Lecture Notes of Internal Medicine

Rheumatology

Dr. Osama Mahmoud Mohamed
Assistant Professor of Internal Medicine
Ain Shams University
Dr. Osama Mahmoud Mohamed
Assistant Professor of Internal Medicine
Ain Shams University
<table>
<thead>
<tr>
<th>CONTENTS</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomy</td>
<td>1</td>
</tr>
<tr>
<td>History and Examination</td>
<td>2</td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>5</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>10</td>
</tr>
<tr>
<td>Polymyositis and dermatomyositis</td>
<td>18</td>
</tr>
<tr>
<td>Vasculitides</td>
<td>20</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>29</td>
</tr>
<tr>
<td>The spondyloarthopathies</td>
<td>44</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>50</td>
</tr>
<tr>
<td>Mixed C.T. disease</td>
<td>53</td>
</tr>
<tr>
<td>Behcet’s disease</td>
<td>54</td>
</tr>
<tr>
<td>Crystal induced arthropathy</td>
<td>55</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>62</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>65</td>
</tr>
<tr>
<td>Osteomalacia</td>
<td>66</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>67</td>
</tr>
<tr>
<td>Inherited disorders of collagen</td>
<td>69</td>
</tr>
<tr>
<td>Fibromyalgia syndrome</td>
<td>69</td>
</tr>
<tr>
<td>Classification of joint disease</td>
<td>70</td>
</tr>
<tr>
<td>Neck pain, back ache</td>
<td>71</td>
</tr>
</tbody>
</table>
RHEUMATOLOGY

- Rheumatology is a medical science devoted to the study of rheumatic diseases that include a range of musculoskeletal and systemic disorders that share the clinical involvement of joints and periarticular tissues.
- The synovial joint is made of two articulating bone surfaces, each covered with articular cartilage, these articular tissues are surrounded by a fibrous capsule lined by synovium. The space within the joint is filled with synovial fluid as lubricant, inflammation of the above structures is described as arthritis.
- The joint is surrounded by so called soft tissues including tendons, ligaments and bursae. The specialized junction where tendon or ligament joins a bone is called enthesis, this can be also inflamed.

**Normal joint**

- **Muscle**
  - Effects movements and maintains stability
  - (shows disuse atrophy in response to joint disease)
- **Bursa**
  - Composed of connective tissue: lined internally by synovial membrane,
- **Capsule**
- **Tendon**
- **Enthesis**
- **Bone**
- **Synovial fluid** — small amount, e.g. 1 ml in knee joint, consists of plasma dialysate, protein and mucin (hyaluronic acid); function is to lubricate joint and nourish articular cartilage.
- **Articular cartilage** which presents a smooth surface to the joint.

**Rheumatological terminology:**
- **Monoarthritis**: is arthritis affecting one joint.
- **Oligoarthritis or pauciarthritis**: is arthritis affecting 2,3 or 4 joints.
- **Polyarthritis**: is arthritis affecting 5 or more joints.
- **Peripheral small joints**: joints of hands and feet.
- **Peripheral large joints**: any other peripheral joint, e.g knee, hip, shoulders.
- **Axial joints**: vertebral column, sacroiliac joint.

Connective tissue diseases means heterogenous disorders that share certain common features including inflammation of skin, joints and other structures rich in connective tissue with altered patterns of immunoregulation including production of autoantibodies and abnormalities of cell mediated immunity.
History and examination of Musculoskeletal system

History:
1- Ask about peripheral joints (UL & LL) for pain, swelling, hotness, redness, limitation of movement (stiffness) or deformity.
2- Ask about axial joints (cervical & lumbar) as regard pain or limitation of movement.

- Ask about weakness either a primary or secondary muscle abnormality.
- Ask about the duration and severity of early morning stiffness.

3- Ask about extraarticular manifestations for example
   - CVS → chest pain, dyspnea
   - Chest → dyspnea, wheezy chest
   - L.N → swelling (cervical, axilla)
   - Skin → rash
   - Eye → redness
   - Kidney → puffiness, hypertension

Examination: Using the GALS screen (see the figures)
1- Inspection of gait for symmetry and smoothness of movement
2- Peripheral joints (UL, LL or Arm, Leg).
   - Inspection: swelling, deformity, wasting of muscle or skin changes, erythema or vasculitic rash.
   - Inspection during movement: is important to observe restriction, hypermobility or pain on usage.
   - Palpation → feel and move the joint, this reveal warmth, tenderness, crepitus, swelling or stability
   - Evaluation of muscle function.

D.D of Swellings of joints (by palpation)
1- Hard bony swelling.
2- Effusion demonstrated by patellar tap in knee.
3- Synovial thickening or synovitis. → firm non fluctant.

3- Axial joints (spine) for pain & limitation.
   - Cervical segments→flexion & extension, lateral flexion.
   - Lumbar segments→flexion & extension, lateral flexion.

4- Other systems (extra articular manifestations)
   - Heart for pericarditis, myocarditis and valve lesions.
   - Lung for pleurisy and I.P.F
   - Liver, spleen, L.N for enlargement.
   - Skin for rash (purpuric eruption) e.g. vasculitis.
   - Eye for redness
   - Renal: hypertension, puffiness.

The GALS (gait, arms, legs, spine) screen is a validated screening system for locomotor abnormality and disability (see later).
Sequence of GALS screening examination

Inspection of gait
- Symmetry, smoothness of movement, see later

Inspection of patient standing from behind
- Straight spine
- Muscle bulk/symmetry of paraspinai, shoulder and gluteal muscles
- Level iliac crests
- No popliteal swelling
- No hand foot swelling or deformity

Press over each mid-supraspinatus
- ?Hyperalgesia of fibromyalgia

Inspection from the side
- Normal cervical and lumbar lordosis
- Normal thoracic kyphosis

Touch your toes
- Normal lumbar spine (and hip) flexion

Inspection from the front
- Full elbow extension
- Shoulder and quadriceps muscle bulk, symmetry
- No knee swelling or deformity
- No forefoot or midfoot deformity

Hands behind head, elbows right back
- Full shoulder abduction, external rotation
- Normal acromioclavicular and sternoclavicular movement
- Full elbow flexion

Place ear on shoulder
- Normal pain-free cervical lateral flexion

Open jaw, move side to side
- Normal temporo-mandibular movement

Hands in front, palms down
- No swelling or deformity of hands/wrists
- Able to extend fingers

Turn hands over
- Normal supination (wrist, distal radio-ulnar joint)
- Normal palms

Make a fist
- Strong power grip

Place tip of finger on tip of thumb
- Examination on couch
- ‘Put your heel on your bottom’ (flex knee and hip, holding knee)

Metacarpal squeeze
- Internal rotation of hip in flexion

Fine precision pinch
- ?Metacarpophalangeal joint tenderness

Full knee and hip flexion
- No knee crepitus

No pain or restriction of hip movement
Conclusion

The clinician should be able to answer the following questions:

1- Is there is arthropathy or not, the normal joints should be asymptomatic, look normal, assume a normal resting position and move smoothly through their range of movement.

2- Is the arthropathy peripheral, axial or both?

3- Is the arthropathy affecting small or big joints, symmetrical or asymmetrical?

4- Is the arthropathy is mono, pauci, or polyarticular?

5- Is the arthropathy erosive or non erosive?

6- Is the condition acute or chronic, inflammatory or non-inflammatory?

7- What about the extra articular manifestations (is the condition limited to the musculo-skeletal system or it is a systemic process)?

8- Is there is a family history of a similar process?

Inflammatory arthropathy is characterized by pain at rest, morning stiffness and improvement with activity. In osteoarthritis and non arthritic musculoskeletal problems, pain is generally not present at rest and is precipitated by activity.
Laboratory Immunological Tests of Rheumatological Disorders

Autoantibodies are antibodies directed against self antigens including immunoglobulins, cell surfaces, circulating molecules as well as cytoplasmic antigens, nuclear antigens they are frequently observed in the sera of patients with rheumatological diseases.

Rheumatoid factor (R.F)

- It is an IgM Ab (occasionally IgG, IgA or IgE) which reacts with Fc portion of human IgG, this occurs usually in patients with rheumatoid disease (70-80% of cases), but is not diagnostic.
- It exists as an (Rf. - Ig.G - C) complex in synovial membrane. So, complement is lowered in synovial fluid and not in the serum.

Methods of detection

1- Latex method (agglutination test)
   Ab (Rh. F. in the serum) +
   Ag (latex coated with Ig G)

2- Rose waaler test. (agglutination test)
   Ab (Rh. F. in the serum) +
   Ag (sheep’s RBCs coated with anti-erythrocyte antibodies)

Latex is more sensitive, but Rose Waaler is more specific.

Conditions in which Rh. F is +ve

- Autoimmune rheumatic diseases...
  - Rheumatoid arthritis (70 % - 80 %).
  - SLE (15-35 %)
  - Polymyositis, dermatomyositis (5-10 %).
  - Mixed connective tissue disease (50-60%).
  - Sjogren’s disease (90 %).
  - Scleroderma (30 %).

- Infections
  - T. B. - Infective endocarditis.
  - Syphilis - Kala - azar
  - HCV - HIV

- Normal population
  - Especially elderly and relatives of patients with rheumatoid arthritis.

- Miscellaneous...
  - Autoimmune hepatitis - Fibrosing alveolitis.
  - Sarcoidosis - Waldenstrom’s macroglobulinemia.
  - Chronic liver disease - Cryoglobulinemia.
ANA (antinuclear antibody)

- It is any autoantibody directed against one or more components of the nucleus.
- It is used to detect a disorder but not to rule out C.T disease as it can be + ve in other unrelated diseases. Immunofluorescence microscopy after serum has been applied to a nucleated tissue substrate e.g (rodent organs) or human cell lines is the standard method of detection giving different patterns of staining.

ANA patterns:
- Speckled pattern.
- Homogenous pattern.
- Nucleolar pattern.

Causes of + ve ANA
1- SLE 95 -100%.
2- Scleroderma 80 %.
3- Polymyositis 80 %.
4- Rheumatoid arthritis 30 %, Sjogren’s disease 70 %.
5- Mixd connective tissue disease 95%. Sjogren’s syndrome 60-70%.
6- Primary biliary cirrhosis, autoimmune hepatitis
7- Normal elderly people, infective endocarditis.

The results of ANA can be expressed by a titre. A titre of 1:40 - 1:80 is considered positive, but 1:160 is significant.
If ANA is positive, it is important to ask about specific antibodies (ANA profile)

Other specific antibodies or specific antinuclear antibodies (ANA profile) i.e tests that measure ANAs specific for certain nuclear antigens.

1- Antidouble stranded DNA (antinative DNA).
   • It is specific for S L E.
   • It determines the activity of the disease, it is positive in about 40-75% of cases (negative in mild or inactive disease). High titre indicates poor prognosis

2- Antihistone antibody.
   It is positive in drug induced SLE. (>90%)

3- Anti-Smith Antibody. (anti-sm)
   Directed against non histone nuclear protein, specific for SLE and indicates a poor prognosis

4- Anti - Scl. – 70
   It is a marker for Scleroderma (20-50%).

5- Ab to Ro and La particles in SLE and Sjogren’s syndrome.

6- Ab to centromere in CREST $'

7- Anti-RNP (ribonucleoprotein) in cases of mixed connective tissue disease and in SLE.
Other Autoantibodies

A - Antimitochondrial Abs.
- In primary biliary cirrhosis.

B - Antismooth muscle Abs.
- Autoimmune hepatitis.
- Primary biliary cirrhosis.

C - Organ specific Abs.
- Anti thyroid Ab in thyroiditis.
- Anti parietal Ab in pernicious anemia.
- Anti islet cell Ab in IDDM.
- Anti GBM in Good pasteur $.
- Anti adrenal Ab in Addison disease.
- Anti platelet Ab in Idiopathic Thrombocytopenic purpura.

Antineutrophil cytoplasmic antibodies (ANCA), see vasculitis
- C-ANCA +ve in wegener’s granulomatisos.
- P-ANCA is less specific, +ve in:
  - Microscopic polyangiitis
  - Churg-strauss disease
  - SLE and rheumatoid disease.
  - Inflammatory bowel disease

- Sero -ve arthropathy = arthropathy with Rh.F -ve (see later)!
  Sero +ve arthropathy = arthropathy with Rh.F +ve
- HLA - B27 related to sero -ve group of arthropathy. e.g. ankylosing spondylitis.

Other laboratory tests in the evaluation of the rheumatic diseases:

1. Erythrocyte sedimentation Rate (ESR)
- Acute phase reactants are proteins e.g fibrinogen are produced in the liver as a response to inflammation i.e acute phase response (APR).
- Increase in the acute phase proteins e.g fibrinogen and gammaglobulins leads to increase of ESR, this is due to change of the repellent electrostatic negative surface charge of RBCs → rouleaux formation.
- So, ESR is increased in cases of inflammatory diseases e.g connective tissue diseases, infections or malignancy.

For details see haematology
(2) **C-Reactive protein (CRP)**
- It is an acute phase reactant produced by the liver as a response to inflammation.
- It starts elevation within 4 hours of tissue injury with peak after 24-72 hours. It is rapidly decline once the cause is abolished.
- It is measured by ELISA technique as follows:
  - 0-1 mg/dl (normal)
  - 1-10 mg/dl (moderate level).
  - >10 mg/dl (high level).
- It is therefore the single most useful direct measure of the APR (acute phase response)

(3) **ASOT → See C.V.S. (Rheumatic fever)**

(4) **Serum uric acid → See Gout.**

**Why your diagnosis is one of the following diseases? (Examples)**

I. **Rheumatoid Arthritis (R.A)**
- It is mainly arthropathy.
- It affects mainly the peripheral joints (symmetrical involvement) e.g:
  - UL.
  - LL.
- It involves the small joints e.g:
  - Hands
  - Feet.
- The arthropathy is erosive (leading to deformity).
- The axial joint affection is uncommon (vertebral column – sacroiliac joint).
- The extra-articular manifestations are present in the following sites:
  - Eye
  - Skin
  - Lung
  - Kidney
  - Heart
  - Blood

II. **Ankylosing Spondylitis**
- It is mainly arthropathy.
- It is mainly axial arthropathy.
  - Vertebral column.
  - Sacroiliac joints.
- Peripheral joints affection is asymmetrical.
- This arthropathy is ankylosing (ankylosis of vertebral column)
- The extra-articular manifestations are present in the following sites:
  - Eye
  - Heart
  - Lung
  - Blood
III. S.L.E

- It is mainly an extra-articular problem.
- The manifestations present in the following sites:
  - Brain.
  - Kidney.
  - Heart.
  - Blood vessels.
  - Skin.
  - Serous membranes
  - Lung
- The arthropathy is non erosive (i.e. No residual deformity)
- The arthropathy affecting mainly the peripheral joints, it is symmetrical and mainly in the form of arthralgia.

**Musculoskeletal disorders are classified into:**

- Inflammatory joint diseases e.g. rheumatoid disease, seronegative spondarthritis, crystals associated disease, juvenile idiopathic arthritis.
- Diseases of bone e.g. osteoporosis, osteomalacia.
- Osteoarthritis.
- Systemic C.T diseases, e.g. SLE, scleroderma, mixed C.T disease, dermatomyositis, vasculitis.

**Diagnostic imaging:**

1. **Plain x rays**
   
   Diagnosis of established rheumatoid arthritis, trauma, osteopenia, osteoarthritis and spondylosis.

2. **Ultrasound**

   It is useful for periarticular structures, soft tissue swelling and tendons, it is also used to guide local injections.

3. **Magnetic resonance imaging (MRI)**

   It can show intraarticular structures and bone changes in detail and very early. Also it is of choice for spinal disorders. Gadolinium injection enhances inflamed tissue. MRI can also detect muscle diseases e.g. myositis.

4. **Computerized axial tomography**

   It is useful for spinal disorders.

5. **Bone scintigraphy (scan) by $^{99m}$Tc**

   It can detect areas of inflammation, infection or malignancy of bone.

6. **DEXA scanning (See Later)**

   It measures bone density, so it is used for screening and monitoring of osteoporosis.

7. **Positron emission tomography (PET) scanning**

   It can detect fluorodeoxyglucose uptake that indicates areas of increased glucose metabolism. It is used to locate tumours, also it can diagnose large vessel vasculitis (Takayasu's arteritis).

8. **Arthroscopy especially for knee** and shoulder, biopsy can be taken, surgery can be performed e.g. repair of meniscal tears.
Systemic lupus erythematosus (S.L.E)

- It is a systemic connective tissue disorder affecting mainly females, female: male ratio (9 : 1) with peak onset in the second and third decade.
- It leads to systemic disorders (extra – articular manifestations), but joint pain is the presenting feature in 50 % of cases. Skin rash and arthralgia are common presentations but renal and cerebral diseases are the most serious problems.

The prevalence varies from 30/100,000 in Caucasians to 200/100,000 in Afro-Caribbeans.

Aetiology (It is an autoimmune disease)

1. Defect in T. suppressor lymphocytes with exaggerated B cell activity leading to production of auto antibodies to a variety of antigens (nuclear, cytoplasmic and plasma membrane), this will lead to immune complexes with systemic manifestations
   - There is hypergammaglobulinaemia and increased level of IL1, IL2 and IL6

2. Expression of novel or hidden antigens on the cell surface during apoptosis (during apoptosis these antigens migrate to cell surfaces). This hypothesis is supported by the fact that environmental factors leading to oxidative stress with subsequent increased apoptosis e.g exposure to sunlight and artificial ultra violet light, pregnancy and infection. The increased apoptosis with expression of antigens triggers T cells that stimulate B cell to produce autoantibodies.

Some contributing factors.

1. Sunlight, artificial ultraviolet light, environmental triggers? as above.
2. Drugs (drug induced lupus).
   - C / P of drug induced SLE:
     1. Drug history, equal sex ratio. 2. Fever and skin rash.
     3. No nephritis or cerebral disease. 4. Arthralgia, serositis.
     5. Resolution on drug withdrawal.
   - Causative drugs: - Hydralazine. - Procainamide. - Phenytion.
   - Investigations:
     - ANA + ve.
     - Anti DNA is - ve , antihistone antibody is +ve
   - Treatment is by withdrawal of the causative agent, short course of steroid can be given if symptoms are severe.

3. Hormonal factor!?
   - SLE is common in child bearing period, and in those using contraceptive pills.
   - Exacerbation in pregnancy. 4. Exacerbation in the puerperium !?
   - Hormonal (estrogen) replacement therapy may lead to flare-ups.
Estrogen binds to receptors on T and B lymphocytes increasing activation and survival of those cells thus favoring prolonged immune responses.

### Pathology

1. **Joint:** synovitis with little cartilage destruction.
2. **Heart:** Libman-Sacks endocarditis (affecting mitral and aortic valves).
3. **Kidney:** thickening of glomerular B.M. due to immune complex deposition.
4. **Skin:** immune complex in demo epidermal junction.
5. **Serositis** and **vasculitis.**
6. **Lung:** vasculitis - interstitial pulmonary fibrosis.
7. **Microscopic changes of tissues in cases of SLE:**
   - **Haematoxylin bodies:** Amorphous masses of nuclear material found in C.T. lesions that become purple blue with hematoxyline, P.N.L that ingest these bodies called LE cells.
   - **Onion skin** lesions occur in splenic arteries due to disposition of collagen around them.
   - **Silver wire** appearance in lupus nephritis.

### Clinical picture

- **Male : female ratio is 1 : 9**
- **The presentation and course are highly variable.**

1. **Fever** of unknown origin.
2. **Musculoskeletal**
   - Joint involvement is mainly arthralgia with mild morning stiffness.
   - The arthropathy is bilateral and symmetrical. The small joints are usually affected mimic rheumatoid disease.
   - It is non deforming but tendosynovitis may lead to deformity (*Jaccoud's arthropathy*), it is due to tendon or ligament laxity.
   - A vascular necrosis of the hip may occur with steroid therapy.
   - Myalgia is common
3. **The skin**
   - **Butterfly rash:** fixed erythema (flat or raised) on the cheeks of the face and across the bridge of the nose, occurs in a photosensitive distribution that spares the nasolabial folds.
   - **Discoid rash:** erythematous raised patches with adherent scaling, atrophic scarring may occur. It may lead to scarring alopecia if present on the scalp.
   - **Photosensitivity:** skin rash as a result of unusual reaction to sunlight.
   - **Purpuric lesion** due to thrombocytopenia or vasculitis.
   - **Leg ulcers.**
- Vasculitic lesions
  - Nail bed and finger bulb infarcts.
  - Purpuric rash with elevated edge.
- Alopecia.
- Lichen planus like.
- Livedo reticularis.
- Raynaud’s phenomenon.
- Urticaria.
- Panniculitis (Lupus profundus)

4- The Eye
- Retinal vasculitis can cause infarcts, cytoid bodies which appear as hard exudates
- Episcleritis, conjunctivitis or optic neuritis may occur.
- Keratoconjunctivitis sicca with Sjogren’s syndrome.

5- The heart
- Pericarditis and pericardial effusion.
- Myocarditis with heart failure.
- Libman sacks endocarditis (affecting mitral or aortic valves causing regurge), It is a sterile endocarditis.
- Blood pressure is increased with renal hypertension.
- Coronary heart disease (accelerated atherosclerosis).

6- The Kidney
Lupus nephritis (WHO classification)
- Type I Minimal pathology (Normal glomeruli)
- Type II Mesangial widening with or without hypercellularity.
- Type III Focal proliferative G.N.
- Type IV Diffuse proliferative G.N.
- Type V Membranous G.N.
- Type VI Advancing sclerosing G.N.

7- GIT Mesenteric vasculitis with acute abdomen. Liver involvement is unusual, pancreatitis is uncommon. Nausea, vomiting and diarrhea can occur with an SLE flare.

8- The Lung
- Pleurisy and pleural effusion
- Interstitial pulmonary fibrosis.
- Shrinking lung syndrome with elevation of the diaphragm due to recurrent pulmonary infarction.
- Pulmonary hypertension with antiphospholipid syndrome.
- Adult respiratory distress syndrome.

9- Neuro psychiatric manifestations
- Psychosis, depression, cognitive dysfunction (difficulties with memory and reasoning).
- Lymphocytic meningitis, transverse myelitis.
- Chorea.
- Cerebral vasculitis leading to cerebrovascular stroke.
- Polyneuropathy.
- Lupus headache.
- Seizures

Psychosis due to lupus must be differentiated from steroid induced psychosis which occurs in the first weeks of steroid therapy at doses of ≥ 40 mg of prednisone or equivalent, it resolves over several days after steroids are decrease or stopped.

10-Blood
- Autoimmune thrombocytopenia and haemolytic anaemia,
- Lymphopenia (guide to disease activity).
- Antiphospholipid $ leading to thrombo-embolism.

11- Polyserositis affecting:
- Pleura. - Pericardium. - Peritoneum.

---

**Case of SLE with**

- Hemiplegia
  - Stroke (cerebral vasculitis)
- Nephrotic, or nephritic$
  - Lupus nephritis
- Abdominal Pain
  - Vasculitis (Mesenteric occlusion)
  - Peritonitis
- Dyspnea
  - Pleural effusion
  - Pericardial effusion
  - Myocarditis
  - Interstitial pulmonary fibrosis

---

**Relation between SLE and Pregnancy**

- The patient is usually fertile
- Exacerbations during pregnancy are common especially in patients with lupus nephritis.
- Steroid therapy during pregnancy is the treatment. It is better to use prednisone or prednisolone at the lowest effective doses for the shortest time required.
- Child born to mother with SLE
  - congenital conduction defects
- Abortion occurs due to Anti- phospholipid $ or renal insufficiency
Revised criteria of diagnosis of SLE

1- Butterfly rash 50%: Fixed erythema - flat OR - raised
2- Discoid rash 20%: Erythematous raised patches + scales
3- Photosensitivity 70%: Rash on exposure to sun light
4- Oral Ulcers 40%: Painless, it may be nasopharyngeal.
5- Arthropathy 95%: Involving 2 or more peripheral joints.
6- Serositis: Pleuritis, pericarditis
7- Renal (50% have clinical nephritis) - persistent protinuria > 0.5 gm/24h (30-50%) Casts, RBCs
8- Neurologic disorders: Seizures or psychosis in the absence of offending drugs or known metabolic disorders.
9- Haematological disorders:
   a- Leukopenia < 4000/mm
   b- Thrombocytopenia < 100000/mm
10- Immunologic disorder:
    a- Anti DNA
    b- Antiphospholipid Ab
11- Abnormal titre of ANA

To diagnose patients with SLE, 4 or more criteria must be present serially or simultaneously or have occurred in the past.

LAB investigations

1- Blood
   a- Anemia of chronic disease (normocytic normochromic).
   b- Autoimmune hemolytic anaemia (positive coomb’s test).
   c- Leucopenia, lymphopenia with activity, thrombocytopenia.
2- ESR ↑ with activity of the disease.
3- Immunological tests
   a- C-reactive protein is low but ↑ with superimposed infection.
   b- Hyper gammaglobulinemia usually IgG and IgM (polyclonal).
   c- ↓ C3 & C4 as they are consumed during disease activity.
   d- ANA + ve (it is positive in almost all cases, 95%), patients with negative ANA are unlikely to have SLE.
   e- Anti DNA is the most specific. It is positive in about 60% of cases, it may reflect disease activity
   f- Rheumatoid factor is positive in 30 % of cases.
   g- Anti Ro, La antibodies (They are asked if ANA is negative, especially anti-Ro).
   Anti Ro is the causal antibody for neonatal lupus and congenital heart block.
   h- Anti-smAb (specific for SLE).
4- Kidney function tests and urine analysis for protein, RBCS and casts to detect renal involvement.
Q Symptoms and signs suggesting active SLE?
• Weight loss, fever, arthritis, seizures, hair loss, anaemia, haematuria, rashes, mouth sores and oliguria.

Q Laboratory diagnosis of disease activity?
• ↓ C₃, C₄ • +ve Anti-DNA (high titre)

Q Patient with SLE + fever?
• Disease activity (see above) • Infection (+ ve C- reactive protein)

Q Patients with SLE + leucocytosis
• Steroid therapy.
  - PNL ↑ - Eosinophils ↓ - Lymphocytes ↓
• Infection:
  Toxic granulations within WBCs, presence of staff cells and positive CRP

Sequences of investigations to diagnose SLE

AN
+ ve (95 % of cases)
To confirm
Anti – DNA

- ve (5 % of cases)
(SLE is unlikely diagnosis)

Anti Ro, La
+ ve

- ve
SLE Possibility of SLE or other conditions (see causes of positive ANA)
SLE It is mostly not a case of SLE.

Subsets of lupus !?.
A- Idiopathic
• Systemic lupus.
• Chronic discoid lupus (CDLE) is a benign variant of the disease in which skin involvement is often the only feature, systemic manifestations may occur with time (5%) ANA is positive in 30%.
• Subacute cutaneous lupus, +ve ANA, +ve anti Ro, anti La, organ involvement is rare.
• Late onset after 50 years age.
• Neonatal Lupus with positive Ab to Ro. and La.
B- Drug induced (see before)
C- Overlop syndrome
Treatment
All patients require education and general prophylactic measures to prevent disease flares:

- Sunscreens and protective clothing are effective in avoiding photosensitivity reactions.
- The use of estrogen containing oral contraceptives is controversial in SLE, but many centers avoid these medications because they may increase the disease activity.
- Avoidance of vasoconstrictive drugs are helpful in treating Raynaud's phenomenon, also patients with SLE may benefit from vasodilator therapy.
- Low dose aspirin for patients with positive antiphospholipid antibodies to prevents thrombotic events.
- Psychological support is essential because SLE may cause depression and anxiety.
- Routine immunizations for influenza and pneumococci are recommended.

1- Arthralgia, mild arthritis, fever and serositis respond to NSAIDs
2- Skin manifestations respond to hydroxychloroquine 400mg/d + topical steroid (hydroxychloroquine is also indicated in arthralgia resistant to NSAIDs)
3- Corticosteroid therapy is the main subject of treatment.

Steroids are used for almost all manifestations of lupus in doses ranging from extremely small alternate day doses to huge pulsed intravenous doses. Prolonged steroid therapy usually lead to DM, accelerated atherosclerosis, osteoporosis, glaucoma, cataract, avascular necrosis and increased risk of infections. To avoid such toxicities, different cytotoxic drugs can be used to provide steroid sparing effect (see below).

Role of steroids
To control the inflammatory reaction → ↓ end organ damage.

Method
Give full dose of steroid 60-80 mg predinsolone / day till activity of the disease disappears i.e.
- Resolution of symptoms and signs.
- - ve Anti-DNA
- Normal C₃ and C₄

Then gradual withdrawal followed by low dose steroid as maintenance.
10-15 mg / day to:
- prevent relapse.
- prevent end organ damage.

Pulse steroid therapy can be used in severe cases (see later).
4- **Immunosuppressive drugs**
Used in severe disease activity e.g severe lupus nephritis or cerebral disease.

- **Azathioprine** (Immuran): - 2mg/kg/d orally. It is used when steroid alone is not fully effective. It is also a steroid sparing drug. i.e it allows a reduction of steroid dose. The side effects are leucopenia, anaemia, infections.

- **Cyclophosphamide** (Endoxan):
  1-3 mg/kg/d orally, also it can given as pulse therapy 0.5-1gm/m Iv. It is important to monitor the side effects e.g Infections, bone marrow depression and infertility. This drug is extremely toxic so, it reserved for the most severe disease manifestations.

- **Cyclosporine** (Sandimmun) and mycophenolate (myfortic) can also be used with severe disease activity and to avoid the side effects of other immunosuppressive drugs.

<table>
<thead>
<tr>
<th>Prolonged use of azathioprine may increase the risk of haematological malignancy</th>
</tr>
</thead>
</table>

5- Plasmapharesis can be used in cases with severe exacerbations refractory to steroid.

6- Immunoglobulin therapy is effective for thrombocytopenia of SLE

**Q Pulse steroid therapy?**

**Dose:**

500 - 1000 mg methyl prednisolone/ day I.V. 3 - 5 days. To be followed by full dose steroid until improvement (laboratory and clinical).

Then low dose steroid as maintenance 10 - 15 mg./ day

<table>
<thead>
<tr>
<th>Pulse I.V cyclophosphamide in combination with pulse steroid is more effective.</th>
</tr>
</thead>
</table>

Pulse steroid therapy can be used in SLE with severe activity. e.g. Vasculitis, crescentic GN, severe cerebral or haematological disease.

**Other indications of pulse steroid therapy:**

1- Crescentic glomerulonephritis (rapidly progressive G.N.)

2- Multiple sclerosis

3- Optic neuritis.
**Precautions**

- Prophylaxis for peptic ulceration by proton pump inhibitors.
- Control blood pressure.
- Control blood sugar.
- Isolation to guard against infection.

**Course and prognosis of SLE**

- The course is characterized by remission and exacerbation.
- Chronic course occasionally seen.
- 5 years survival rate is about 90 %.
- Severe renal or neurological disease have the worst prognosis.

**Polyomyositis (PM) and Dermatomyositis (DM)**

These are connective tissue disorders with inflammatory reaction in skeletal muscles and / OR skin of autoimmune pathogenesis !?

**Pathology** (Lymphocystic Infiltration of skeletal muscles)

**Classification**

1- Primary idiopathic polymyositis.
2- Primary idiopathic dermatomyositis (polymyositis + skin lesion).
3- Dermatomyositis or polymyositis associated with malignancy.
4- Childhood dermatomyositis.
5- Polymyositis or dermatomyositis associated with other connective tissue disorders e.g. (mixed connective tissue disease).

**Clinical picture** . . . It is an inflammatory myopathy, occurs at age of 30-60 years, female to male ratio 3 : 1 with insidious onset.

1- **Muscle** There is bilateral proximal weakness (shoulder and pelvic girdle muscles). The muscles may be wasted but are not usually tender. Face and distal limb muscles are not usually affected. Tendon jerks are preserved.

2- **Skin** **Heliotope rash** → It is a violaceous discoloration of the upper eyelids, forehead and nasolabial folds.

**Gottron’s sign** → erythematous eruption over the extensor surfaces of P.I.P joints and M.P joints.

3- **Joint** Arthralgia.

4- **Heart** Myocarditis causing heart failure, arrhythmias.
5- **Malignancy** this occurs particularly in males with dermatomyositis with age of 50 years or more so, you must to search for malignancy:
- Lung  
- Prostate, ovary  
- Colon  
- Cancer breast

6- **Raynaud's phenomenon**

7- **Lung**: Interstitial pulmonary disease.

8- **GIT**: Dysphagia due to esophageal dysmotility (myositis of striated muscle in the upper one third of esophagus

| Violaceous discoloration similar to heliotrope rash may occur on the upper back, chest and shoulders (Shawl distribution). |

**Investigations**

- Electromyography ➔ showing myopathic changes.
- Muscle biopsy from quadriceps or deltoide ➔ features of fibre necrosis, regeneration and inflammatory cell infiltrate.

| MRI is a useful means of identifying areas of abnormal muscle that are suitable to biopsy as the myositis may be patchy. The ideal muscle to sample for biopsy is one that is involved but not atrophic |

- Creatine kinase (CK) is usually raised and is a guide to disease activity, however a normal CK does not exclude the diagnosis.
- ANA positive in 50-80 of cases, rheumatoid factor positive in 50% of cases.
- Myositis specific antibody e.g. Anti-Jo-1 (antibody to histidyl tRNA synthetase) 30 %.
- ESR is high during disease activity in about 50%.

**Antisynthetase syndrome**:

About 20-30% of patients with PM or DM have antibodies to tRNA synthetase enzymes, these patients are more liable to interstitial pulmonary fibrosis, arthritis, Raynaud's phenomenon and fissuring of skin over the pulp of the fingers (mechanic's hand).

**Treatment**

1- Search for neoplasm any where.

2- Steroids ➔ 60 mg / day Prednisolone till improvement i.e. S and S ↓, CK ↓ Then ➔ maintenance 10-15 mg / day.

3- Immunosuppressive drugs can be used with small dose steroid e.g. azathioprine, or methotrexate. If these drugs are ineffective we can use cyclosporin, cyclophosphamide or tacrolimus

| Pulse steroid therapy may be used in cases with severe weakness or with respiratory or pharyngeal weakness |
This term refers to an inflammation and necrosis of the vessel wall often with associated organ involvement. Vasculitides include arteritis or venulitis or both. Some vasculopathies involve only skin and surface areas, whereas others involve deep tissues with systemic manifestations. The tissue and organ damage is due to ischaemia (vascular occlusion).

**Classification of systemic vasculitis**

1. **Large vessels** (Aorta and its major branches).
   - Giant cell arteritis.
   - Takayasu's disease.
2. **Medium sized vessels** (medium and small sized arteries and arterioles).
   - Polyarteritis nodosa
   - Kawasaki disease.
3. **Small vessels** (small arteries, arterioles, venules and capillaries).
   - Wegener's granuloma.
   - Churg strauss vasculitis.
   - Hypersensitivity vasculitis and its types e.g. Henoch-Schonlein purpura.
   - Cryoglobulinemia.

**Other conditions associated with vasculitis i.e secondary vasculitis:**
(Inflectual) e.g. infective endocarditis, (non infective) e.g. vasculitis associated with rheumatoid disease, SLE, Scleroderma, polymyositis and serum sickness. Also vasculitis may be associated with lymphoma, leukemia or myeloproliferative diseases. Behcet's disease and inflammatory bowel disease are also associated with vasculitis.

**Pathology**

Deposition of Ag - Ab and complement (immune complex) can be identified and associated with the blood vessel wall → vasculitis leading to.

- Vascular occlusion and ischemia
  (The main problem)
- Increased fragility with bleeding tendency
**Polyarteritis Nodosa**

**Definition**
Polyarteritis nodosa can occur at any age but usually occur in the 40s and 50s with $\varphi : \alpha$ ratio $2 : 1$, it is a necrotizing arteritis, with transmural inflammation affecting medium sized arteries.

**Etiology**
1- Circulating immune complex with low $C_3, C_4$
2- Hepatitis HBsAg +ve in 25 % (serum sickness like syndrome), also there is an association with HCV.
3- Other viruses are implicated e.g. hepatitis A, CMV, parvovirus.

**Pathology**

Fibrinoid necrosis of small and medium size blood vessels. Healing with fibrosis

(weak points) → Micro-aneurysms

This process → ischemia and bleeding tendency

**Clinical picture** *(Vascular occlusion)*

1- **Kidney** *(The most common involved organ)*
   - Affection of arcuate arteries with narrowing → multiple renal infarcts → renal hypertension and renal impairment.
   - Rapidly progressive glomerulonephritis may occur.
   - Spontaneous rupture of aneurysms can result in retroperitoneal hemorrhage or perinephric hematoma.

2- **Lung** *(involvement is rare)*
   - Pleurisy, lung infiltrates may occur.

3- **Skin lesion**
   - Palpable purpura, infarcts.
   - Livedo reticularis, urticaria. → Ulcers.
4- CVS
   • Coronary heart disease (angina pectoris or infarction).
   • Pericarditis may occur.

5- Nervous system.
   • Stroke.
   • Mononeuritis multiplex (arteritis in vasa nervorum)

6- Musculoskeletal:
   • Arthralgia, myalgia.

7- Abdomen
   • Mesenteric occlusion → acute abdomen.
   • Intestinal bleeding.
   • Pancreatitis.

LAB.
   • ESR ↑, +ve CRP
   • Hb ↓, platelets ↑
   • ANA -ve, if it is positive it is mostly lupus vasculitis !?
   • Rh.F -ve, if it is positive it is mostly RA complicated with vasculitis.
   • HB s Ag +ve 25 %
   • C₃ ↓, C₄ ↓ (Hypocomplementemia), ANCA is rarely positive.
   • Tissue biopsy from the kidney, muscle or sural nerve.
   • Eosinophilia.
   • Angiography of renal, hepatic or mesenteric arteries showing multiple micro aneurysms.

Treatment
   • The recommended initial therapy is prednisone 1-2 mg / kg / d
     and cyclophosphamide 2 mg / kg / d, gradual tapering with improvement, then maintenance therapy to maintain remission.
   • Steroid plus interferon if there is positive hepatitis B or C.

Churg - Strauss – vasculitis (Allergic angiitis)
It is a systemic necrotizing vasculitis with granulomas and often affects the lung, symptoms may be similar to those of polyarteritis nodosa plus pulmonary symptoms, also glomerulonephritis can occur.
Late onset asthma (resistant), allergic rhinitis, pulmonary infiltrates with wheezy chest and eosinophilia are the major features of this syndrome.
ANCA is positive (either c or p) in 40% of cases. The treatment is based on steroids but cyclophosphamide is sometimes used in an attempt to allow successful tapering of steroids. The prognosis is fairly good but relapsing disease is common.
**Giant Cell Arteritis (GCA)**
*(Temporal Arteritis)*

- It is a large vessel vasculitis, predominately affecting the cranial vessels especially branches of temporal & ophthalmic arteries.
- There is inflammatory infiltrate of lymphocytes, plasma cells and giant macrophages.

**Clinical picture**

It usually affects individuals with mean age around 70 years with female: male ratio 4 : 1.

- **Headache** (usually the first symptom)
  - Unilateral (temporal or occipital).
  - Temporal or occipital arteries are thick and tender.

- **Visual disturbance**
  The optic nerve is supplied by the posterior ciliary artery, vasculitis of which leads to occlusion with acute anterior ischaemic optic neuropathy, leading to loss of visual acuity and field in one eye, blindness usually occur rapidly. Fundus examination showing pale optic disc with haemorrhages, but these changes may take 24-36 hours to develop (fundi may initially appear normal). Once blindness has occurred steroid therapy of no value other than preventing blindness in the other eye.

  - **Arthralgia.**
  - **Jaw claudication** brought on by chewing or talking due to ischaemia of the masseters.
  - **Tenderness of the scalp** (combing the hair may be painful).
  - **Transient ischaemic attacks**, brain stem infarcts and hemiparesis may occur.

**Diagnosis**

- ↑ TLC, ESR ↑, + ve CRP (ESR may be normal so CRP is helpful in this situation).
- Temporal artery biopsy showing, necrosis of media with inflammatory cells e.g lymphocytes and plasma cells, negative biopsy does not exclude the diagnosis.
Old age with severe headache on one side + tender temporal or occipital arteries.

↓

Ask for ESR ....... If ↑ (GCA must be suspected)

↓

Give steroid prednisolone 60 mg/d before the result of investigations to prevent visual loss.

- So new onset of headache in old persons should raise the suspicion of giant cell arteritis.
- The elevated ESR remains a sine qua non for the diagnosis of giant cell arteritis.

**Treatment**

- Good prognosis with treatment.
- Prednisolon 60 mg / day, it produces dramatic response within 24-48 hours.
  It must be started early for fear of blindness.
- The steroid dose can be tapered with clinical and laboratory improvement, maintenance therapy may be required for at least one year.

**Wegener’s Granulomatosis**

- The peak incidence occurs in 30s and 40s.
- This form of systemic vasculitis presents with upper and lower respiratory tract lesions in association with a focal G.N.
- It may be preceded by months or years with recurrent rhinitis, epistaxis (nasal crusting), sinusitis, otitis media (serous) or history of pulmonary symptoms such as cough, haemoptysis, chest pain or dyspnea. The most common ocular abnormality is proptosis due to inflammation of the retro-orbital tissue, diplopia may occur due to entrapment of the extraocular muscles.
- Limited wegener’s granulomatosis, there is minimal systemic necrotising vasculitis and local granuloma predominates with chronic sinusitis, nasal and orbital destruction with proptosis or cavitating lung lesions.
Investigations
1- ESR ↑, normochromic normocytic anaemia of chronic disease + PNL ↑ + thrombocytosis.
2- Eosinophilia is a characteristic in patients with churg - strauss vasculitis and Wegner’s granulomatosis with pulmonary lesions.
3- Anti-neutrophil cytoplasmic antibodies (ANCA), two patterns of immunofluorescence are distinguished:
   a- Cytoplasmic granular staining of neutrophil (C-ANCA) +ve in 80 % of Wegner’s granuloma.
   b- Perinuclear staining (P-ANCA) in microscopic polyangiitis.

Positive ANCA occur in many other diseases including malignancy, infection, inflammatory bowel disease, rheumatoid arthritis, systemic lupus and pulmonary fibrosis so, the diagnosis of these conditions cannot be made on the ANCA test alone

Treatment
• Steroid and cyclophosphamide
• Plasmapharesis
• Mycophenolate recently can be used.

Takayasu’s Disease
• It is called pulseless disease or aortic arch.
• It is a chronic granulomatous panarteritis affecting the aorta and its branches and the carotid, ulnar, brachial and radial arteries.
• It occurs in young females. It is rare except in Japan.

C / P (female : male ratio 8 : 1), age (25 – 30 yrs)
• Fever, weight loss, anaemia, and arthralgia.
• Angina, arm claudication.
• Hypertension - Aortic incompetence.
• Absent peripheral pulses.

Investigations
1- Hb ↓ due to chronic disease, TLC ↑, ESR ↑.
2- Angiography → narrowing of the vessels (four types):
   • Type I in aortic arch.
   • Type II in descending aorta.
   • Type III mixed (I + II).
   • Type IV involves the pulmonary artery.

Treatment:
• Steroid and cyclophosphamide.
• Reconstructive vascular surgery should be avoided during periods of active inflammation.

Prognosis: Good in more than 90% of cases.
KAWASAKI DISEASE (KD)

Systemic disease affecting children under 5 years. It is also called mucocutaneous lymph node $. It predominately occurs in Japan. It may be associated with mycoplasma and HIV infection in some cases.

C / P
- Fever than bilateral conjunctival congestion, dryness and redness of lips and oral cavity, redness of the palms and soles.
- Vasculitis in the coronary arteries with coronary aneurysm or myocardial infarction. Myocarditis or pericarditis may occur.
- Cervical lymph node enlargement.

Investigations:
- ↑ TLC, ↑ ESR, ↑ CRP, thrombocytosis.
- Positive anti-endothelial cell antibodies.
- Two-dimensional echo or angiography to detect coronary aneurysms.

Treatment
- Intravenous gamma globulins 400 mg/kg/d for 4 consecutive days, followed after the acute phase by aspirin 200-300 mg/d.
- Steroids should be avoided because of worsening the coronary artery dilatation.

Polymyalgia RHEUMATICA (PMR)
- It is a clinical syndrome characterized by muscle pain with stiffness in the neck, back, shoulders, upper arms, thighs and buttocks, classically there is increased ESR.
- Polyarthralgias or true synovitis can be present.
- It is not a true vasculitis but there is a close association with giant cell arteritis.

C/P (It is a disease of elderly, the mean age of onset is 70)
- The cardinal features are muscle stiffness and pain affecting mainly the proximal muscles of the neck, upper arms and less commonly the buttocks and thighs.
- Early morning stiffness with night pain.
- Weight loss, depression, night sweats.
- On examination there may be painful restriction of active shoulder movement but passive movements are preserved, muscles may be tender.
Conditions that may mimic polymyalgia rheumatica

- Fibromyalgia.
- Inflammatory myopathy.
- Cervical spondylosis.
- Rheumatoid arthritis.
- Malignancy.

**Investigations**  High ESR, very occasionally the ESR is low (early). CRP may be elevated prior to ESR.

**Treatment**

- Dramatic response within 72 hours to steroid 15 mg prednisolone /day and then tapering after 4-8 weeks, low dose maintenance may be required for a time 5-10 mg/day. Osteoporosis prophylaxis with bisphosphonates should be considered.
- Some patients require steroid sparing drugs e.g. methotrexate or azathioprine.

**Hypersensitivity Vasculitis**

- It is the most common form of vasculitis.
- The characteristic histopathological picture is a leukocytoclastic vasculitis (leukocytoclasis refers to inflammation and fibrinoid necrosis of vessel walls and deposition of cellular debris in the surrounding tissue of the skin).
- There are variety of cutaneous lesions appear first on the lower extremities e.g. palpable purpura.
- ESR can be either normal or elevated, also complement can be normal or depressed.
- Hypersensitivity vasculitides are seen in the following conditions:
  - Henoch schonlein purpura (see haematology).
  - Serum sickness.
  - Vasculitis associated with infectious diseases, neoplasms or connective tissue diseases.
- Henoch schonlein purpura showing high levels of IgA, complement levels are usually normal, IgA deposits can be demonstrated in the vessel wall.
- Hypersensitivity Vasculitis is also seen in cases of essential cryoglobulinemia which is characterized by arthralgia, purpura, hepatosplenomegally, lymphadenopathy and G.N.
- Treatment of hypersensitivity vasculitis includes management of the associated conditions e.g. drug reactions, bacterial infections. This form of vasculitis is usually self limited but sometimes patients require NSAID, steroids or immunosuppressive agents.
Cryoglobulinaemic Vasculitis

- Cryoglobulins are circulating immunoglobulins that precipitate out in the cold.
- The clinical feature are palpable purpura, arthralgia, neuropathy and Raynaud's phenomenon.
- They are classified into three types.
  - **Type I** with monoclonal IgM, it is associated with B-cell disease e.g Waldenstrom's disease, lymphoma and multiple myeloma.
  - **Type II** (Mixed essential) with monoclonal IgM and anti-IgG antibody (RhF), it is associated with hepatitis C, SLE and B cell malignancy.
  - **Type III** with polyclonal IgM and anti IgG antibody (RhF), it is associated with RA, SLE, chronic infections.

- Type II is secondary to hepatitis C virus infection in most patients.
- Treatment of cryoglobulinaemia: steroids + cyclophosphamide, plasmapharesis with treatment of the cause e.g interferon therapy for hepatitis C.

- **ANCA positive vasculitis:**
  - Wegner's granulomatosis.
  - Churg-strauss granulomatosis.
- **Non ANCA positive small vessel vasculitis:**
  - Henoch-schonlein purpura.
- **Granulomatous vasculitis:**
  - Wegner's granulomatosis.
  - Giant cell arteritis.
- **Necrotizing vasculitis:**
  - Polyarteritis nodosa.
  - Churg-strauss vasculitis.
  - Wegner's granulomatosis.

**How can you suspect vasculitis?**

Palpable purpura, digital infarcts and livedo reticularis plus presence of constitutional symptoms e.g fever and presence of musculoskeletal or renal manifestations (see different types of vasculitis).

**DD of vasculitis.**

1. You must to differentiate different types of vasculitis.
2. You must to exclude other diseases causing vascular occlusion simulating vasculitis e.g
   - Antiphospholipid syndrome.
   - Atherosclerotic disease (cholesterol emboli).
   - Embolisation from the heart e.g infective endocarditis, left atrial myxoma.
RHEUMATOID ARTHRITIS

- Rheumatoid arthritis (RA) is the most common inflammatory arthritis and hence an important cause of potentially preventable disability.
- It is a chronic systemic disease leading to symmetrical inflammatory polyarthritis affecting mainly peripheral joints, with progressive joint damage, also it is associated with extra-articular manifestations.

Aetiology
- Unknown (triggered by T lymphocyte activation)
- Possible factors !?
  - Autoimmune (infiltration of synovial membrane with plasma cells and lymphocytes).
  - HLA association e.g. in HLA-DR4.
  - Infection, bacterial or slow virus infections have been implicated (no definite evidence).
  - Smoking also is a risk factor for RA and for positivity of rheumatoid factor in non RA subjects!?

Pathogenesis
- Production of autoantibodies or rheumatoid factors (Ig M) in the blood which react with Fc altered portion of Ig G with activation of the complement, causing immune complex in synovial membranes with release of inflammatory mediators, cytokines e.g TNF, IL1, IL6. Rheumatoid factors are positive (sero positive cases) in 80% of cases of rheumatoid disease. The triggering, antigen remain unclear, it is suggested that the glycosylation pattern of immunoglobulins may be abnormal in RA rendering them potentially antigenic
  - T lymphocyte activation and macrophages in genetically predisposed persons e.g. HLA-DR4.
  - The presence of activated T cells and macrophages and production of rheumatoid factor autoantibodies in RA suggests that immune dysregulation plays a major role in pathogenesis.

Pathology
The earliest change is swelling and congestion of the synovial membrane and the underlying connective tissue.
- **Synovial membrane** is infiltrated with lymphocytes, plasma cells and macrophages. Effusion of synovial fluid into the joint space takes place during active phases of the disease.
- The inflamed synovial membrane becomes thick oedematous and proliferating forming villi filling the joint space.
• Later an inflammatory granulation tissue is formed (pannus) spreads over and under the articular cartilage which is progressively eroded and destroyed.
• By time pannus will be organised → fibrous tissue → ankylosis of joint.

b- Capsule → Thickened with fibrosis.
c- Juxta articular bone → osteoporosis.

**Rheumatoid nodules** *(subcutaneous)*
- They are granulomatous lesions that occur in approximately 20% of patients (almost exclusively in seropositive patients).
- Present at sites of friction and over pressure points.
  - Tendon sheath.
  - Extensor of the forearm and sacrum.

It is a central zone of fibrinoid material and surrounded by a palisade of proliferating mononuclear cells.

**Clinical picture**
- ♀ > ♂ (3:1) it is usually occur at age 30-40 years, but it can occur at any age from 10-70 years.
- It affects 1% of population.

**Mode of onset**
- Acute polyarthritis + fever + leucocytosis.
- Acute monoarthritis as rheumatic fever.
- Chronic monoarthritis (Insidious painful swelling of a large joint).
- Soft tissue lesions
  - Tenosynovitis.
  - Carpal tunnel $.
- Typical onset which is gradual and slowly progressive.
  Symmetrical polyarthritis affecting small joint of the hands, feet and wrist (the commonest).
- Palindromic onset with recurrent acute episodes of joint pain and stiffness for 24-48 hours, 50% progress to other types of RA.
Clinical course: It is usually life-long with intermittent remissions and exacerbations

I. Musculoskeletal manifestations

- Painful, swollen, stiff joints. (mainly of the hands and feet)
- Effusion in large joints may occur.
- Morning stiffness (duration is an index of activity, it \( \downarrow \) towards end of the day).

The affected Joints (symmetrical arthropathy)

1- Hands \( \rightarrow \) - Proximal interphalangeal joint.
- Metacarpophalangeal joint.
  (The distal interphalangeal joints are usually spared)

Common deformities:-

- Ulnar deviation of Metcarpo-phalangeal joint due to sublaxation.
- Swan Neck deformity (flexion of the distal interphalangeal joint and hyperextension of proximal interphalangeal joint).
- Boutoniere (flexion of proximal interphalangeal joint and hyperextension of distal inter phalangeal joint).
- Trigger finger inability to extend finger at metcarpophalangeal joint (tenosynovitis with nodules of flexor tendons) causes intermittent locking of the finger in flexion.
- Z deformity of the tumb (Hyperextension of the interphalangeal joint and flexion of the metcarpo-phalangeal joint).

2- Wrists, subluxation may occur.

3- Feet
- Metatarsophalangeal and inter phalangeal arthritis.
- Achilley tendinitis.

4- Elbows

5- Cervical spine \( \rightarrow \) atlanto-axial sublaxation with cord compression producing pyramidal and sensory signs. Atlanto axial sublaxation should be suspected in any patient with R.A complaining of new onset of occipital headache

6- Knee
- Progressive flexion deformity.
- Inflammation with hypertrophy or effusion of the bursa of calf and semi membranous muscle \( \rightarrow \) Baker's cyst (tender swelling of popliteal fossa).

7- Tempromandibular joint is:
  - Painful.
  - Tender.
8- Other joints e.g. acromioclavicular, sternoclavicular, cricoarytenoied can be affected.

9- Other musculoskeletal manifestations e.g Bursitis, periarticular osteoporosis, disuse muscle wasting especially the small muscle of the hand.

II .. Extra-articular manifestations

1- Constitutional symptoms
   - Fever.
   - Weight loss.
   - Easy fatigue.

2- Skin
   - Subcutaneous rheumatoid nodules (see before).
   - Hyperhidrosis.
   - Raynaud’s phenomenon.
   - Palmar erythema.
   - Vasculitis.

3- Spleen and LNs enlargement. (it is a feature of Felty’s syndrome).

4- Eye
   - Scleritis - Iritis – Episcleritis (inflammation of the superficial sclera).
     - Kerato - Conjunctivitis - sicca (with sjogren’s syndrome)
     - Scleromalacia which is painless thining of the sclera with the affected area appearing blue (the colour of the underlying choroid).

5- Heart :
   - Asymptomatic Pericarditis.
   - Myocarditis.
   - Aortic incompetence, pericadial effusion in 30% of patients with positive rheumatoid factor.
   - Conduction defects.
   - Coronary vasculitis with coronary artery occlusion.
   - Endocarditis.

6- Respiratory
   - Circ-oartenoid arthritis \(\rightarrow\) hoarseness of voice.
   - Pleural effusion, it is common and occurs in 30% of patients especially with positive rheumatoid factor, the effusion fluid is an exudative with high LDH and low glucose level.
   - Rheumatoid pulmonary nodules do not usually cause symptoms and are detected by chest x-ray performed for other reasons. They are multiple and subpleural. Solitary nodule can mimic bronchial carcinoma, but multiple can mimic metastatic disease. Cavitation of nodules can raise the possibility of tuberculosis and cause pneumothorax.
- **Caplan’s syndrome** is the combination of rheumatoid nodules and pneumoconiosis.
- Diffuse interstitial pulmonary fibrosis.
- Pulmonary vasculitis with pulmonary hypertension.
- Bronchiolitis.

7- **Haematological features.**
- Normocytic normochromic (anaemia of chronic disease).
- Iron deficiency (blood loss) due to drug induced gastritis (NSAID).
- Hypersplenism with felty’s syndrome causing normocytic normochromic anaemia plus thrombocytopenia.
- Thrombocytosis with disease activity.

8- **Neurological features.**
- Entrapment neuropathies result from compression of peripheral nerves due to hypertrophied synovium or joint subluxation. Median nerve compression is the most common (carpal tunnel syndrome).
- Polyneuropathy and mononeuritis multiplex may occur due to vasculitic neuropathy (vasculitis of vasa nervorum).
- Cervical cord compression can result from subluxation of the cervical spine at the atlanto axial joint. It can lead to cord compression or sudden death following minor trauma or manipulation.

Atlanta axial subluxation should be suspected in any patient with RA who developed new onset of occipital headache, especially if symptoms of parathesia or electric shock are present in the arms.

9- **Renal**
- Rheumatoid arthritis itself usually doesn’t lead to G.NI? 
- Main cause of glomerulonephritis is drug induced
  - NSAIDs
  - Gold
  - Pencillamine
- Rheumatoid arthritis → amyloidosis kidney.

10- **Vasculitis.**
- A large vessel arthritis, histologically resembling P.A.N. It may lead to mesenteric, coronary, renal and cerebral artery occlusion, nail fold infarcts may also occur.
- Skin necrosis or digital gangrene (malignant rheumatoid disease).

**Tempro mandibular joint syndrom:**
(Associated with abnormality of bite)
- It occurs in anxious persons who grind their teeth at night (there is pain, clicking in one or both joints).
- It is treated by dental correction of bite.
- Low dose tricyclic antidepressant may be helpful if there is no dental abnormality.
**Rheumatic fever**
- Large joint, non-erosive.
- Usually not > 6 weeks
- Extra articular manifestations are.....
- Investigation ............

**Rheumatoid arthritis**
- Small joint, erosive.
- Chronic disease.
- Extra articular manifestations are .......
- Investigation ............

**Q Patient with rheumatoid arthritis then he developed lower limb oedema DD:**
1. Nephrotic syndrome (due to drugs or amyloidosis)
2. Intersitial pulmonary fibrosis → cor pulmonale.

**Q Patient C/O of arthropathy then developed proteinuria DD:**
1. Rheumatoid arthritis → nephrotic (drugs OR amyloidosis).
2. SLE → GN (nephrotic OR nephritic).
3. Any arthropathy → NSAID → minimal lesion GN.
4. FMF
   - Arthritis
   - Serositis
   - Amyloidosis kidney (late)

**Q Complications of rheumatoid disease**
- Septic arthritis (staph)
- Cervical cord compression
- Cerebrovascular stroke
- Amyloidosis
- Digit gangrene
- Coronary vasculitis

**Criteria of rheumatoid arthritis**
1. Morning stiffness lasting > 1 hour.
2. Arthritis of 3 or more joints areas.
3. Arthritis of hand joints and wrists (at least in one area e.g. wrist, MCP or PIP joint).
4. Symmetric arthritis i.e. simultaneous involvement of the same joint areas on both sides.
5. Rheumatoid nodules.
7. Typical radiological changes (Hand and wrist)
   - Erosions, Loss of joint space.
   - Juxta-articular osteoporosis.
   - The above criteria must be present for at least 6 weeks.
   - Our diagnosis is made with 4 or more criteria.
Grading of function in rheumatoid disease

I  Fit for all activities.  II  Moderate restriction.
III Marked restriction.  IV  Confined to chair or bedbound.

DD of rheumatoid disease
- Connective tissue diseases.
- Seronegative arthropathies.
- Gout, pseudogout and osteoarthritis.
- Viral arthritis.

Investigations

1- Blood
- Normocytic normochromic anemia (anemia of chronic disease) or hypersplenism. Iron deficiency anaemia due to chronic blood loss (NSAID).
- WBCs:  
  ↑ in acute phase.
  ↓ (suspect Felty’s syndrome)
- Platelets ↑ (phase reactants), ↓ with felty’s syndrome.

2- ESR
- ↑ In active stage.
- ↑↑↑ In severe cases.
- Normal with treatment and remission.

3- C-reactive protein parallel with ↑ ESR

Markers of active diseases (activity).
- ↑ ESR
- ↑ c-reactive protein  
  • Hb ↓
  • Thrombocytosis

4- Serology
- Rheumatoid factor (RF) positive in 80 % of cases.
- ANA positive in 20 % of cases (non specific).
- Anti-DNA (negative)
- Recently Anti CCP (cyclic citrullinated peptide antibodies) are present in up to 80% of patients with RA with 90% specificity. They can detect early disease when RF is negative. CCP can predate the disease by several years.
- Normal complement level.

5- Synovial fluid
- ↓ protein, ↓ glucose, ↓ Complement.
- Also it is cloudy with increased white cell count.

6- X-ray
- Early
  - Soft tissue swelling.
  - Periarticular osteoporosis.
  - Narrow joint space (due to destruction of cartilage)
- Late
  - Bony ankylosis + deformity.
Stages of x-ray progression in rheumatoid disease.
I. Periarticular osteoporosis
II. Loss of articular cartilage (joint space narrowing).
III. Erosions.
IV. Subluxation and ankylosis.

7- Other investigations
- Synovial biopsy.
- U/S - C.T scan - MRI for joint involvement.

Investigations and monitoring of rheumatoid arthritis
To establish diagnosis:
- Clinical criteria
- X-ray
- Serological tests
- Acute phase reactants.

To monitor disease activity and drug efficacy:
- Pain
- Morning stiffness.
- Joint tenderness
- Acute phase reactants.

To monitor disease damage:
- X-ray
- Functional assessment

To monitor side effects of drugs (drug safety):
- Urine analysis
- Blood chemistry e.g. kidney functions.
- Blood picture.

Treatment
The goals of treatment are:
- Relief of symptoms.
- Suppression of inflammation.
- Conservation and restoration of function.
- Reduction of mortality.

1- Rest in bed  ➔ It is valuable in early cases and during exacerbation.

2- Splinting  ➔ • to decrease pain and muscle spasm.
               • to prevent deformity.

3- Physiotherapy: It can be started when the phase of exacerbation disappears.
**Drug Therapy of Rheumatoid Disease**

(1) **NSAIDs**  
(for relieve of pain and stiffness), no disease modifying effect.
- e.g. - Phenylbutazone 100mg/8 hrs
- Diclofenac 50 mg/8 hrs
- Piroxicam 20 mg/8 hrs
- Fenoprufen 60mg/8hr.
- Ketoprofen 100mg/8hr.
- Indomethacin 25-50 /8 hrs.
- Aspirin 600-900 mg/4hr.

- **Side effects**
  - Antiplatelet effect → haemorrhage.
  - Nephrotoxicity, bronchospasm.
  - Hepatotoxicity.
  - GIT irritation.
  - Salt, water retention.

**Mode of action** antiprostaglandins through inhibiton of cyclooxygenase enzyme.

**COX-2 selective NSAID**
- Celecoxib (celebrex) 100-200 mg twice daily.
- Meloxicam (mobic or melocam) 7.5-15 mg/day.

(2) **Glucocorticoids**
- Low dose of prednisolone can be given 5-10 mg (average 7.5mg) daily for symptomatic relieve.
- The addition of 7.5 mg prednisolone daily to NSAID with disease modifying antirheumatic drug, may slow the rate of radiological progression over 2 years in patients with early R.A.
- Prophylaxis against osteoporosis is important in patients under long term steroid therapy.
  
  We can use hormone replacement therapy and/or calcium and vitamin D or bisphosphonate.

**Side effects of steroids:**
- Hypertension   - DM   - osteoporosis - Myopathy
- Cataract        - Weight gain       - Peptic ulcer

I.M. depot injections (40-120mg) methyl prednisolone help to control severe disease flares, but should be used infrequently.
**Intra-articular steroids**

We use long acting steroids.

**Indications**
- Used for joints that remain painful despite of general measures.
- It is the treatment of choice in:
  - Bursitis.
  - Tenosynovitis.
  - Carpal tunnell syndrome.

**Side effects**
- 1- Septic arthritis.
- 2- Arthropathy.
- 3- Rebound pain.

---

(3) **Disease Modifying Anti-Rheumatic Drugs (DMARDs)**

- The introduction of DMARDs is central to the modern management of RA.
- These drugs decrease progression of erosive changes and decrease activity of the disease. These drugs can be used either singly or in combinations.
- These drugs do not have immediate anti-inflammatory or analgesic effects but will improve symptoms and acute phase response and reduce radiographic progression as later effects so, it is better to be used in early cases.

**(A) Antimalarial (Hydroxychloroquine)**

**Mechanism:**
- \( \bigtriangledown \) PG
- \( \bigtriangledown \) phagocytic activity of PNL

**Dose:**
- 200 mg / 12 hr

**Response:**
- within 3-6 months.

**Side effects:**
- Retinopathy
- GIT disturbance

**Monitoring:**
- Fundus examination every 6 months.

**(B) Sulphasalazine**

**Mechanism:**
- Anti-inflammatory.

**Dose:**
- 1000 mg / 12 hr.

**Response:**
- within 3-6 m

**Side effects:**
- Rashes, BM depression
- Megloblastic anemia.

**Monitoring:**
- Blood picture and transaminases
(C) Penicillamine (less commonly used)
- **Does**: 250 mg / day.
- **Response**: within 3 - 6 months.
- **Side effects**:
  - Nephrotic syndrome.
  - Pancytopenia (B.M depression).
  - Skin rash.
- **Monitoring**: Urine analysis, kidney function tests and blood picture.

(D) Gold IM (less commonly used)
- It alters the function of macrophages and complement.
- **Dose**: after does of 10 mg (for idiosyncrasy)
  - Give 50 mg /week.
- **Response**: within 4-6 months, stopped if there is no response after 6 months.
- **Side effects**:
  - Skin rash, thrombocytopenia, leucopenia.
  - Nephrotic syndrome.
- **Monitoring**: Blood picture, urine analysis and kidney function tests.

(E) Oral Gold (less commonly used)
**Dose**: 3 mg/12 hr.
**Side effects**: Leucopenia, Diarrhea.
**Monitoring**: Blood picture, urine analysis.

(F) Methotrexate:
**dose**: 7.5-15 mg/week.
It can be given oral or s.c. injection, oral folic acid should be given.
**Response**: 1-3 months.
**Side effects**:
- Hepatotoxicity, Leucopenia, thrombocytopenia, anaemia.
- Alopecia, nausea, diarrhea.
**Monitoring**: blood picture, liver enzymes.

(G) Leflunomide (Avara)
It prevent pyrimidine production in proliferating, lymphocytes, it is effective as methotrexate but is less likely to suppress bone marrow.
**Dose**: 100mg/day for 3 days
Then 20 mg/day
**Side effects**:
- Alopecia, Diarrhea, Skin rash
- Leucopenia, thrombocytopenia. Hypertension.
- Disturbed liver biochemistry. e.g increased transaminases.

(H) Azathioprine
**Dose**: 1-2 mg/kg/d orally
**Side effects**: BM depression – Nausea – Infection
(1) **Cyclosporin**

**Dose:** 2-4 mg/kg/d orally.

**Side effects:** Nephrotoxicity, heptotoxicity, hypertension, gum hypertrophy.

- Methotrexate is current first choice DMARDs for RA, many Clinicians select methotrexate as a first line therapy.
- Leflunomide (Avara) can be used as alternative if methotrexate can not be tolerated due to side effects.
- Hydroxychloroquine and sulphasalazine can be used in mild cases or if there is contraindication to methotrexate or leflunomide.
- Gold, penicillamin, cyclosporine and azathioprine have less favourable toxicity/efficacy ratio.
- Combination therapy of DMARDs can be used if the use of single drug is not effective.

(4) **Biological Therapy**

Anticytokine therapy is now being used:

(a) Blockade of IL-1 and IL-6 with receptor antagonists showing rapid anti-inflammatory effects e.g Anakinra (Kineret) 100mg S.C once daily.

(b) Anti TNF monoclonal antibody.

**Biological agents are highly effective for control of disease activity and prevention of joint damage. They can be used in patients with active disease with failure of DMARDs.**

(5) **Surgical treatment**

- Tendon repair.
- Nerve decompression.
- Correction of deformity.
- Synovectomy.
- Arthrodias.
- Joint replacement.

**Medical synovectomy if pain, effusion and synovitis persist despite local steroid injections, yttrium for large joints and erbium for small joints.**

**Sequences of drug therapy of rheumatoid disease**

1- NSAID
2- Disease modifying anti-rheumatic drugs.
3- Disease modifying anti-rheumatic drugs + steroid.
4- Biological:
   - Anticytokine therapy (blockers of IL$_1$, IL$_6$ receptors).
   - Anti TNF monoclonal Ab.
5- Surgery and other mechanical aids.
Juvenile chronic or idiopathic arthritis (JCA or JIA)

- Juvenile chronic arthritis is chronic inflammatory arthritis before age 16 years for at least 6 weeks.
- It can be divided into the following types:

(1) Systemic onset arthritis (Still’s disease)
  - It affects boys and girls, adult onset Still’s disease is rare.
  - Prominent systemic complaints and extra articular involvement.
  - Fever, rash (non pruritic fleeting maculopapular rash).
  - Lymphadenopathy, hepatosplenomegally.
  - Pericarditis, pleurisy.
  - Arthritis or arthralgia and myalgia.
  - Rheumatoid factor usually is negative.
  - High ESR and CRP, neutrophilia and thrombocytosis.

(2) Polyarticular arthritis (5 joints or more)
  - Bilateral symmetrical polyarthritis specially hands, wrists, PIP and DIP.
  - Rheumatoid factor +ve in 10-20% of cases.
  - ANA is positive in 20-40% of cases.

(3) Pauciarticular arthritis.

(a) Oligoarthritis and anterior uveitis:
  - Affects up to 4 joints (four or fewer joints) especially wrists, knees, ankles.
  - -ve rheumatoid factor.
  - Uveitis, this requires regular screening by slit-lamp, blindness may occur.
  - Positive ANA in 60% of patients, which identifies those at higher risk factor for chronic uveitis.
  - Negative rheumatoid factor.

(b) Axial skeleton oligoarthritis:
  - Asymmetrical knee, ankle arthritis, followed by sacroiliac joints, uveitis can occur, 50% of patients have HLA-B27 but few have positive rheumatoid factor.

(4) Psoriatic arthritis:
  - This affects fingers and toes, also polyarthritis involving large and small joints may occur, psoriasis may be present in the child or a first degree relative.
Treatment of juvenile chronic arthritis

- Salicylates are no longer the primary drugs used in the treatment of juvenile arthritis due to the potential precipitation of Reye's syndrome.
- Other NSAIDs with low doses and paracetamol are helpful as regard pain and stiffness.
- Methotrexate, the most commonly used second line agent. Leflunomide is also effective. Sulfasalazine is also used.
- Corticosteroids are used with systemic complaints e.g. pericarditis, also in the treatment of chronic uveitis (Local or systemic).
- Intravenous infusion of gamma globulin to control severe systemic onset or polyarticular disease.
- Physical and occupational therapy.

Felty's Syndrome

- It is a variant of rheumatoid disease.
- It is a rheumatoid disease + splenomegally + leucopenia.
- C/P ↳ Picture of rheumatoid disease.
  - LN++ (they are palpable in the distribution of affected joints) and splenomegally with hypersplenism.
  - Liver enlargement (due to lymphocytic infiltration of the liver).
  - Anaemia of chronic disease usually occur or due to iron deficiency (blood loss) due to NSAIDs or rarely haemolytic anaemia (coomb's positive).

- Investigations
  - As rheumatoid disease (sero +ve) i.e +ve rheumatoid factor.
  - Blood picture showing pancytopenia (hypersplenism).
- Treatment ↳ directed to joint disease + splenectomy if needed.

Sjogren's Syndrome

Definition: It is a keratoconjunctivitis sicca with xerostomia, the disease may be primary or secondary in association with other autoimmune disorder often rheumatoid disease, SLE or lymphoproliferative diseases.

Primary Sjogren syndrome i.e. sicca syndrome is absence of rheumatoid arthritis or any other autoimmune diseases.
Secondary Sjogren syndrome i.e. there is associated another autoimmune or C.T. disease e.g. rheumatoid disease, SLE, PM, primary biliary cirrhosis or thyroditis.
Associated autoimmune disorders in cases of Sjogren’s syndrome:
- SLE
- Chronic active hepatitis
- Primary biliary cirrhosis
- Progressive systemic sclerosis
- Myasthenia gravis

- **C/P**
  - Occular dryness confirmed by schirmer tear test using a standard strip of filter paper placed under each lower eye lid. Wetting of < 5 mm in 5 minutes indicates defective tear production (A young person normally moistens 15 mm).
  - Xerostomia.
  - Salivary and parotid enlargement is seen.

- Non erosive arthritis. Raynaud’s phenomenon.
- Cryoglobulinaemia.
- Peripheral neuropathy.
- Lymphadenopathy, there is increased incidence of lymphoma.
- Renal tubular acidosis, glomerulonephritis.

- **Investigations**
  - Rheumatoid factor +ve.
  - +ve ANA in 80% of cases.
  - Antisalivary duct Ab (Sjogren’s Ab).
  - Anti Ro.
  - Antiparietal cell antibodies.
  - Rose Bengal staining of the eye shows punctate or filamentary keratitis.

- **Treatment..**
  - Xerophthalmia can be treated with artificial tears e.g (hypromellose) and lubricating ointment at night. Soft contact lenses can be useful for corneal protection.
  - Sugar free chewing gum or lozenges can stimulate saliva flow. Using a saliva substitute containing carboxy methylcellulose as mouth wash, drugs causing disease salivary secretion should be avoided (anticholinergics).
  - Vaginal dryness is treated with lubricants e.g K-Y jelly.
  - Extra glandular and musculoskeletal manifestations may respond to steroids, azathioprine can be added.
  - If there is massive lymphadenopathy, biopsy should be performed to exclude malignancy.
The spondyloarthropathies (seronegative arthropathies)

These are group of sero negative arthritis (negative rheumatoid factor) that share certain epidemiologic, clinical and pathologic features. They all show considerable overlap and similarity of articular and extra-articular clinical features.

They include

- Ankylosing spondylitis.
- Reiter's disease.
- Psoriatic arthritis.
- Post infectious reactive arthropathies.
- Enteropathic arthropathies associated with:
  - Ulcerative colitis.
  - Chron's disease.

General features

- Sacroiliitis and/or spondylitis.
- Asymmetrical peripheral arthritis.
- Familial association.
- High prevalence with HLA - B<sub>27</sub>.
- Negative rheumatoid factor.
- Uveitis.
- Aortic root fibrosis ---> aortic incompetence.
- Erythema nodosum.
- Enthesitis i.e inflammation at the enthesis (the site of insertion of ligaments or tendons into bone).

Why possession of HLA - B<sub>27</sub> predispose towards seronegative arthropathies!?

- There is a cross reactivity between HLA - B<sub>27</sub> and an antigen carried by some invading organisms e.g. yersinea, Chlamydia, klebsiella?
- The invading organism in HLA - B<sub>27</sub> initiates an autoimmune reaction or render the cells more susceptible to cytotoxic lymphocytes?

The suggested pathogenesis for the seronegative arthropathies is that they are caused by an aberrant response to infection in genetically predisposed persons (the reactive concept). In some situations a triggering organism can be identified as in reiter's disease but in others the environmental trigger remains obscure.
Ankylosing Spondylitis (AS)

It is an inflammatory arthropathy starting in the sacroiliac and spinal joints with tendency to ankylosis of the axial skeleton.

**Aetiology**
- The prevalence is about 0.2% of the general population.
- Age of onset: 15 - 40 years.
- Sex: ♂ : ♀ = 3 : 1
- HLA - B27 association (95% of patients have HLA-B27).
- High incidence of prostatic infection by klebsiella? So, there may be an association between this disease and klebsiella infection!

**Pathology**
1. Vertebral column.
   - Limited lumbar movement.
   - Chest pain aggravated by breathing results from affection of costovertebral joints.
   - Neck pain.
   - Atlanto - axial subluxation.

2. Enthesopathy
   - Inflammation at the site of ligamentous insertion.
   - e.g. Achilles tendinitis.

3. Peripheral joint
   - Asymmetrical arthritis.
   - Shoulder and hip joint are usually affected.

Sacrolilits lead to low back ache. It is tested by pushing the sacrum forward.
4- Extra-articular manifestations
- Amyloidosis kidney.
- Aortic incompetence, cardiac conduction defects, pericarditis.
- Apical lung fibrosis.
- Prolonged fever.
- Uveitis.

How can you differentiate between mechanical and inflammatory back ache e.g. AS?
1- Character of pain.
   - Inflammatory. → ↑↑ at night, it is improved by movement.
   - Mechanical ↑↑ with movement and improved with rest.
2- Laboratory findings.
   - ESR, CRP ↑↑ in inflammatory back ache.

Schober test:
It is a useful measure of forward flexion of the lumbar spine to detect spinal stiffness. The patient stands erect with heels together, a mark is made over the spine 5cm below and 10cm above the lumbosacral junction (identified by a horizontal line between the posterior superior iliac spines). The patient then bends forward maximally, and the distance between the two marks is measured. The distance increases 5cm or more in normal lumbar mobility and less than 4cm in case of decreased lumbar mobility.

DD of AS
- The inflammatory back pain of AS is usually distinguished by the following features.
  - Age of onset < 40 years - Insidious onset
  - Duration > 3 m - Improvement with exercise.
- AS must be differentiated from other causes of backache (see later).
- Diffuse idiopathic skeletal hyperostosis (DISH) must be differentiated from AS as it leads to marked calcification and ossification of paraspinous ligaments.

Investigations
1- X ray Sarco iliac joint → erosion, sclerosis. It is often the first abnormality.
2- X ray Spine (The disc is preserved, unlike in spondylitis).
   - Square shaped vertebrae.
   - Calcification of longitudinal ligament.
   - Bony bridging between vertebral bodies = syndesmophytes → bamboo spine.
3- Laboratory finding (there is no specific laboratory test).
   - Normochromic anemia.
   - ESR ↑, ↑ CRP during activity.
   - Rheumatoid factor -ve.
- HLA Testing is rarely of value because of the high frequency of HLA-B27 in the population.
- Alkaline Phosphatase ↑ with activity !?

**Treatment** (The principles are to relieve pain and spinal stiffness).
- The key of treatment is early diagnosis to start preventive exercise program before syndesmophytes have formed. Exercises aim to maintain spinal mobility, posture and chest expansion (swimming is recommended).
- NSAIDs ➔ relieve symptoms, but don't alter the course of the disease
- Local steroid ➔ for enthesopathy and planter fasciitis.
- Genetic counselling.
- Systemic steroid sometimes required for treatment of uveitis.
- Sulfasalazine and methotrexate may be of value for peripheral arthropathy.
- TNF blockers are effective
- Surgery: plaster jackets to correct kyphosis, hip arthroplasty.

**Prognosis.**

With exercise and pain relief, the prognosis is excellent and over 80% of patients are employed.

---

**Reactive Arthritis**

- It is a sterile arthritis which occurs following an infection.
- The infection is either sexually transmitted or gastrointestinal which occurs before the onset of arthritis by 1-4 weeks.
- The arthritogenic bacteria causing reactive arthritis are salmonella, yersinia, shigella, helicobacter or klebsiella pneumoniae, also Chlamydia can cause arthritis.
- Reactive arthritis may be just arthritis, but sometimes the full picture of Reiter’s disease may occur.

---

**Reiter’s Syndrome**

**Aetiology**

It is an inflammatory arthritis which is usually associated with sexually acquired infection e.g non specific urethritis in males, non specific cervicitis in females. Also it may follow an acute attack of gastrointestinal infection. A variety of organisms can be the trigger (see below) so Reiter’s syndrome may follows sexually acquired infection or gastrointestinal infection.)
**Clinical picture** (predominantly a disease of young men).
- The onset is typically acute with development of uderitis, conjunctivitis and arthritis.
- Sex $\Rightarrow \delta > \varphi$ with ratio of 15-1
- Age $\Rightarrow$ 20 - 40 years
- Asymmetrical arthritis $\Rightarrow$ big joint of L.L. (knee, ankles, and feet).
- Planter faciitis and achilles tendinitis $\Rightarrow$ painful heel syndrome.
- Sacroiliitis and spondylitis may occur
- Eye $\Rightarrow$ conjunctivitis, uveitis.
- Skin - keratoderma $\Rightarrow$ yellow brown papules with desquamating margins on the soles and plasms. Circinate balanitis (ulcers on glans penis), present in 20-50% of patients.
- Heart $\Rightarrow$ A.I. - pericarditis.
- Neurological $\Rightarrow$ meningoencephalitis and neuropathy.
- Buccal ulceration (tongue, palate, buccal mucosa and lips), they are painless.

**Investigations**
- ESR $\uparrow$, CRP $\uparrow$  
- Rheumatoid factor -ve.
- HLA B$^{27}$ is present in 80% of patients
- Anemia. (normocytic, normochromic)  
- Sterile pyuria.
- X-ray showing soft tissue swelling, narrowing of joint spaces with or without sacroiliitis.

**Treatment**
- Rest.
- NSAIDs $\Rightarrow$ for arthritis.
- Steroid (not for arthritis), it is used for:
  - Achilles tendinitis (local injection.)
  - Eye (topical)
- Systemic corticosteroids are rarely required.
- Methotrexate, azathioprine or sulphasalazin may be used.
- The non-specific urethritis or any infection should be treated with short course of antibiotics e.g tetracycline.
- Anterior uveitis is a medical emergency requiring topical, subconjunctival or systemic steroids.

- **Arthritogenic bacteria causing reactive arthritis**
- Salmonella, Yersinia and Shigella.
- Chlamydia causing urethritis.

**Spondylolisthesis:**
It is subluxation of lumbar vertebrae usually occurring in adolescence, it occur due to congenital pars interarticularis defects $\Rightarrow$ instability that permit the vertebrae to slip. It may lead to cauda equina syndrome, it may require orthopedic assessment.
Psoriatic Arthropathy

- It is an inflammatory arthritis that occurs in about 10% of patients with psoriasis.
- It shares symptoms, signs and x-ray finding of spondyloarthritis.

Clinical picture (there are five clinical subsets)

1- Asymmetric oligoarthritis:
   - There is asymmetric involvement of both large and small joints
   - There is a sausage finger or toe (dactylitis) due to interphalangeal joint synovitis, tenosynovitis and inflammation of the intervening tissues.

2- Symmetric polyarthropathy like rheumatoid disease.

3- Arthritis mutilans:
   - This is a severe destructive arthropathy of fingers and toes with periarticular osteolysis and bone shortening causing telescoping of digits i.e the encasing skin appears invaginated and telescoped.

4- Psoriatic spondylitis with sacroiliitis.

5- Psoriatic nail disease with distal interphalangeal joint involvement.

Investigations

- Rheumatoid factor is negative.
- Anaemia
- Hyperuricemia.
- Polyclonal hypergamma globulinemia.
- There is osteolysis of the metatarsal heads and central erosion of the proximal phalanges causing (pencil cup) appearance.
- Bone resorption giving opera-glass appearance. Also sacroiliitis and spondylitis may present.

Treatment

- Rest, NSAIDs, local synovitis responds to intraarticular steroid injection.
- Gold and methotrexate are tried.
- Photochemotherapy and long wave U.V light for skin lesions.
- TNF blockers can be used in resistant cases.
Arthritis associated with inflammatory bowel disease  
(Enteropathic synovitis)

- It occurs in 10-15% of patients with ulcerative colitis and Crohn's disease, 50% of patients have HLA-B27
- Acute, often migratory.
- Non erosive.
- Affects mainly knees and ankles.
- There is sacroiliitis or spondylitis.
- It is treated by NSAIDs.
- Intra articular steroids for monoarthritis
- Sulphasalazine is frequently prescribed as this may help both bowel and joint disease.

**Scleroderma**  
**SYSTEMIC SCLEROSIS**

- Systemic sclerosis is a connective tissue disease characterized by degenerative changes and fibrosis of the integument (skin) associated with vessel oblitative disease and internal organ Lesions in:
  - Heart.
  - Lung.
  - Kidney.
  - GIT.

So it is a multi system disease to be differentiated from localized scleroderma syndromes e.g. morphea that do not involve internal organ.

**Pathology and pathogenesis**

1- **Vascular lesions:**
- Endothelial damage with release of endothelin causing vasoconstriction.
- Also there is release of cytokines (IL 1,4,6,8 ), transforming growth factor (TGF), and platelets derived growth factor (PDGF) with activation of fibroblasts, this leads to damage of blood vessels and widespread obliterative arterial lesions with subsequent chronic ischaemia

2- **Fibrotic features:**
- The activated fibroblasts synthesize increased quantities of collagen types I and III and fibronectin producing fibrosis of the dermis of the skin and internal organs.
Clinical picture

- Mainly ♀ (4:1)
- 4th and 5th decades.
- Rarely visceral scleroderma occurs in absence of the skin changes.

- Skin changes:
  * Initially the skin is oedematous (non pitting edema) and then becomes tight.
    The skin tightening begins on the fingers and hands then the proximal parts of the extremities, in addition to the thorax and abdomen with restriction of movement of the fingers.
  * Later skin becomes shiny with atrophy and ulceration, areas of hyperpigmentation or hypopigmentation are common, calcinosis may occur.
  * Raynaud’s phenomenon: It is vasospasm of peripheral arteries causing color changes (pallor, cyanosis and erythema). It occurs in most patients with systemic sclerosis.

- Musculoskeletal
  * Non erosive arthritis or arthralgia.
  * Myopathy (= sclerodermatomyositis)

- GIT
  1. Dysphagia (esophageal hypomotility)
  2. Reflux, (due to loss of lower esophageal tone).
  3. Malabsorption syndrome (due to over bacterial growth).
  4. Colonic involvement with constipation, intestinal pseudo obstruction may occur.
  5. Primary biliary cirrhosis.

- Heart
  * Cardiomyopathy with heart failure.
  * Pericarditis, pericardial effusion.
  * Coronary heart disease.

- Lung
  * Interstitial pulmonary fibrosis.
  * Pulmonary hypertension.
  * Aspiration pneumonia (due to oesophageal dysfunction).

- Kidney
  * Scleroderma kidney (thickness of intima of the interlobular arteries) leading to:
    - Malignant hypertension.
    - Renal failure.
  * Scleroderma renal crisis i.e abrupt onset of accelerated hypertension, oliguria and microangiopathic hemolysis.

Diffuse skin disease, pulmonary hypertension and renal involvement are associated with poor prognosis.
Investigations

1- ANA +ve in 90% of patients.
2- Auto Ab against sclero nuclear protein called anti-topoisomerase (Anti-Scl 70) in 20-30% of patients (it is specific).
3- Rheumatoid factor +ve in 30%.
4- Microangiopathic haemolytic anemia.
5- Skin biopsy → collagen in dermis.
6- Ba swallow for impaired oesophageal motility.
7- X-ray hand showing calcification around fingers, late erosion and resorption of the tuft of the distal phalanges

Treatment (no specific satisfactory drug therapy)

- Penicillimine (antifibrotic drug) causing minimal skin softening.
- Raynaud’s may be treated by hand warmers, vasodilators e.g calcium channel blockers e.g verapamil, delliazem and nifedipine as well as nitroglycerin ointment.
- Steroids are indicated for treatment of inflammatory myositis, pericarditis or pulmonary fibrosis.
- Oesophageal symptoms can be treated by prokinetic drugs e.g domperidone.
- ACE inhibitors for treatment of hypertension and prevention of renal failure. Also they are used in renal crisis.
- Bacterial over growth due to intestinal stasis respond to broad spectrum antibiotic.
- Steroids and cyclophosphamide may be of value in treating alveolitis and pulmonary fibrosis.
- Endothelin receptor antagonist (bosentan) can be used for severe pulmonary hypertension and digital ulceration.
- Sympathectomy to prevent auto amputation.
- Other novel agents currently under study include mycophenolate and tacrolimus.
Subsets of systemic sclerosis and scleroderma syndromes

Systemic sclerosis
- Diffuse cutaneous scleroderma.
- Limited cutaneous (CREST syndrome), +ve anticentromere Ab.

Localized scleroderma
- Morphoea and linear scleroderma, limited to well demarcated lesion of the skin and subcutaneous C.T, serology like systemic sclerosis occasionally systemic features develop, Raynaud’s phenomenon is rare.

Overlap syndrome (scleroderma associated with other autoimmune disease)

Scleroderma like syndromes i.e other conditions in which indurations or brawny oedema of skin occur and considered as D.D. of scleroderma include sclerodema, scleromyxoedema, amyloidosis, acromegally and eosinophilic fasciitis.

- CREST Syndrome
  - C → Calcinosis.
  - R → Raynaud’s phenomenon.
  - E → Esophageal dysfunction.
  - S → Sclerodactyly.
  - T → Telangiectasia.

There is minimal visceral involvement, positive anticentromere antibodies.
- Systemic sclerosis may occur in association with features of other connective tissue diseases. The term overlap syndrome has been to describe such patients.

Mixed Connective Tissue disease

- This syndrome involving mixed features of :-
  - Myositis.
  - SLE.
  - Scleroderma.

C/P
- It is of gradual onset. - Renal affection is rare.

Features (according to the frequency)
1- Arthritis or arthralgia.
2- Raynaud’s phenomenon.
3- Oesophageal dysmotility.
4- Lymphadenopathy.
5- Serositis.
6- Myositis.
7- Skin rash.
8- Fever.
9- Renal disorder.

Investigations
- ANA +ve.
- Positive anti-ribonucleoprotein (RNP) antibodies.

Treatment
Good response to steroid.
# Behcet’s Disease

- It is a systemic vasculitis of unknown etiology
  - Viral.!?
  - Autoimmune.!?

### Diagnostic criteria
- Recurrent oral ulcers, at least three times in a 12 month period.
- Plus two of:
  - Uveitis or retinal vasculitis
  - Skin lesions e.g. erythema nodosum.
  - Recurrent genital ulcers.
  - Positive pathergy test

| Oligoarthritis, thrombophlebitis and neurobehcet (multiple sclerosis like) may also occur. |

## Treatment
- Oral ulcers can be treated by topical steroids.
- Colchicine is effective for erythema nodosum and arthralgia.
- Systemic steroids in combination with other immunosuppressive drugs for systemic manifestations e.g. ocular or neurological disease.

| The pathergy test or reaction is highly specific to Behcet’s disease!?, skin inflammatory reactivity to any scratches or intradermal saline injection, this leads to papule or pustule formation within 24-48 hours. |
**Crystal Induced Arthropathy**

**Gout and Hyperuricemia**

- The term gout refers to a disorder characterized by defect in purine metabolism, and manifested by:
  1. Hyperuricemia.
  2. Crystalline deposition of monosodium urate in tissues (tophi).
  4. Uric acid stones and gouty nephropathy.

\[ \text{AMP} \xrightarrow{\text{HGPRT}} \text{Adenine} \]
\[ \text{Purines} \rightarrow \text{IMP} \rightarrow \text{Hypoxanthine} \rightarrow \text{Xanthine} \rightarrow \text{Uric acid.} \]
\[ \text{AMP} \rightarrow \text{GMP} \xrightarrow{\text{HGPRT}} \text{Guanine} \]

- AMP = Adenosine monophosphate.
- IMP = Inosine monophosphate.
- GMP = Guanosine monophosphate.
- XO = Xanthine oxidase.
- HGPRT = Hypoxanthine-guanine-phosphoribosyl-transferase

**Classification of hyperuricemia**

**Primary (Genetic)**

1. **Metabolic over production**
   - Idiopathic, 10-20% of patients with primary gout.
   - Enzymatic defects. e.g: (Hypoxanthine - guanine – phosphoribosyl - transferase) which is essential for reconversion of guanine, hypoxanthine into their mother substance so this enzymatic defect \( \rightarrow \) accumulation of uric acid.

   - Glucose 6 phosphatase deficiency.

2. **Renal**
   - Idiopathic under excretion (Isolated tubular defect), more than two thirds of individuals with primary gout.

**Lesh-Nyhan syndrome**

- X linked recessive.
- Uric acid ↑,
- Choreaathetosis, mental retardation and self mutilation.
**Secondary**

I- **Metabolic over production.**
- ↑ nucleic acid turnover e.g.
  - Haemolysis.
  - Myelo or lympho proliferative diseases.
- Alcohol (↓ clearance)

II- **Renal**
- Acute or chronic renal failure.
- Altered tubular handling by drugs e.g thiazides, low dose aspirin and cyclosporine → decrease renal excretion of uric acid.
- Lactic acidosis, alcohol.
- Lead nephropathy has long been associated with gout (saturnine gout).

- Glucose 6 phosphatase deficiency with glycogen storage disease may lead to hyperuricemia due to impaired uric acid excretion due to lactic acidosis and also due to over production.
- Phosphoribosyl pyrophosphate (PRPP) defect. → ↑↑ uric acid synthesis.

---

- One third of the body uric acid is derived from dietary sources and 2/3 from endogenous purine metabolism.
- One third of uric acid produced / day excreted through GIT.
- Two thirds of uric acid produced / day excreted through kidney.
- Over production of uric acid detected by excretion of > 1100 mg / day.
- Causes of hypouricemia
  1- Pregnancy. 2- Fanconi. 3- Xanthenuria.
  4- Patient under allopurinol.
- Drugs affecting serum uric acid.
  Drug ↑ uric acid
  - Thiazides. - Lasix. - Low dose aspirin
  Drug ↓ uric acid
  - Probencid
  - Large does of Asprin
  - Allopurinol → ↓ production of uric acid
  → renal excretion.
- Hyperuricemia is defined as a serum uric acid >7mg/dL in males and >6mg/dL in females

---

**Pathology**

- **Acute gouty arthritis**
  Urate crystals themselves are not irritating and urate crystals can be found in asymptomatic joints.
  - When urate crystals become phagocyted by leucocytes → θ their lysosomal enzymes, cytokines and chemotactins which can elicit an inflammatory reaction → Acute arthritis.
  - Colchicine leads to ↓ leucocytes migration and modifies their phagocytic activity.
Chronic tophaceous gout (Deposition of urate)
Deposition of urate:
- In joint → chronic erosive arthropathy.
- In kidney → gouty nephropathy.
- Tophi (see later)

Attacks of gout may result from trauma e.g. of the first metatarsophalangeal joint from walking (trauma leading to shedding of crystals from local deposits). Also dehydration, acidosis, alcohol ingestion and rapid lowering of uric acid precipitate attacks.

**Clinical picture** *(prevalence is about 1% of population)*
- It is chiefly a disorder of adult ♂, 5% in ♀.
- Gout is uncommon before 2nd decade.
- Peak of onset in ♂ (45 years) usually after 20–30 years of sustained hyperuricemia, and in post menopausal females above 60 years.

**There are 4 clinical presentations**

I. **Asymptomatic hyperuricemia** refers to elevation of serum uric acid prior to the development of arthritis.

   Probably 95% of hyperuricemic subjects never develop gout.

II. **Acute gouty arthritis**
- There is a painful arthritis.
- 90% of cases of the initial attacks are monoarticular usually in the first metatarsophalangeal joint *(podagra)*
- Other initial sites:
  - Ankles, wrist, heels, finger, knee, elbow.
- It may be precipitated by:
  - Trauma  
  - Surgery  
  - Ingestion of alcohol – Exercise  
  - Diuretics.
- Minority of patients showing acute gout with normal serum uric acid.
- Dramatic relief of pain with colchicine is suggestive.
- In severe attacks, overlying crystal cellulitis makes gout difficult to distinguish clinically from infective cellulitis.
- The typical attack is rapid onset reaching maximum severity 2-6 hours, often waking the patient in the early morning, it is self limiting over 5-14 days. Milder episodes for few days called peptite attacks.
- There is … ↑ temperature, ↑ TLC, ↑ ESR.
- Intercritical periods are asymptomatic periods between attacks.
III. **Chronic tophaceous gout (chronic arthropathy, tophi, nephropathy)**

a- **Joints.**
- Polyarthritis.
- Asymmetrical joint affection.
- Exacerbation and remission.
- Late → joint destruction.

b- **Tophi**
- Tophi are deposits of solid urate crystals that elicit a foreign body reaction of mononuclear cells with granuloma formation, this occurs after longstanding severe hyperuricemia.
- Tophi deposits occur usually in the skin, around joints and ear lobule, extensor surface of fingers, achilles tendon or in elbows. Large deposition may cause overlying skin to ulcerate and extrude urate crystals.
- Periarticular deposition lead to a halo of radio-opacity on x-ray

c - **Chronic gouty nephropathy (see below)**

IV. **Renal disease.**

a- **Uric acid nephropathy** due to precipitation of uric acid in renal tubules, especially with myelo or lympho proliferative diseases during chemotherapy (tumour lysis syndrome)(uric acid > 25 mg/dl) → Acute renal failure.

b- **Chronic gouty nephropathy (chronic urate nephropathy)**
Urate precipitation in renal interstitial tissue → chronic renal failure.

c- **Uric acid stones**
Uric acid precipitation in acidic urine → obstructive uropathy.

### Investigations

- Serum uric acid > 7 mg/dl in males
  or > 6 mg/dl in females
  (it may be normal)  
  **Normal level is**
  - 3.5 - 7 mg/dl in males
  - 2.5-6 mg/dl in females
- ESR ↑
- TLC ↑
- Aspiration of tophi → urate crystals (by polarized microscope).
- Uric acid in urine > 1100 mg / 24 hours = overexcretion.

**Normal serum uric acid does not exclude the diagnosis of gout.**

### Joint X-ray

- In early disease → Normal, but narrowing of joint space with sclerosis may develop with time.
- Gouty erosions (bony tophi) occurring as para articular punched out defects with well defined borders.
- Tophi: eccentric soft tissue swellings.
Hyperuricemia is frequently associated with obesity, hypertension D.M, hyperlipidemia (syndrome x) but still there is no relation between ↑ uric acid and hypertension, DM or atherogenesis.

### Treatment

**I. Asymptomatic hyperuricemia.**
- There is controversy.
- 20% of patients with asymptomatic hyperuricemia develop arthritis.
- So no treatment except with
  - Family history of renal stone.
  - Urinary excretion > 1100 mg / day.
  - Serum uric acid > 11 mg/dl.
- It is treated by allopurinol (See below).

**II. Acute gouty arthritis**

A. NSAIDs in large dose.
   - Indomethacine 75mg immediately, then 50 mg 6-8 hourly
   - Diclofenac 75-100 mg immediately then 50 mg 6-8 hourly
   - After improvement (24-48) hours, use low dose for one week.
   - In patients with renal impairment or with history of peptic ulcer, it is better to use colchicines or steroids.

B. Colchicine 1 mg immediately then 0.5 mg/6 hour, it can be used in patients with gastritis.
C. Short term corticosteroids can be used e.g predisolone 30mg/day with tapering within 7 days, IM methyl prednisolone can be used.

**III. Long term management**
By hypouricemic drug to keep uric acid < 7 mg %
Prolonged hypouricaemic drug treatment is indicated for:
- Recurrent attacks of acute gout.
- Tophi
- Evidence of joint damage.
- Associated renal disease.

**- Allopurinol (zyloric )**
  - 300 mg / day, lower doses (100mg/day) should be used in older patients or if renal function is impaired.
  - It inhibits xanthine oxidase enzyme.
  - Side effects - ↑ liver enzyme - Acute gouty arthritis.
  - - Diarrhea - B.M depression
  - - Allpurinol hypersensitivity syndrome (skin rash, eosinophilia, hepatic necrosis and renal failure).
- **Uricosuric drugs** can achieve equivalent reductions in serum uric acid to allopurinol, these drugs must be taken with alkalinization of urine + plenty fluids e.g probencid (0.5-1 gm/12hr) or sulfipyrazone 100mg/8hr.

- Allopurinol is not used during acute gouty arthritis because it may aggravate the attack.
- It can be initiated 1-2 weeks after an acute attack and while patient is on prophylactic chlochicine.
- The sharp reduction in tissue uric acid levels that follows initiation of treatment can partially dissolve the urate crystals and trigger acute attack, this can be minimized by using a lower starting dose (100mg/d) or by concurrent use of oral colchicine (0.5mg/12h) for the first few weeks.

IV. **Gouty kidney**
- Plenty fluids.
- Alkaline urine by sodium citrate.
- Allopurinol.

**Diet in Gout** (this can reduce serum urate by 15%)
- There is no need for severe dietary restrictions but excessive purine intake and alcohol should be avoided.
- Weight reduction, Severe caloric restriction must be avoided as $\rightarrow$↑ lactic acid $\rightarrow$↑ uric acid.
- Excessive meat intake $\rightarrow$ ↑ risk of gout!?, but vegetable protein $\rightarrow$ ↓ risk of gout.

**Pyrophosphate Arthropathy** *(chondrocalcinosis)*

**Definition**
It is a crystal deposition of calcium pyrophosphate dehydrate (CPPD) in cartilage (chondrocalcinosis). It is a common age associated phenomenon (>55) that particularly targets the knee.

**Etiology:**
It is idiopathic, it can occur with certain metabolic diseases e.g. hemochromatosis, Wilson’s disease, hyperparathyroidism and chronic renal failure patients under regular hemodialysis.
C/P

There are different clinical patterns

1-
- Mono arthritis.
- Especially in the knee. \{ Attacks of pseudogout
- \( \text{♂} = \text{♀} \), old age.

2- Pseudo-rheumatoid arthritis with polyarthritis for months.

3- Pseudo-osteoarthritis.

4- Pseudo-neuropathic with severe destruction (charcot joint like)

5- A symptomatic (common).

**Diagnosis**

- X ray \( \rightarrow \) calcification of articular cartilage.
- ESR \( \uparrow \) - \( \uparrow \) CRP
- TLC \( \uparrow \)
- Examination of joint fluid crystals by polarizing microscopy.

**Treatment**

- NSAID
- Intra articular corticosteroids if indicated.

**Pseudo-Pseudo Gout** (Hydroxy appatite arthropathy).

- \( \♀ > \♂ \) - Shoulder joint is the commonst site, but it may occur at knee, hip or elbow.
- Treatment with NSAID or intraarticular corticosteroids.

**Q. Crystals induced arthropathies**

- Gout (uric acid).
- Pseudogout (pyro-phosphate arthropathy).
- pseudo-pseudo gout (Hydroxy-appatite arthropathy).
Osteoarthritis

- Osteoarthritis (osteoarthrosis) also termed degenerative joint disease, it may be primary or secondary. Usually it is the end result of a variety of pattern of joint failure.
- It is characterized by degeneration of articular cartilage with simultaneous proliferation of new bone, cartilage and connective tissue leading to remodelling of joint contour, inflammation of synovial membrane is minor and secondary.

**Risk Factors**

1. Wear and tear.
2. Aging.
4. Obesity (loading stress on weight bearing joint e.g. knee).
5. Smoking

**Pathogenesis**

1. Matrix loss is due to release of proteases and collagenases. The interleukin 1 and TNF are the mediators of these catabolic effects, also these cytokines leading to synovial inflammation.
2. Growth factors e.g insulin like growth factor and transforming growth factor are involved in stimulating collagen repair and production of the over growth at the joint margin (osteophytes).

- Cartilage is a matrix of collagen fibres enclosing a mixture of proteoglycans and water.
- Under normal circumstances there is a dynamic balance between cartilage degradation by wear and its production by chondrocytes.
- Early, in cases of osteoarthritis the cartilage becomes fissured and ulcerated due to collagen matrix breakdown.
- Cartilage ulceration exposes underlying bone to increased stress producing microfractures and cysts. The bone attempts repair but produces abnormal sclerotic subchondral bone and over growth at joint margin called osteophytes.

**Classifications (Types)**

1. Primary (osteoarthritis):
   - Localized.
   - Generalized (3 or more joint areas)
Primary osteoarthritis may affect knee, hips and hands i.e distal and proximal interphalangeal joints.

2- Secondary osteoarthritis:-
   • Mechanical e.g. occupational, hypermobility, cruciate tears.
   • Metabolic: Haemochromatosis, Wilson’s disease.
   • Inflammatory: Rheumatoid arthritis, Gout, sero-ve arthropathy.
   • Developmental: Epiphyseal dysplasia.
   • Miscellaneous: Haemophilia, neuropathies.

C / P (patient over age 45 and often over age of 60)

Osteoarthritis affects many joints with insidious onset. Hip and knee osteoarthritis is the major cause of disability.

1- Pain (progressive i.e. months to years) which worsens with activity and is relieved by rest.
2- Morning stiffness (brief < 15 minutes).
3- Gelling phenomenon refers to the sense of renewed stiffness in diseased joint after prolonged inactivity (<1 minute)

Signs

1- Tenderness with limitation of range of movement (capsular thickening, blocking by osteophyte).
2- Crepitus on movement due to rough articular surfaces.
3- Joint enlargement due to soft tissue swelling or osteophytes.
4- Deformity e.g - (varus) \( \rightarrow \) medial angulation.
   - (valgus) \( \rightarrow \) lateral angulation
5- Joint effusion, wasting of muscles.
6- Osteoarthritis of the hands leading to:
   • **Heberden’s nodes**: Bony swelling of distal inter-phalyngeal joint.
   • **Bouchard’s nodes**: Bony swelling of proximal inter-phalyngeal joint.

Investigations

• Blood picture ESR, and CRP are normal.
• Rheumatoid factor and ANA are negative
• X ray - Joint space narrowing (loss of cartilage).
  - Marginal osteophytes.
  - Subchondral sclerosis.
• MRI Showing early cartilage changes
• Arthroscopy can reveal surface erosion and fissuring of the cartilage.
Treatment

Non pharmacologic treatment:
- Weight loss, joint rest.
- Knee cage, cervical collar or lumbar corset.
- Exercise to support muscle around joint (the best is swimming), strengthening exercises for quadriceps.
- Heat modalities.

Pharmacologic therapy:
- Topical NSAIDs are safe and relatively effective.
- Oral paracetamol 1gm TDS and when needed, it is safe and well-tolerated.
- Oral NSAIDs are more potent than paracetamol but they may lead to gastritis, peptic ulcer, nephrotoxicity.
- Oral glucosamine sulphate, may have chondroprotective effect.
- Intra articular steroids may be of temporary benefit in flar-ups (relieve pain for 2-6 weeks), frequent injections in the same joint should be avoided.
- Intraarticular hyaluronic acid derivatives may be of value.

Surgery:
- Total joint replacement
- Osteotomy. by arthroscope

<table>
<thead>
<tr>
<th>Osteoarthritis</th>
<th>Rheumatoid arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Degenerative.</td>
<td>- Inflammatory.</td>
</tr>
<tr>
<td>- Weight bearing joints.</td>
<td>- Small joints of the hands.</td>
</tr>
<tr>
<td>- Affects DI joint.</td>
<td>- DI joint is spared.</td>
</tr>
<tr>
<td>- Gelling phenomenon</td>
<td>- Morning stiffness.</td>
</tr>
<tr>
<td>- - ve extra-articular manifestations</td>
<td>- +ve extra-articular manifestations.</td>
</tr>
<tr>
<td>- - ve laboratory tests</td>
<td>- +ve Laboratory tests</td>
</tr>
</tbody>
</table>

Neuropathic joints (Charcot’s joints)
- They are joints damaged by repeated trauma as a result of the loss of the protective pain sensation. They occur with the following conditions:
  - Tables dorsalis especially in the knees and ankles.
  - In diabetes mellitus (tarsal joints).
  - Syringomyelia (shoulder).
- The joints are swollen with abnormal painless movement, they are liable to crystal deposition.
- The treatment is symptomatic, surgery may be required.
Septic Arthritis

This can accompany bacteraemia or septicemia, the most common organism is staphylococcus aureus. It is a medical emergency as it leads to severe joint destruction within short time.

**Causes**
- Staph aureus.
- Streptococci, gonococci.
- Haemophilus influenza and other Gram negative bacilli.

**Risk factors**
- Increasing age.
- Pre-existing joint disease e.g. rheumatoid disease.
- DM and immunosuppression.
- Artificial joints (prostheses).

**C / P**
1. Fever, malaise.  
2. Painful swelling usually in one large joint.  
3. Signs of inflammation (redness, hotness, tenderness ± effusion).

**Investigations**
- ↑ TLC ↑ - ↑ ESR-blood culture.
- X ray showing soft tissue swelling then articular erosions.  
- Synovial fluid examination showing ↑ PNL, positive culture.

**Treatment**
- Rest of joint, analgesics.  
- Drainage of the joint and arthroscopic joint washouts are helpful in relieving pain, initially the joint should be aspirated daily to keep the effusion at a minimum.  
- Intravenous antibiotic for 3 week e.g I.V flucloxacillin 2 gm/6hrs followed by oral treatment for 6 weeks in total.  
- The joint should be immobilized initially and then physiotherapy should be started to prevent stiffness and muscle wasting.

**Viral arthritis.**
- Viral arthritis are usually self limiting.  
- The usual presentation is with acute polyarthritis, fever or viral prodrome and rash.  
- Parvovirus is the most common.  
- Polyarthritis may also rarely occur with hepatitis B, C and HIV.  
- Diagnosis is confirmed by viral serology.
Osteomalacia

- Osteomalacia is characterized by defective bone mineralization, bone pain, muscle weakness and pathological fractures.
- There is failure to replace the turn over of Ca and P in bone matrix → bone become demineralised and the bony substance becomes replaced by soft osteoid tissue so it is mainly a qualitative bone defect.

Pathogenesis

The most common cause is vitamin D deficiency, the low levels of vitamin D causes a reduction of calcium absorption from the intestine. The low calcium absorption stimulates parathyroid hormone secretion which restores serum calcium levels towards normal by increasing bone resorption and renal tubular calcium reabsorption. The level of parathyroid hormone also promotes phosphaturia and causes phosphate depletion. It is the combination of calcium loss from bone and phosphate depletion that leads to impaired bone mineralization.

Causes of osteomalacia

- Vit. D deficiency
  - Dietary ↓ - Lack of synthesis in skin. - ↓ absorption.
  - Defective metabolism - Anticonvulsants - CRF
- Low P with normal vit. D
  - Familial hypophosphatemic rickets.
  - Renal tubular disease.
- Osteomalacia with normal Ca, P and vit. D
  - Hypophosphatasia.
  - Fibrogenesis imperfecta.
  - Aluminium bone disease.

C / P (Osteomalacia is the adult counterpart of rickets).

- Skeletal discomfort (from bone and muscle pain).
- Bone tenderness. Tetany may be manifested.
- Muscular weakness with marked proximal myopathy with waddling gait.

Investigations

- S. Ca ↓, S. P ↓ but ↑ in CRF
- Alkaline phosphatase ↑, parathyroid hormone ↑, ↓ vitamin D level.
- X ray → bone rarefaction with translucent band (pseudofraction or loosers’s zones) i.e linear areas of low density surrounded by sclerotic borders.

Treatment

- Treatment of the cause.
- Vit. D, Ca supplements.
- Diet e.g milk, cheese or yoghurt
- Alfacalcidol especially in cases of renal failure.
Osteoporosis

- It is defined as a decrease in the absolute amount of bone mass leading to enhanced bone fragility with increased risk of pathological fractures.
- Unlike osteomalacia, the defect in osteoporosis is that the bone that is present is normally mineralized but is deficient in quantity, quality and structural integrity.

Pathogenesis

- Bone mass increases rapidly up to the age of puberty and rises slightly more in the twenties and thirties and then begins to decline around age of 40 years.
- In males there is a gradual decline but females show an accelerated loss in the 10 years following the menopause.
- Osteoporosis occurs as the end result of many years mismatch between the rate of bone resorption and bone formation.

Risk factors

- ♂ , Family history, early menopause.
- ↓ Ca intake, reduced activity, smoking, alcohol, Al antacid, excessive caffeine, corticosteroids therapy and genetic factors.

Causes and types

- Type I: Post menopausal osteoporosis.
- Type II: Senile osteoporosis.
- Secondary osteoporosis:
  - Cushing's syndrome.
  - Acromegaly, D.M.
  - Chronic renal failure
  - Rheumatoid arthritis.
  - Drugs e.g corticosteroids.

C / P

- Boney aches, back pain, Pathological fractures
- Loss of height due to thoracic kyphosis and collapsed vertebrae.

The most common sites of pathological fractures are the forearm (colles fracture), spine (vertebral fracture) and femur (hip fracture).
Investigations

- Plasma chemistry is normal (normal serum ca, P and alkaline P).
- Alkaline phosphatase may be ↑ following a recent fracture.
- X ray → ↓ bone density (rarefaction or osteopenia).
- DEXA scan to measure bone density by dual-energy x ray absorption scanning (DEXA), it may show osteopenia (low bone mass), osteoporosis or severe osteoporosis.
- Investigations of the cause e.g serum creatinine, blood urea, thyroid function tests, cortisol level.

Treatment

Prevention of osteoporosis

- Exercise.
- Calcium supplements 1000-1500 mg/day, also diary products are recommended e.g Milk, cheese and Yogurt.
- Restriction of caffeine intake.
- Stop smoking and alcohol intake.
- Estrogen replacement therapy in early menopause.

Definite treatment of osteoporosis

- Bisphosphonates, they are osteoclast antagonist e.g Alendronate 10 mg/day (osteomax or fosamax) orally at morning, it can be given 70 mg one dose/week. Bisphosphonates should be used with caution in patient with renal impairment.
- Calcitonin 100 I.U every other day by S.C or IM injection. It can be given by nasal spray 200u/day.
- Calcium 1000 – 1500 mg/d orally.
- Vitamin D 400-800 IU/d orally, alfacalcidol (vit D analogue) can be used.
- Estrogen therapy.

- Oesophageal ulceration is a major side effect of Alendronate therapy so, this can be minimized if the patient takes the tablets before breakfast on an empty stomach (poorly absorbed) with a full glass of water and remains up right for 30 minutes.
- Ostrogen should be conjugated with progestron to prevent endometrial hyperplasia and carcinoma.
- Recently, Raloxifene is a selective oestrogen receptor modulator (SERM) which acts as oestrogen receptor in certain tissues and antagonists in others, i.e. activates oestrogen receptors in bone with no stimulatory effect on endometrium or breast. Raloxifene 60mg/d with calcium and vitamin D → ↑ bone mass. No risk of endometrial or breast cancer!?
Inherited Disorders of Collagen

I Osteogenesis imperfecta
It is a rare inherited disorder of collagen (autosomal dominant), characterized by brittle bone and abnormalities of the skin, tendon, teeth and sclera.

II Marfan syndrome
It is an inherited condition (autosomal dominant) characterized by:
- Span > height
- Lens dislocation
- High arched palate
- Arachnodactyly
- Sternal depression
- CVS
- Mitral valve prolapse
- Aortic incompetence
- Aortic dissecting aneurysm.

III Ehlers-Danlos syndrome
Ten different types have been recognized
Characteristic features:
- Skin laxity.
- Hypermobility of joints.
- Short stature.
- Skin bruising.

Fibromyalgia Syndrome

- Fibromyalgia (fibrositis) is a controversial diagnosis that is not universally accepted. It is a useful diagnosis of exclusion.
- It is characterized by chronic diffuse pain with characteristic tender points. It is considered as a nonarticular rheumatism.
- It affects about 2% of all patients seen in general practice and 20% of patients referred to rheumatologists!?
- All investigations are normal and the value is for exclusion.

Aetiology: The condition is poorly understood, two abnormalities have been reported: sleep abnormality and reduced threshold to pain at certain sites.

C / P

- Diffuse muscle pain, stiffness and fatigue.
- Focal tender points:
  - Occiput → bilateral at suboccipital muscles insertions.
  - Low cervical → bilateral at C 5 – 7 (interspinous ligaments).
  - Trapezius → bilateral at mid point of the upper border.
  - Supraspinatus → bilateral above the medial border of the scapular spine.
  - Second rib → bilateral at 2"nd costochondral junctions.
  - Lateral epicondyle → bilateral 2 cm distal to the epicondyles.
- Gluteal → bilateral in upper outer quadrants.
- Greater trochanter → bilateral posterior to trochanteric prominence.
- Knees → bilateral at the medial fat pad proximal to the joint.
- Other additional symptoms e.g tension headache, irritable bowel syndrome.

- Diagnosis requires at least 11/18 tender points.
- Palpation should be done with and approximate force of 4 kg.

**Treatment**

- Reassurance
- Aerobic exercise
- Analgesics or NSAIDs may be helpful
- Low doses of sedative antidepressant e.g 10-25 mg amitriptyline (tryptizole) few hours before bed time.
- Selective serotonin reuptake inhibitors e.g fluoxetine 20mg/d may be of value.

**Classification of joint disease**

**1- Non Inflammatory**

- Trauma.
- Charcot Joint.
- Osteoarthritis.
- Haemoarthrosis.

**2- Inflammatory**

- Peripheral
  - Monoarticular
  - Polyarticular
- Axial
  - Ankylosing spondylitis
  - Reiter's syndrome
  - Brucellosis
  - Rheumatic fever
  - Psoriatic arthritis
- Symmetric:
  - Rheumatoid A
  - Hepatitis B
  - Serum sickness
- Septic arthritis
- Gout
- Pseudogout
- SLE
### Differential diagnosis of neck pain

<table>
<thead>
<tr>
<th>Differential diagnosis of neck pain</th>
<th>Differential diagnosis of back ache</th>
</tr>
</thead>
<tbody>
<tr>
<td>I- Mechanical</td>
<td>1- Mechanical</td>
</tr>
<tr>
<td>- Cervical spondylosis.</td>
<td>- Disc prolapse.</td>
</tr>
<tr>
<td>- Muscle spasm.</td>
<td>- Lumber spondylosis.</td>
</tr>
<tr>
<td>II- Inflammatory</td>
<td>- Sero-ve arthropathies.</td>
</tr>
<tr>
<td>- Sero-ve arthropathies</td>
<td>- Brucellosis.</td>
</tr>
<tr>
<td>- Rheumatoid disease</td>
<td></td>
</tr>
<tr>
<td>III- Metabolic</td>
<td>2- Inflammatory</td>
</tr>
<tr>
<td>- Osteomalacia</td>
<td>- Sero-ve arthropathy.</td>
</tr>
<tr>
<td>- Osteoporosis</td>
<td>- Brucellosis.</td>
</tr>
<tr>
<td>IV- Neoplasm</td>
<td>3- Metabolic</td>
</tr>
<tr>
<td>- Metastases</td>
<td>- Osteoporosis.</td>
</tr>
<tr>
<td>- M. myeloma</td>
<td>- Osteomalacia.</td>
</tr>
<tr>
<td>V- Referred pain</td>
<td>4- Neoplasm</td>
</tr>
<tr>
<td>- Angina pectoris</td>
<td>- Metastasis.</td>
</tr>
<tr>
<td>- Pancost tumor</td>
<td>- M. myeloma.</td>
</tr>
<tr>
<td>- Aortic aneurysm</td>
<td>- Lymphoma.</td>
</tr>
<tr>
<td></td>
<td>5- Referred pain</td>
</tr>
<tr>
<td></td>
<td>- Cancer pancreas</td>
</tr>
<tr>
<td></td>
<td>- Renal colic.</td>
</tr>
<tr>
<td></td>
<td>- Retroperitoneal haematoma</td>
</tr>
<tr>
<td></td>
<td>- Diseases of cervix or prostate</td>
</tr>
</tbody>
</table>

### D.D. of arthritis in children?

1- Rheumatic arthritis.  
2- Septic arthritis.  
3- FMF  
4- Viral arthritis.  
5- Henoch-schonlein purpura  
6- Haemophilia.  
7- Still’s disease.

### D.D. of recurrent arthritis or transient arthritis?

1- Rheumatic arthritis  
2- Gout or pseudogout.  
3- FMF  
4- Sero-ve arthropathies.  
5- Rheumatoid disease.

### D.D. of monoarthritis?

1- Rheumatic arthritis  
2- T.B.  
3- Septic arthritis.  
4- Haemophilia.  
5- Gout.  
6- Pseudogout  
7- Traumatic.  
8- Monoarticular presentation of oligo or polyarthritis. e.g. rheumatoid disease or seronegative arthropathies

### D.D. of oligoarthropathy?

1- Seronegative arthropathy.  
2- Juvenile idiopathic arthritis.  
3- Infective endocarditis.
References

- Cecil Textbook (Textbook of Medicine).
- Kumar (Clinical Medicine).
- Davidson's (Principles and Practice of Medicine).
- Henry/Thompson (Clinical Surgery).
- Robbins (pathologic basis of disease).
- Cecil Essentials of Medicine.
- The National Medical Series for Independent Study (Medicine).
- Oxford Handbook of Endocrinology and Diabetes.
- Basic and Clinical Endocrinology.

Author's available books

2. Gastroenterology.
4. Rheumatology.
5. Cardiology.
7. Hematology.
8. Neurology and psychiatry.
9. Infectious diseases, tropical diseases, immunology, nutrition, genetics, geriatric, toxicology and therapeutics.
10. Respiratory diseases.
11. Clinical medicine (symptoms and examination).
   - Cardiology.
   - Chest.
   - Abdomen.
   - Neurology.
   - General.

 حقوق الطبع محفوظة للمؤلف
ممنوع النسخ أو التصوير