جامعة الملك سعود
King Saud University

Pathology

Team 435

Lecture (4,5): Osteomyelitis & Arthritis

Objectives:

- Understand the aetiology, pathogenesis, and clinical features of osteomyelitis.
- Be familiar with some of the terminology used in bone infections like: sequestrum, involucrum, Brodie abscess, and Pott's disease.
- Understand the clinicopathological features of tuberculous osteomyelitis and infective arthritis.
- Know the pathogenesis and clinicopathological features of osteoarthritis (degenerative joint disease), rheumatoid arthritis, gout, and calcium pyrophosphate arthropathy (pseudogout).

Table of contents:

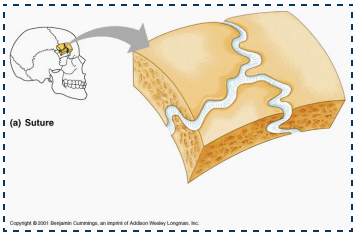
Structure and function of joints (recap)

A joint is the area where two bones connect. Joints are of two types: (Anatomy Lecture)

- **Solid joints** :

  These joints are fixed and rigid and allow only minimal movement. Examples of solid joints include:

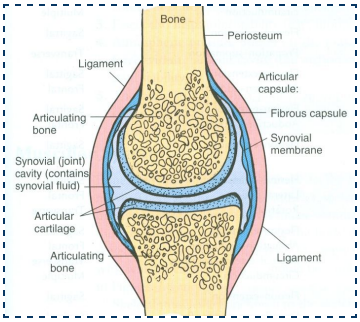
  - The skull sutures: Where the skull bones are bridged by fibrous tissue.
  - The symphysis pubis: Where the bones are joined by cartilage.



- **Synovial joints:**

  These joints have a joint space, which allows a wide range of movement. The articular cartilage in synovial joints is a specialized hyaline cartilage which is an excellent shock absorber. The synovial membrane (lined by synovium cells) secretes synovial fluid (usually few milliliters) into the joint space.

  ➔ Synovial fluid acts as a lubricant[1] and provides nutrients for the reticular hyaline cartilage and it can be aspirated for analysis of diseases, synovial fluid accumulation inside a joint is called an effusion[2].



General etiology of arthritis:

We have 4 main causes that will lead to arthritis:

- Degenerative (in osteoarthritis): Degeneration due to age causing tear and wear on the cartilage.
- Infection (in septic arthritis, tuberculous arthritis): Bacterial infections are the most prevalent.
- Autoimmunity (in rheumatoid arthritis, SLE, rheumatic fever): The body loses self-recognition and attacks its own cartilage.
- Crystal deposition (in gout and other crystalline arthropathies).

Osteoarthritis: Although the term "osteoarthritis" implies an inflammatory disease, it's not.

It's primarily a degenerative joint disease (degeneration of articular cartilage). It's the most common type of joint disease characterized by the **degeneration** and **progressive erosion** of articular cartilage in weight bearing joints (hip, knee, ankle, back).

It's more common in women and those above the age of 50 (its incidence increases with age) could be on shoulder or other joints depend on individual.

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[1] A substance which is used for minimizing friction.

[2] Other types of effusion:

1. Pleural effusion: accumulation of fluids in the lungs.
2. Ascites: accumulation of fluids inside the abdomen.

Causes: Osteoarthritis can be:

Primary	Secondary
Due to wear and tear (aging). With no apparent initiating causes. In such cases, the disease is usually oligoarticular (i.e. affects only a few joints.) Most commonly affected joints: Weight bearing joints mostly - **Hands:** Proximal and distal inter-phalangeal joints of the fingers and first carpometacarpal joints. - **Knees. - Hips. - Feet:** first tarsometatarsal joints. - **Spine:** lower lumbar and cervical vertebrae.	Occurring in younger patients and could be due to predisposing[3] conditions such as: - Underlying systemic disease such as ochronosis, hemochromatosis, marked obesity or diabetes. - A congenital or developmental deformity of a joint. - A previous trauma including repetitive minor trauma, informants factor. - Surgeries. The secondary osteoarthritis occurs in less than 5% of the cases.

Relation between gender and osteoarthritis:

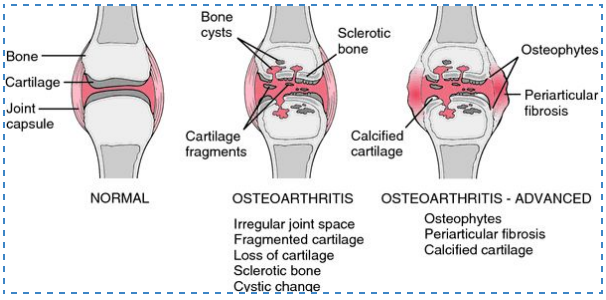
Gender has some influence in the location of osteoarthritis occurrence. For example, in females, knees and hands are commonly affected, whereas in males, hips are more commonly affected.

Doctor's note: If a women were to have large breasts that she has to carry everyday, she may acquire osteoarthritis in her shoulder joint.

Pathogenesis:

Articular cartilage bears the brunt[4] of the degenerative changes in osteoarthritis. The normal articular cartilage performs two functions:

- ➢ Provides virtually friction-free movement within the joint (along with the help of synovial fluid.)
- ➢ In weight-bearing joints, it spreads the load across the joint surface in a manner that allows the underlying bones to absorb shock and weight.



These functions require the cartilage to be elastic and to have high tensile strength. These attributes are provided by proteoglycans and type II collagen, both produced by chondrocytes.

Remember: As with adult bone, articular cartilage constantly undergoes matrix degradation and replacement. Normal chondrocyte function is critical to maintain cartilage synthesis and degradation; any imbalance can lead to osteoarthritis. Chondrocyte function is affected by a variety of influences. The risk of osteoarthritis is increased with increasing bone density, as well as sustained high estrogen levels.

[3] leading to
[4] Bears the brunt is an expression that means receiving the worst part of something harmful

Early osteoarthritis is marked by:

- Degenerating cartilage containing more water and less proteoglycan.
- The type II collagen network also is diminished, presumably as a result of decreased local synthesis and increased breakdown.
- Chondrocyte apoptosis is increased.
- Overall, cartilage tensile strength and resilience are compromised

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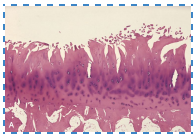
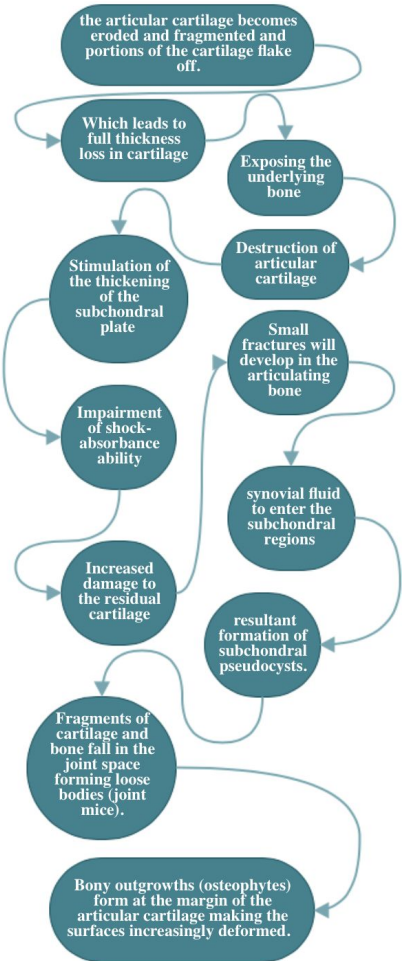
The proteoglycan component conveys turgor and elasticity. In response to these degenerative changes, chondrocytes proliferate and attempt to "repair" the damage by synthesizing new collagen and proteoglycans. Although these reparative changes initially are able to keep the pace, matrix changes and chondrocyte loss eventually predominate.

Steps of pathogenesis:

- ➔ The articular cartilage becomes eroded and fragmented **(**fibrillated[5]**)** and portions of the cartilage flake off as the superficial layers are degraded.
- ➔ Gross examination at this stage reveals a soft granular appearing articular cartilage surface. A condition known as Chondromalacia.



- ➔ In contrast with joints affected by simple wear and tear, these changes occur well away from the articular margins eventually leading to a full loss of thickness in cartilage exposing the underlying bone and smoothing it with friction. Afterwards, developing a polished ivory appearance **(eburnation[6])**.
- ➔ Which eventually causes destruction of articular cartilage.
- ➔ Later on, Loss of articular cartilage will stimulate the thickening of the subchondral plate and the adjacent cancellous bone (joint capsule and synovium) reinforced with osteoblastic activity which impairs the shock absorbance ability of the joint. Leading to increased damage to the residual cartilage (with Inflammation).
- ➔ Small fractures will develop in the articulating bone allowing **synovial fluid to enter the subchondral regions** with resultant formation of subchondral pseudocysts(fibrous walled cyst).
- ➔ Fragments of cartilage and bone fall in the joint space forming loose bodies called joint mice.
- ➔ Osteophytes "mushroom-like bony outgrowths" form at the margin of the articular cartilage making the surfaces increasingly deformed.
- ➔ In severe cases, a fibrous synovial pannus covers the peripheral portions of the articular surface.



What are joint mice?
Pieces of osteophytes in the patient that has been detached are swimming inside the joint synovium causing irritation. Articular surface is diminished as result of the contact of the bones with each other without any protection by articular cartilage causing pain.

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[5] مجزأ
[6] انعواج

The reason why articular cartilage becomes predisposed to this damage appears to be related to biochemical alterations in the hyaline.

In hyaline cartilage affected by osteoarthritis:

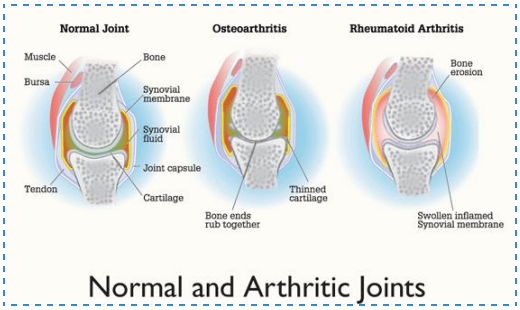
- Water content is increased.
- Proteoglycan content is decreased.

Therefore, elasticity and compliance of the cartilage is reduced.

The first change seen in osteoarthritis is proliferation of chondroblasts which produce enzymes that induce the effects (biochemical changes) on hyaline cartilage. Thus, most changes are mainly seen in the cartilage as opposed to the synovium.

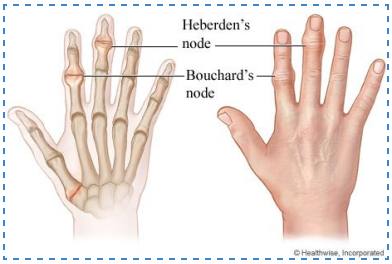
Course:

- Slowly progressive, chronic joint disability.
- Elderly sufferers may eventually become confined to wheelchairs.
- Recent advancements in the technique of joint replacement with prostheses have improved the outlook of these patients.



Normal and Arthritic Joints

Clinical features:



➔ As we've mentioned before the most commonly affected joints are the hips, knee, cervical and lumbar vertebrae. Alongside those we have the proximal and distal interphalangeal (PIP and DIP) joints of the hands, the first metacarpophalangeal joint, the first metatarsophalangeal joint and tarsometatarsal joint of the feet. Osteophytes at the DIP joints in women produce nodular swellings called Heberden's nodes. (Heberden's nodes at the **distal phalanx** and Bouchard's node at the **proximal phalanx**.)

➔ Insidious, predominantly affecting patients beginning in their 50s and 60s.

➔ With increasing deformity of the joint the typical **symptoms** develop which are:

- Pain (worsens with use) - Morning stiffness - Swelling of affected joints. - Crepitus[7]
- Osteophyte impingement on spinal foramina can cause nerve root compression with radicular pain, muscle spasms, muscle atrophy, and neurologic deficits.
- Loose bodies: may form if portion of articular cartilage breaks off. - Limitation in joint movement.
- Mild inflammation.
- Important cause of physical disability in individuals older than 65 years of age.

[7] Popping sensation in the joint

NOTE: If the joint affected is of the cervical or lumbar spine, bony outgrowth (osteophytes) may impinge on the nerve roots causing symptoms such as severe pain, pins and needles in the arms or legs. The overall result is **disability** in a process that cannot be halted.

NOTE: Osteoarthritis usually affects one joint and is not symmetrical (both hands or both legs).

Rheumatoid Arthritis:

A chronic inflammatory multisystem disorder in which the joints are invariably involved (principally small joints). It is a polyarticular arthritis (3+ joints). It's a common condition. with a prevalence of 1% of adults.

- Unlike osteoarthritis it's an **autoimmune** disease as opposed to a degenerative disease.
- It can affect all age groups but commonly occurs earlier in age (20-40 yrs).
- When children are affected, we call it Still's Disease.
- Females are affected more often than males.

On a histologic examination the affected joints show chronic papillary synovitis which is characterized by:

- Hyperplasia of the synovium.
- Lymphoplasmacytic infiltrate (frequently forming lymphoid follicles) in the synovium composed of:
  - CD4+ T cells.
  - Plasma cells.
  - Macrophages.

  And it clinically improves with movement.
- Increased vascularity due to angiogenesis.
- Neutrophils and aggregates of organizing fibrin on the synovial surface and in the joint space.
- Increased osteoclast activity in the underlying bone, leading to synovial penetration and periarticular bone erosion.

Pathogenesis:

RA is disorder in which genetic and environmental factors contribute to the breakdown of tolerance of self-antigens.

Pathologic changes are caused by:

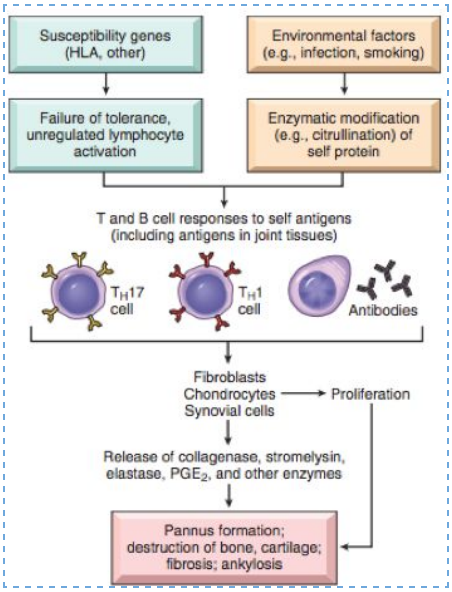
- ➔ Cytokine-mediated inflammation.
- ➔ With CD4+ T cells being the principal source of the cytokines.

Many patients produce antibodies against cyclic citrullinated peptides (anti-CCP)

NOTE: CCPs are derived from proteins in which arginine residues is converted into citrulline residues.

Diagnostic markers may form immune complexes that deposit in the joints and may be involved in tissue injury, they are:

- Anti-CCP - Type II collagen - α-enolase - Vimentin



Genetic factors	Environmental factors
- HLA-DRBI locus - PTPN22 gene = tyrosine phosphatase that inhibit T cell activation	Smoking, infections and inflammation may induce the citrullination of some self protein creating epitopes that trigger autoimmune reactions " e.g.: Anti-CCP that may be produced during inflammation"

What you can find in an inflamed synovium?	
• CD4+ TH1 cells. • CD4+ TH17 cells. • Activated B cells. • Activated plasma cells. • Activated macrophages. • Other inflammatory cells.	• Numerous cytokines, including IL-1, IL-8, TNF, IL-6, IL-17, and interferon-γ. "by T cells" • proteolytic enzymes, such as collagenase. "by macrophages " • TNF family cytokine RANK ligand. "by activated T cells" • In severe cases, well-formed lymphoid follicles with germinal centers may be present.

It is initiated in a genetically predisposed person by activation of CD4+ helper T cells responding to some arthritogenic agent (microbial, or to a self-antigen such as CCP).

➔ Therefore, cytokines produced by the activated T cells recruit leukocytes (such as macrophages), whose products cause tissue injury, and also activate resident synovial cells to produce proteolytic enzymes, such as:

Collagenase which mediates destruction of the cartilage, ligaments, and tendons of the joints.

➔ Production of TNF family cytokine RANK ligand will increase osteoclast activity in the joints and that will lead to bone destruction.

- TNF appears to play a pivotal role. This is demonstrated by the remarkable effectiveness of TNF antagonists "blockers" in patients with the disease, even those who are resistant to other therapies.

80% of patients have serum IgM autoantibodies that bind to the **Fc** portions of their own (self) IgG. These autoantibodies are called rheumatoid factor (RF). They may form immune complexes that deposit in joints and other tissues, leading to inflammation and tissue damage.(Hypersensitivity)

In comparison with Osteoarthritis which presents with mild inflammation; rheumatoid arthritis causes inflammation in the synovium and is mediated by **CD4 T Cells Cytokines** (IL-1, IL-6,IL-7,IL-17 and **TNF**)

Some of the pathological features:

- Bones: Patients are at increased risk of localized and generalized osteoporosis.

- Skin:

  The most common cutaneous lesions are the rheumatoid nodules. Which arise in areas exposed to pressure such as the extensor surfaces of the arms and elbows. They arise in the subcutaneous tissue and manifest as oval or rounded masses, firm, non-tender skin nodules (2 cm in diameter). They are caused by necrosis in the collagen and the inflammatory reaction around it which is a palisade of histiocytes and fibroblasts rimmed by granulation tissue and lymphocytes "palisading granuloma".

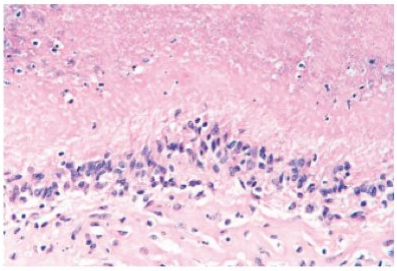


Figure 20–20 Rheumatoid nodule. Serpiginous area of necrobiotic collagen surrounded by palisading histiocytes.

- Joints:

  The most severe morphological changes manifest in the joints. Typically manifests as symmetric arthritis affecting small joints. And it is primarily seen in the **synovium** and NOT in the cartilage. (Unlike osteoarthritis)

  Morphology of the joints: (summarized in the diagram to the right)

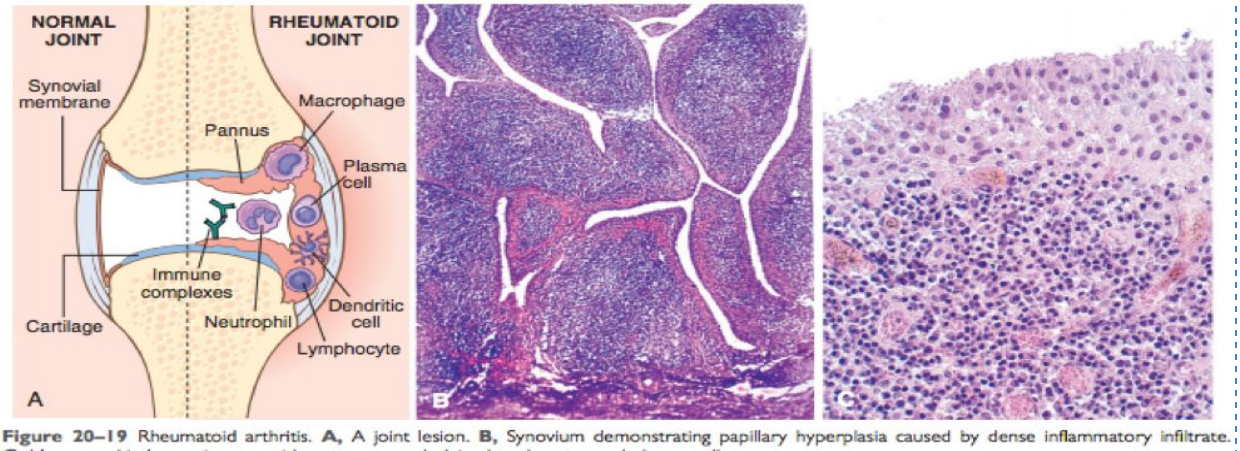


Figure 20–19 Rheumatoid arthritis. **A,** A joint lesion. **B,** Synovium demonstrating papillary hyperplasia caused by dense inflammatory infiltrate. **C,** Hypertrophied synoviocytes with numerous underlying lymphocytes and plasma cells.
(A, Modified with permission from Feldmann M: Development of anti-TNF therapy for rheumatoid arthritis. Nat Rev Immunol 2:364, 2002.)

pannus slowly spreads and degrades the underlying cartilage

causing erosions and the development of subchondral cyst in the underlying bone.

Then, small detached fragments fall into the joint space and are called rice bodies.

The fibrous pannus eventually bridge the opposing bones

causing limitation of movement and ossification of the fibrous tissue

leading to bony ankylosis (formed of vascular granulation tissue + fibrin).

As it advances cartilage is completely lost

Clinical course:

The clinical course of is very variable. It causes nonsuppurative (not pus-forming) proliferative synovitis that progress to destroy articular cartilage and underlying bone resulting in disabling arthritis

➔ Initially, Patients may suffer constitutional symptoms "weakness, malaise, and low-grade fever" and only after a few weeks or months do the joints become involved.

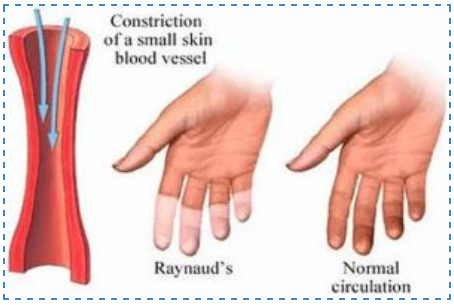
- The small joints (most often proximal interphalangeal and metacarpophalangeal) are affected before the large joints.
- Axial involvement is rare but when it occurs, it is limited to the upper cervical spine.
- Hip joint involvement is extremely uncommon.

➔ The affected joints are swollen, painful and stiff following a period of inactivity.

➔ The arthritis first appears insidiously, with aching and stiffness of the joints, particularly in the morning.

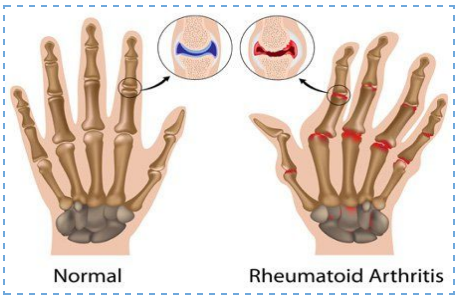
➔ As the disease advances, the joints become enlarged, motion is limited, and in time complete ankylosis "stiffness of joints bone" may appear.

➔ Vasculitic involvement of the extremities may give rise to Raynaud Phenomenon[8] and chronic leg ulcers.



➔ As a result of the pathological process within the articular and periarticular tissues, characteristic deformities develop, these include:

- Radial deviation at the wrist.
- Ulnar deviation at the fingers.
- Flexion and hyperextension deformities of the fingers (Destruction of tendons, ligaments, and joint capsules that leads to swan neck deformity and boutonniere deformity in the thumb).



Tests for detecting the disease:

Such multisystem involvement must be distinguished from other diseases as well as other forms of arthritis. Helpful in making the correct diagnosis are:

- Rheumatoid factor(RF) test:
  Look for IgM/IgA antibodies that react with FC region of IGG; if (+), the patient has RA. This test is sensitive but not specific because it's positive in about 8% of the population.

- ESR (Erythrocyte Sedimentation Rate):
  Nothing will be evident in this test however it'll tell you that there is an inflammation in the joint which may be useful to the diagnostic process.

- Anti-CCP(Cyclic Citrullinated Peptides):
  During inflammation of synovium the Arginine gets converted enzymatically into citrulline. It is sensitive and very specific test, present in 80%of patients with rheumatoid arthritis.

- Characteristic radiographic findings.

- Sterile, turbid synovial fluid with decreased viscosity, poor mucin clot formation, and inclusion-bearing neutrophils.

Crystal arthropathies:

A group of diseases caused by the deposition of crystals within the joint resulting in acute and chronic arthritis. Such crystals may be endogenous or exogenous. The most common crystal arthropathies which are gout and calcium pyrophosphate arthropathy are due to endogenous crystal deposition.

[8] Recurrent vasospasm (sudden constriction of a blood vessel) of the fingers and toes and usually occurs in response to stress or cold exposure.

Gout (gouty arthritis):

A **metabolic syndrome** which is caused by excessive amounts of uric acid accumulation within tissues and body fluids. Gout is more common in men than in women; usually asymptomatic before the age of 30.

Risk factors for the disease include:

- Obesity (with an increased waste/trunk size). - Excess alcohol intake. - Consumption of purine-rich foods.
- Diabetes. - The metabolic syndrome. - Renal failure. - Uricemia. - Dyslipidemia (high cholesterol and fat in blood).

Basically those that have a horrible life style that needs to be changed. It more commonly affects obese affluent men.

How does it occur?

Occurs due to the crystallization (needle shaped, elongated crystals) of monosodium urate within a joint, resulting in an acute gouty arthritis, which is characterized by:

- Extreme localized pain. - Erythema. - Exquisite tenderness of the affected joint.

The most commonly affected joint is the metatarsophalangeal joint of the great toe, followed by the ankle and the knee joints.

The disorder is primarily linked to raised serum uric acid levels, however only 3% of people with **hyperuricemia** will develop gout.

Basically, uric acid is the end product of purine metabolism and is excreted by the kidneys. Purine can either be derived from the breakdown of nucleic acid or synthesized from scratch.

Tip: To understand this part of the lecture better go back and read the 4th lecture in biochemistry (purine degradation and gout)/Pharmacology lecture.

Elevated uric acid levels can result from overproduction or reduced excretion of uric acid, or both.

Possible triggers that lead to the deposition of urate crystals in the joint include: - Alcohol. - Trauma. - Surgery. - Infection.

The presence of the monosodium urate crystals within the joint causes the accumulation of numerous inflammatory cells.

We have two types of gout:

- Primary gout (90%):

  Unknown cause, most cases are primary overproduction of uric acid. (90% of the cases) due to an inborn metabolic defect that causes hyperuricemia.

- Secondary gout (10%):

  Hyperuricemia can be caused by either one of the following or both: (10% of the cases)

  - Increased urate production (e.g., rapid cell lysis during chemotherapy for lymphoma or leukemia)
  - Decreased excretion (chronic renal insufficiency)

NOTE: reduced excretion may also be caused by drugs such as "thiazide diuretics" because of its effects on uric acid tubular transport.

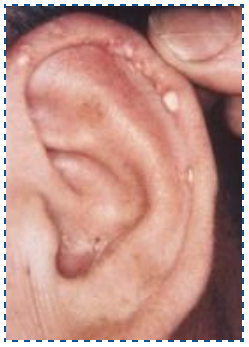
Pathogenesis: There are four stages in gout which are classically recognized:

1. **Asymptomatic hyperuricemia:**
   Appears around puberty in males and after menopause in women.
2. **Acute gouty arthritis:**
   Appears in the form of sudden onset, excruciating joint pain associated with localized erythema, and warmth; constitutional symptoms are uncommon, except possibly mild fever. The vast majority of first attacks are monoarticular; 50% occur in the first metatarsophalangeal joint and 90% in the instep, ankle, heel, or wrist.
3. **Intercritical gout:**

   Untreated, acute gouty arthritis may last for hours to weeks, but it gradually completely resolves, and the patient enters an asymptomatic intercritical period.
4. **Chronic tophaceous gout:**

   Most people experience a second episode within months to a few years. In the absence of appropriate therapy, the attacks recur at shorter intervals and frequently become polyarticular. Eventually, symptoms fail to resolve completely after each attack, and the disease progresses to chronic tophaceous gout. At this stage, radiographs show characteristic juxta-articular bone erosion caused by the crystal deposits and loss of the joint space. Progression leads to severe crippling disease.

Morphology:



The major morphologic manifestations of gout are:

1. Acute arthritis.
2. Chronic tophaceous arthritis.
3. Tophi in various sites. (picture)
4. Gouty nephropathy (renal complications associated with urate deposition).

How does it exactly happen? We have two possible pathways:

(Think of it as two different stories with the same not so happy ending)

First pathway:

Monosodium urate crystals **accumulate** in the joint irritating it.

- ➔ Crystals are then opsonized → failure of phagocytosis by macrophages and neutrophils.
- ➔ Urate crystals directly activate the complement system and chemotaxis.
- ➔ Production of chemotactic and pro-inflammatory mediators (increase in neutrophils and **lysosomal enzymes**).
- ➔ Lysosomal enzymes will cause: necrotized tissue → inflammation → appearance of cardinal signs.

Second pathway:

In this second story (pathway), the macrophages and neutrophils succeed at phagocytosis of opsonize crystals.

- ➔ Then they're recognized by the intracellular sensor called the inflammasome which is activated and stimulates the production of the cytokine IL-1.
  - IL-1 is a mediator of inflammation, and causes local accumulation of neutrophils and macrophages in the joints and synovial membranes.
- ➔ These cells become activated, leading to the release of a host of additional mediators including chemokines, other cytokines (IL 1, IL 7, IL 8, TNF), toxic free radicals, and leukotrienes— particularly leukotriene B4. The activated neutrophils also liberate destructive lysosomal enzymes.
- ➔ The cytokines can also directly activate synovial cells and cartilage cells to release proteases (e.g., collagenase) that exacerbate tissue injury.
- ➔ Inflammation → Appearance of cardinal signs.

The resulting acute arthritis typically remits in days to weeks, even if untreated.

Repeated bouts[9], however, can lead to the permanent damage seen in chronic tophaceous gouty arthritis. Where the affected joint is damaged and the function is impaired.

In severe cases, extreme inflammation will lead to local ischemia or ulceration → secondary rheumatoid arthritis.

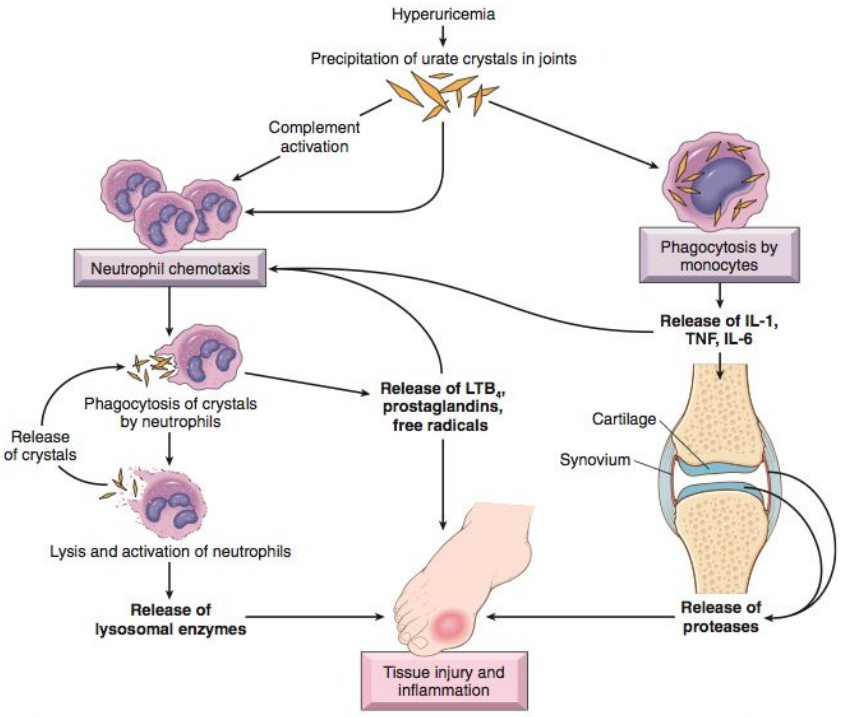


Figure 20–22 Pathogenesis of acute gouty arthritis. IL, interleukin; LTB_4, leukotriene B_4; TNF, tumor necrosis factor.

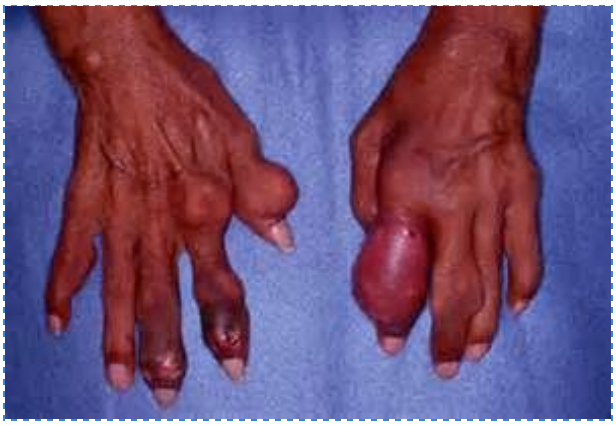
[9] Repeated **attacks**

Pseudogout (chondrocalcinosis): Also: Calcium pyrophosphate arthropathy

This condition is due to the deposition of **calcium pyrophosphate crystals** in the synovium (pseudogout) and articular cartilage (chondrocalcinosis). It's common in older people (50 years and above). it becomes more common with increasing age, and eventually reaching a prevalence of 30% to 60% in those age 85 or older.

It can occur in three main settings:

1. Sporadic (more common in the elderly).
2. Hereditary.
3. Secondary to other conditions, such as:
   - Previous joint damage.
   - Hyperparathyroidism.
   - Hypothyroidism.
   - Haemochromatosis.
   - Diabetes.



Calcium pyrophosphate crystals are smaller than monosodium crystals and affect the phalange joints and are present with similar symptoms. Crystals first develop in the articular cartilage (chondrocalcinosis) such as menisci, intervertebral discs, and articular surfaces which is usually asymptomatic, from here the crystals may shed into the joint cavity resulting in acute arthritis which mimics gout and is therefore called pseudogout.

It's known as chondrocalcinosis, why?

Because it caused by deposition of calcium pyrophosphate in small joints (such as the hand)

So, its calcium pyrophosphate crystal deposition disease

Pseudogout can be differentiated from gout in three ways:

- The knee is most commonly involved.
- X-ray shows the characteristic line of calcification of the articular cartilage.
- Aspiration + Fresh tissue (wet preparation) sample; the crystals will look different under polarizing microscopy, they are **rhomboid** in shape and exhibit positive birefringence[10] with a red filter. And we will see neutrophils in gouty crystals.

How do the crystals form and accumulate?

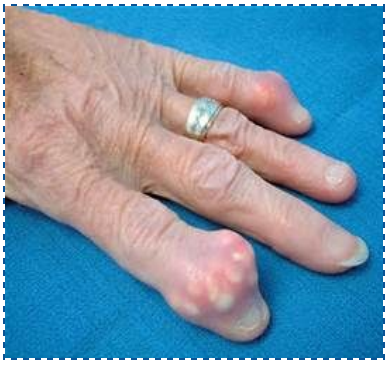
They are likely to involve the overproduction or decreased breakdown of pyrophosphate, resulting in its accumulation and eventual crystallization with calcium in the matrix surrounding chondrocytes. When the deposits enlarge enough, they may rupture, inducing an inflammatory reaction.

[10] Double refraction of light

Duration of clinical signs can be from several days to weeks, and joint involvement may be monoarticular or polyarticular; the knees, followed by the wrists, elbows, shoulders, and ankles, are most commonly affected.

In pseudogout patients the uric acid is normal, but the crystals are rhomboid in shape NOT needle shaped as in gout, they cause pain and they are idiopathic.

Gout	pseudogout
Monosodium urate crystals	Calcium pyrophosphate crystals
Affect small joints usually big toes	Affect small joints
Male > female	Male = female
Middle aged males, postmenopausal females	elderly



Osteomyelitis

Osteomyelitis refers to the inflammation of the bone and marrow and is usually the result of an infection.
If it was the joints instead, it would be Septic Arthritis. Pyogenic=suppurative =septic arthritis
It can be secondary to systemic infection but more frequently occurs as a primary isolated focus of disease; it can be acute or chronic.
Although any microorganism can cause osteomyelitis, the most common etiologic agents are pyogenic bacteria and Mycobacterium tuberculosis.

Causes:

- **Inflammatory focus:**

  Most cases of acute osteomyelitis are caused by bacteria. Bacteria can go through the bloodstream and get deposited in bone which causes osteomyelitis. For example: if someone has Bronchopneumonia, pneumonia, undomesticated in heart

- **Compound fracture:**

  Common cause of osteomyelitis following trauma , considered as secondary osteomyelitis. (Bacteria can reach the bone after traumatic implantation following compound fractures or orthopedic procedures).

- **Surgical intervention:**

  Very common, if we had a fracture and we did an internal fixation (using wire, screw, plate, etc.) which is considered a foreign body.

  Once we put these foreign bodies inside the tissue of a human body we are INVITING Bacteria to come. It is common in people having inflammatory focus elsewhere in the body e.g. endocarditis in heart, septic focus, chronic tonsillitis.

  Also sometimes in joint replacement they may have secondary osteomyelitis.

- **TB:**

  Mycobacterial infection of bone has long been a problem in developing countries; with the resurgence of tuberculosis (due to immigration patterns and increasing numbers of immunocompromised persons) it is becoming an important disease in other countries as well.

  A lot of patients have osteomyelitis because of TB, leading to chronic osteomyelitis which is likely to affect the spine.

  * TB ينتقل عن طريق الدم ويذهب للمفاصل ويعمل عمايله*

DON'T FORGET: TB can affect the distal end of the femur, the proximal end of tibia and the end of humerus (those are the favorite areas for TB); also TB can be near epiphysis; it can occur elsewhere.

TB occurs (focus) usually at lymph nodes or lung and bacteria moves through blood and settles in joints WHY? Because joints have many vessels and this bacteria (TB) loves oxygen, it really needs areas where there is a lot of blood supply and a lot of oxygen. This is why it goes to the lungs, joints and bones (they have a lot of blood).

Pyogenic osteomyelitis:

Organisms may gain access to bone by bloodstream spread from a distant infected site by:

- contiguous spread from neighboring tissue
- direct access via a penetrating injury.

Almost any organism can cause osteomyelitis. For example, mixed bacterial infections, including anaerobes, typically are responsible for osteomyelitis secondary to bone trauma.

However, the most frequently implicated organisms are:

- The most common bacteria that causes osteomyelitis is staphylococcus aureus.
- Newborns (neonates) get infected with:
  - E.coli (Escherichia coli) gram-ve
  - Beta Hemolytic streptococcus (Group B streptococcus)
- Patients with sickle cell disease are predisposed to salmonella osteomyelitis.

* مافيه مشكله اذا كان شخص عنده sickle cell والبكتيريا المتواجده staphylococcus لأنها الأكثر شيوعا في الأطفال والكبار *

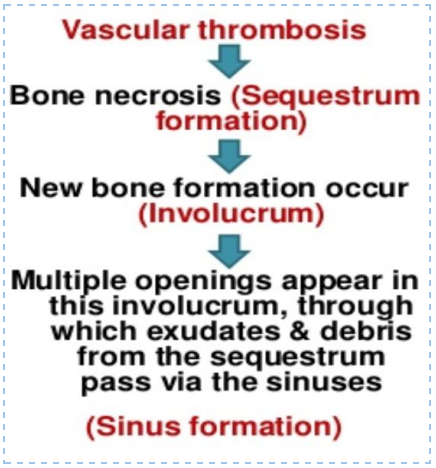
Note: mixed bacterial infections, including anaerobes, are responsible for osteomyelitis secondary to bone trauma

Pathogenesis:

The location of the lesions within a particular bone depends on the intraosseous vascular circulation (which varies with age).

Location of the lesions:

- In infants less than a year old , the epiphysis is usually affected.
- In children the metaphysis is usually affected.
- In adults the diaphysis is most commonly affected.

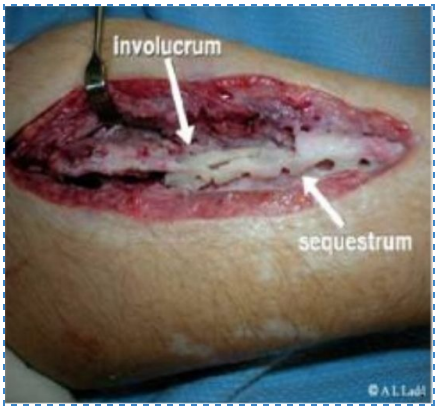


➢ In acute osteomyelitis, once the infection has become localized in bone, an intense acute inflammatory process begins.

➢ The release of numerous mediators into the haversian canals leads to compression of the arteries and veins which will result in vascular thrombosis , resulting in localized bone death (osteonecrosis).

➢ The bacteria and inflammation spread via the haversian systems to reach the periosteum[11].

➢ Subperiosteal (below the periosteum) abscess formation and lifting of the periosteum also occurs, which will impair the blood supply to the bone, resulting in further necrosis (the dead piece of bone is called the sequestrum)



* When the bacteria enters, what does it do? It will create an inflammatory reaction which is destructive to the bone. The other thing, it can cause microabscess especially in children, so it makes something called subperiosteal abscesses.So we have pus tracts from the medulla (it goes to the medullary bone first) especially metaphysis of bone.When you have sclerotic lesion and lytic lesion in metaphysis "think" about osteomyelitis and do necessary tests along with examining the patient and asking about history.*

➢ If osteomyelitis becomes chronic, a rim of viable new bone is formed around the sequestrum and below the periosteum.

➢ This new bone is called an involucrum**,** an intraosseous abscess may also form which is called Brodie's abscess.

* When the bone reacts and tries to repair → we have bone sclerosis that we see in x-ray. When we take biopsy, we see involucrum.*

➢ Rupture of the periosteum leads to formation of drainage sinuses or fistula, which drain pus onto the skin.

➢ Usually it creates this inflammatory reaction and it tracks from the medulla into the subperiosteal; sometimes it causes periosteal abscess.(periosteal abscess open into skin, when it opens into the skin we get sinus (common); because patients having osteomyelitis come with a lot of discharging sinus.)

➢ Diabetes can predispose to osteomyelitis. WHY? Because they have reduced immunity and chemotaxis of neutrophils.

[11] Periosteum: thin membrane covering the cortical bone.

Clinical features:

Osteomyelitis classically manifests as an acute systemic illness, with malaise, fever, leukocytosis, and throbbing pain over the affected region.

Acute osteomyelitis usually present with localized pain and soft tissue swelling, however, the symptoms can be subtle, with only unexplained fever "particularly in infants" , or only localized pain "in the adult".

*They may also have sinus in metatarsophalangeal joint.*sinus: It is an inflammatory tract lined by inflammatory vascular granulation tissue and have one opening. *it is Common in CHRONIC osteomyelitis*

- Many times patients have osteomyelitis and they think the patient has a tumor WHY?
  Because tumor makes lytic changes in bone + sclerosis.
- Some patients have fever and some do not; in those who have fever it may lead toward thinking about osteomyelitis + don't forget that some tumors cause fever by themselves, this is a problem, this is why we have to be very careful and we have to aspirate this joint, do other tests, do blood culture, do ESR, do c-reactive protein, do blood cell count and look at the clinical features of the patient very well.

In children and infants, presentation may be extremely subtle (may be present with only pyrexia -حمى- of unknown origin PUO)

Characteristic X-ray changes consist of a lytic focus of bone surrounded by edema and a zone of sclerosis.

· This is a child (that is known from observing the epiphyseal line -many open epiphyseal lines-) has extensive osteomyelitis, look at the sclerosis. They may think that this patient has osteosarcoma -from observing the x-ray- but after knowing that the patient has fever, (e.g. 39.5◦) , make C-reactive protein, high ESR, blood culture that reveals the presence of Staphylococcus aureus in blood → they know it is osteomyelitis.

- *When we have necrotic bone we see lytic bone lesion in x-ray.

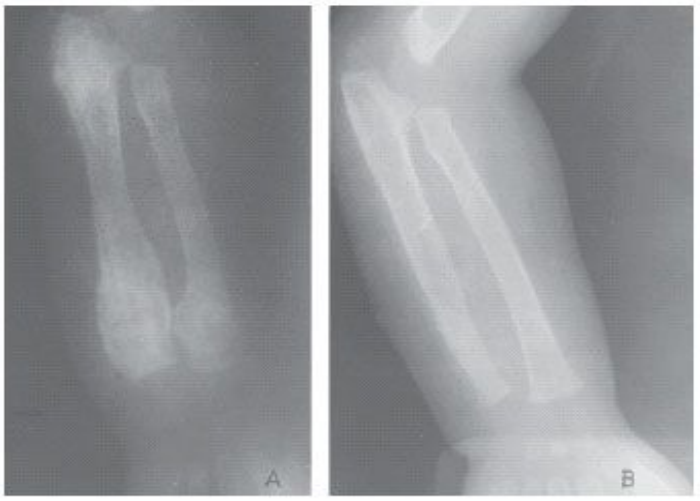


Fig. 2. a) Initial X-ray of right forearm shows osteolytic lesions consistent with osteomyelitis. b) Normal X-ray findings after treatment.

- Other thing occurring in the bone, apart from the change explained above, the bone will necrotize, areas in trabecular bone and cortical bone are necrotized. WHY? Because when we have inflammation we have septic emboli, activation of coagulation factors, microthrombi in vessels, poor blood supply for bone → bone necrotized → formation of sequestrum.

Complications:

Chronicity may develop with delay in diagnosis, extensive bone necrosis, abbreviated antibiotic therapy, Inadequate surgical debridement, and weakened host defenses and chronic osteomyelitis may be complicated by:

- ➔ Pathologic fracture
- ➔ Secondary amyloidosis
- ➔ Endocarditis
- ➔ Sepsis
- ➔ Development of squamous cell carcinoma if the infection creates a sinus tract
- ➔ rarely osteosarcoma.
- ➔ May be complicated by septicemia :·The difference between bacteremia and septicemia:

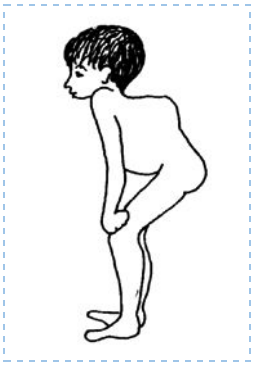
BACTEREMIA	SEPTICEMIA
We are talking about bacteria passing through the blood, but not reproducing or dividing in the bloodstream. It passes through blood and then it goes to bone, joint, lung, etc.	There is bacteria in blood and multiplying inside the blood.

- ➔ Osteomyelitis can be from septicemia (blood) to bone or from the bone to the blood; and those bacteria produce coagulase may result in the formation of sequestrum.

Osteomyelitis tuberculosis (TB) (Tuberculous Arthritis):

The organisms usually reach the bone through the bloodstream (haematogenous spread); usually from the lungs. It commonly infects diaphysis of long bone and vertebrae. It's focus is usually the lymph node or the lung and may move to the joints.

Osteomyelitis TB is endemic in the kingdom of Saudi Arabia.



Presenting features of osteomyelitis TB are:

- Cold abscess.
- Chronic inflammatory cells.
- Granuloma formation.

This condition usually presents with insidious development of a joint pain associated with limitation of movement.

If the vertebral column is involved (and it's commonly involved), we call it **Pott's disease of the spine**, it's a clinically serious form of osteomyelitis that causes vertebral deformity, collapse and posterior displacement (image on right) leading to neurologic defects (عجز عصبي).Extension of the infection to the adjacent soft tissues with the development of psoas muscle abscesses is fairly common.

Why is there neurological defects? Because the spinal cord is in the vertebrae and will be compressed in Pott's disease.

*One of the special types of osteomyelitis is Tubercular Osteomyelitis caused by acid-fast bacilli, mycobacterium tuberculosis. Chronic osteomyelitis because of TB is common in the Middle East countries. TB has to be focused in somewhere (e.g. lungs, lymph nodes….etc.) and goes to the bone; as it is rare to start in the bone.

* Bone infection complicates an estimated 1% to 3% of cases of pulmonary tuberculosis.

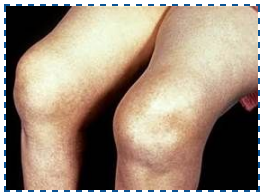
*TB likes to affect the spine especially, and when it affects the spine, the pus may track to the psoas muscle. So, the patient might come with abscess in the inguinal area; when we aspirate it we discover that it is pus and chronic inflammatory cells, WHY?

Because TB is always chronic you can find giant cells and necrosis. TB makes granuloma type 4 hypersensitivity reaction (cell mediated) to bacteria.

Infective Arthritis: (Septic Arthritis)

Its inflammation which occurs in the joints. Organisms can gain access to the joint by three main routes:

- Haematogenous spread from a distant infected site (most common).
- Direct access via a penetrating injury.
- Direct spread from a neighbouring infected site, e.g osteomyelitis, soft tissue abscess.



If the organisms enter the joint cavity, effusion and pus are formed, with destruction of bone and cartilage. Infected arthritis, particularly bacterial and TB arthritis is **potentially serious** because of its rapid destruction of the joint.

Infectious arthritis is serious, why? Because it can cause rapid joint destruction and permanent deformities.

Suppurative[12] arthritis:

Typically caused by a bacterial infection in the joint.

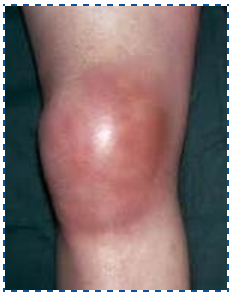
Any bacteria can be causal:

- Haemophilus influenzae predominates in children under age 2 years.
- S. aureus is the main causative agent in older children and adults (G.negative).

Both genders are affected equally except for gonococcal arthritis (occur mainly in sexually active women). Those with deficiency of certain complement proteins (C5, C6, and C7) are particularly susceptible to disseminated gonococcal infections and hence arthritis.

[12] Pus producing

Clinical features:



- Sudden onset of pain.
- Redness, and swelling of the joint with restricted range of motion.
- Fever, leukocytosis, and elevated erythrocyte sedimentation rate.
- Diabetic patients are exposed to it more than others because of:
  - Reduced immunity. - Chemotaxis of neutrophils is weak.
- The course tends to be more subacute.
- Joint aspiration typically yields a purulent fluid in which the causal agent can be identified.

In 90% of cases of nongonococcal suppurative arthritis, the infection involves only a single joint usually the knee.

NOTE: Septic/suppurative arthritis and "bacterial arthritis" are sometimes considered equivalent, but there are exceptions. For example, Borrelia burgdorferi can cause infectious arthritis, but is not associated with suppurative arthritis.

Lyme arthritis :

It's a cross-reactive immune responses to systemic infections that can lead to joint inflammation and injury. It's caused by infection of the spirochete borrelia burgdorferi. And transmitted by deer ticks. It involves mainly large joints, especially the knees, shoulders, elbows, and ankles, in descending order of frequency.

Bacterial Arthritis:

Most causes of infective arthritis are caused by bacteria. Most common organisms are:

- Gonococcus (neisseria). - Staphylococcus. - Streptococcus. - Haemophilus influenzae.
- Gram-negative bacilli.

➔ In general, children are affected more commonly than adults.

➔ Gonococcal arthritis is seen mainly in late adolescence and adulthood.

➔ Patients with sickle-cell disease tend to develop Salmonella Arthritis at any age.

Symptoms: - Pain and swelling of the affected joint. - Systemic indicators of infection e.g. fever.

Viral arthritis:

Some infections may be complicated by an arthritis, such as:

- Viral hepatitis.
- Rubella.
- Parvovirus B19.

Symptoms are of a mild arthralgia (aching joints).

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قال صلى الله عليه وسلم: من سلك طريقاً يلتمس به علماً سهل الله له به طريقاً إلى الجنة.

دعواتنا لكم بالتوفيق.