will keep mounting until it breaks through the cortex and then it will rupture through the periosteum.

If the periosteal rupture occurs, the blood supply will interrupt because the blood supplies the bone through the periosteum. this leads to necrosis and then separation of the dead bone (formation of the sequestrum).

The site of periosteal damage then becomes the site of new bone formation (involucrum) and the vessels will help in producing the envelope.







the initial site of infection increasing

it has broken through the periosteum and forming a subperiosteal abscess.

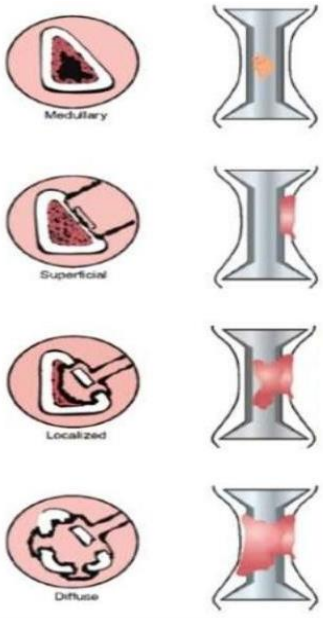
this is the dead bone "sequestrum" and the new bone formation "involucrum" on top of the previous abscess

pus may keep continue to escape and may even fistula all the way to the skin

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 I = **medullary osteomyelitis**; inside the medulla of the bone.

stage II = **superficial osteomyelitis;** only superficial.

stage III = **localized osteomyelitis**; going through the medulla but it's not breaking through the other side.

stage IV = **diffuse osteomyelitis;** will break through the other side, from one periosteum into the next.

There are three physiological classes:

A. normal host
B. host with local (BL) or systemic (Bs) compromise
C. treatment worse than the disease.

Etiology

- Hematogenous osteomyelitis is usually monomicrobial, Contiguous osteomyelitis monomicrobial, or polymicrobial. Why?

The bacteria have to break through so many barriers to reach the blood; the skin little acidity than the tears, saliva than the stomach and so on.

Imagen this...

your body is like a castle with multiple defenses so if the bacteria has to break through the core of the castle which is the hematogenous system is probably be monomicrobial. continuous osteomyelitis will be like breaking through just the Castle wall so can be mono or polymicrobial, doesn't matter whatever has gone through at the skin side.

- In patients with sinuses formation in the bone, the superficial flora may not represent the true pathogen.
- The most common bacteria (>50%) cause of osteomyelitis is Staphylococcus aureus and Coagulase-negative.
- Gram-ve organisms such as *Pseudomonas aeruginosa* and *Escherichia coli, enterococci, and Propionibacterium* may also be found.
- 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 the route of infection:

1. **Prosthetic joint implants and stabilization devices** (all foreign objects) are being used more frequently in orthopedic surgery and even the ones that are not needed thus developed complex infections that changing the way that osteomyelitis happened.

2. **Trauma** if a wound is involved with the 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 slow down the circulation which creates a favorable condition for bacterial growth.

Normally, low-level bacteremia circulates in the blood and doesn't cause infection because of the speed of the blood flow but in damaged tissues, low-level bacteremia from peripheral veins or lymphatic channels may be sufficient to cause infection in the site of the damage (bone, muscles).

Bacteremia

Is a frequent cause of osteomyelitis, maybe arising from endocarditis or from the seeding of other infection sites (abscess, boils..etc)

- Studies show that S. aureus bacteremia causes a rate of metastatic osteomyelitis approaching 28% if there is a prosthetic joint in place; prosthetic joint associated with tissue damage + S. aureus through the skin with low-level bacteremia can be complicated by the involvement of methicillin-resistant strains (MRSA), which are progressively replacing strains that are more susceptible to antibiotics.

- 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).
- Limited vascular supply; other predisposing factors, limited arterial and venous blood supply which limit perfusion to bone to the point of inadequate response and poor healing.
- 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, about 30–40% of adults with diabetes develop osteomyelitis.

MRSA has been steadily replacing MSSA over the last few decades, The morbidity and economic burden are greater for MRSA osteomyelitis than that causes by MSSA.

MRSA more likely to get more virulence factors, survive longer, and become more aggressive because it has acquired virulence genes in addition to resistance antibiotics genes.

Certain countries that have more aging populations and populations with more DM and obesity contribute to the frequency of osteomyelitis because with aging, osteoarthritis and other diseases would increase which increase the orthopedic and prosthesis operations.

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 viability, blood supply, sensation, This damaged tissue suffers from reduced oxygenated arterials supply and hindered venous and lymph outflow (less blood in, less blood out), these are prime factors that provide bacteria with optimal growth conditions (O2, 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 the progression of the disease much worse, as the patient would be unaware for any symptoms (pain sensation reduced), which makes DM a significant cause for many amputations due to Osteomyelitis.

Similarly, other causes of immunosuppression will predispose to serious and frequent infections and Osteomyelitis is not exception.

Bacterial pathogenesis:

Bacterial pathogens that cause Osteomyelitis perpetuate themselves (maintain their presence) by secreting toxins that continually damage surrounding tissue.

S. aureus is especially strong in this respect, where it keeps colonizes the nasal area in about one-third of healthy people and can produce a variety of

cytokines, enzymes, and toxins that destroy tissue and affect the neutrophil response.

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

Basically, we have two populations of S. aureus, intra, and extra cellular populations; in an area where has a very little entry of white blood cells, some of the S. aureus population are hiding inside these blood cells and maintain themselves there (intracellular pop.), the other population (extracellular pop. (Fighters)) keep causing damage. So, whenever the extracellular pop. (Fighters) decreases in the number, the intracellular pop. would keep replenishing the extracellular ones. this also happened in other areas than the bone such as the urinary tract or in places where the biofilm formation happened or when the ability of pathogen's cells to have a part of its life cycle intracellular.

Any bacteria that can evade the immune system through destruction inside the vacuoles in the phagocytes will have this kind of populations. so, we never can reach sterility. sterility and healthiness can only be achieved with a proper immune system.

the only reason why we are healthy is because of our immune system and as the immune system wanes, all the bacteria show their potential.

S. aureus can **remain dormant** where it turns off all its gens and stops its vital processes so, no respiration, no protein or DNA production thus it becomes unculturable (Dormant form of bacteria called NCBV- not culturable but viable). So, these are resistant forms that hibernate and remain inactive for decades before infection erupts at sites of old injuries (especially penetrating wounds, shrapnel…)

Although Coagulase-negative 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. So it's not uncommon to show no symptoms and suddenly show infection after 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. so, initial antibiotic therapy might make it worse if the bacteria find an area where they want to cause destructions, they can compete with themselves to see who will become dominant or synergize if there is threat or anaerobes to make a place for anaerobic so, sometimes you want to wait before makes the decision.

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 a synergistic role with other pathogens, these are usually targeted with specific therapy.

Clinical features

Acute osteomyelitis

presentation usually in pediatric patients due to hematogenous spread.

The onset of pain around the affected site, then Local and systemic signs of inflammation such as swelling, tenderness, warmth, and erythema may or may NOT be present! (especially in the vertebra, hip, or pelvis-not long bones) because it's deep infection.

Chronic osteomyelitis

subacute to chronic usually in adults because they have a more competent immune system.

The 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 the bone is felt when palpating an ulcer can be sufficient to diagnose osteomyelitis.

Diagnosis

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

1. Blood tests

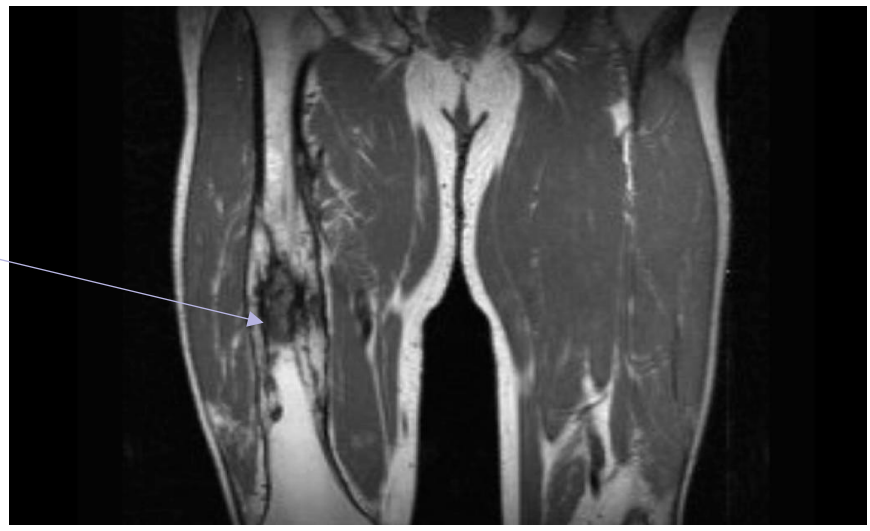
- ☑ White cell count may be raised but can be normal.
- ☑ Inflammatory markers (ESR and CRP); are usually high. CRP changes occur earlier in bacterial infection. However, ESR and CRP are not specific and can be elevated in conditions other than osteomyelitis.

- ☑ Blood cultures are more likely positive in vertebral infection and in hematogenous spread (clavicle, pubis) and less likely positive in the contiguous spread.

2. Radiology

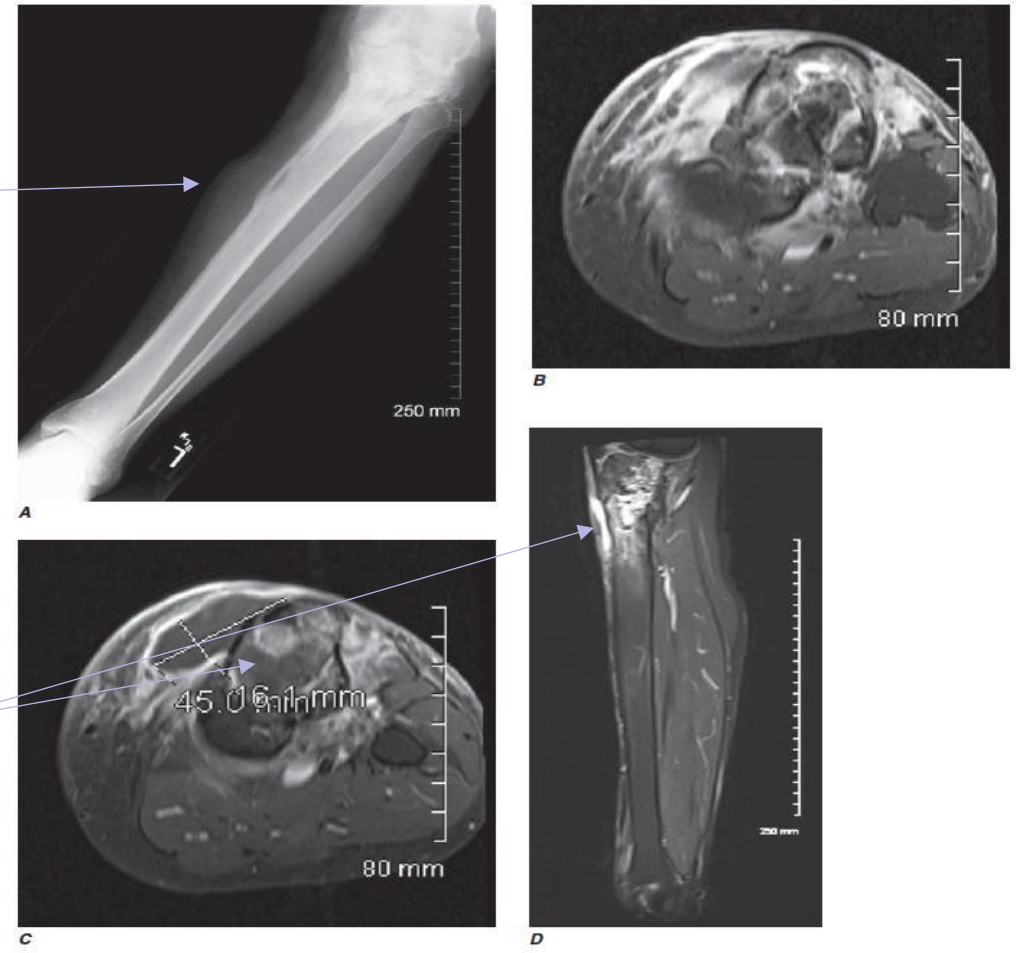
- ☑ plain X-ray may show changes after 1-2 weeks, may eliminate the need for further imaging studies.
- ☑ Bone loss, sequestra, periosteal elevation or swelling (which can develop early on), and shadows around foreign bodies are hallmarks of bone infection.
- ☑ CT or MRI scans are the investigations of choice (MRI is both specific and sensitive), MRI may be contraindicated in patients with metalware; these may also cause artifacts on CT.

This is the site of osteomyelitis, which may cause a fracture or it's an old fracture that isn't healing.



we notice the elevation in the periosteum. maybe there's a swelling in the soft tissues here.

This is probably an abscess.



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 debridement 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.

The problem with PCR that You cannot directly know the causative agent. instead, you must target a specific gene only at one time; meaning you have to ask a specific question each time (ex. Is this staph?). So Multiple PCRs should be done for each suspectable organism, clinical data can help you to direct your questions.

Management General principles

Treatment aims to eradicate the causative agent and restore or at least preserve the function of the bone. Osteomyelitis in adults is usually treated with a combination of surgical debridement and antibiotic therapy.

Surgery the principles of surgical therapy is 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 antibiotics therapy is based on culture and sensitivity results. duration is unknown and most experts treat for 4-6 weeks of IV therapy! The addition of rifampicin to β-lactams was shown to be effective in certain staphylococcal osteomyelitis animal models is often used in infections, particularly those involving prosthetic material. Patients are usually discharged once they are clinically stable and treated as an 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) to change the direction of fluids from inside to outside. 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 More difficult than cephalosporins to administer for long periods
	Cephalosporins	Cefazolin: 2 g IV q8h Ceftriaxone: 1–2 g IV q24h	Ceftriaxone advantageous with OPAT
	Clindamycin[a]	600–900 mg IV q8h	Not well studied for osteomyelitis Oral form possible (300–600 mg q8h) Resistance significant and increasing 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 Bacteriostatic
Streptococci	Penicillin	5 mU IV q6h or 20 mU/d by continuous infusion	Not all streptococci are susceptible. Ceftriaxone (1 g/d IV or IM) and ampicillin (12 g/d IV) are alternatives.
Enterococci	Penicillin plus gentamicin	As above 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 4-6 week course of IV therapy remains the standard and is the usual recommended minimum. Although in the pediatric population, some studies are suggestive of 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 sequestrate make that specific area of bone less able to bear weight and is prone to fracture.
- ☒ Hematogenous spread and sepsis, especially in aggressive disease.
- ☒ Tumors, in patients with long-standing osteomyelitis (4–5 years).
- ☒ In rare instances, chronic inflammation and infection may lead to malignant transformation into squamous cell carcinoma or sarcoma due to the continuous replacement of cells like what happens due to smoking and constant exposure to chemicals.
  e.g. squamous cell carcinoma (commonest), fibrosarcoma, myeloma, lymphoma, plasmacytoma, angiosarcoma, rhabdomyosarcoma, and malignant fibrous histiocytoma.

Prognosis

It Varies, on all the factors that are included in the classification systems.

- Vertebral in immunocompromised-late diagnosis →poorer prognosis
- Mandible following a tooth extraction, early proper treatment→ better prognosis.

Prevention

- ☑ Osteomyelitis can be prevented with better preoperative 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 osteomyelitis).
- ☑ Early Dx and treatment of other infection routes (abscess, bacteremia, boil…etc).

- ☑ Early surgical treatment of wounds (esp extensive ones) have a better outcome.
- ☑ Sacral ulcers can be often a point of infection –bedridden patients- and easily overlooked.

You will eat the fruit of your labor; blessing and prosperity will be yours ♥

Thank you so much for bearing!