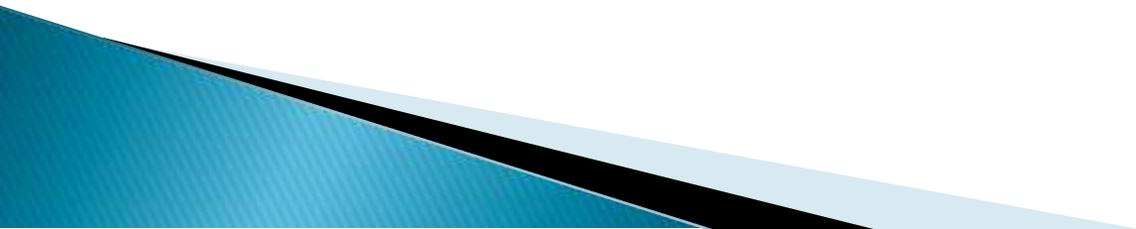


بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Arthritis and rash



ARTHRITIS AND RASH

Viral arthritis:

- ▶ HBV , HAV , HCV
Arthralgia and rash 10–14% (arthritis is rare).
- ▶ Parvovirus : B19
Rash and arthralgias/arthritis in adults and children.

Viral arthritis

- ▶ Enteroviruses (coxsackie virus):
 - maculopapular rash, sore throat , pleuritic pain, conjunctivitis.
 - short-lived (less than a week).
- ▶ Herpes viruses:
 - Varicella , EBV , CMV

HIV

- ▶ Psoriatic arthritis.
- ▶ Septic arthritis.
- ▶ Reactive arthritis.





Adult onset Still's disease

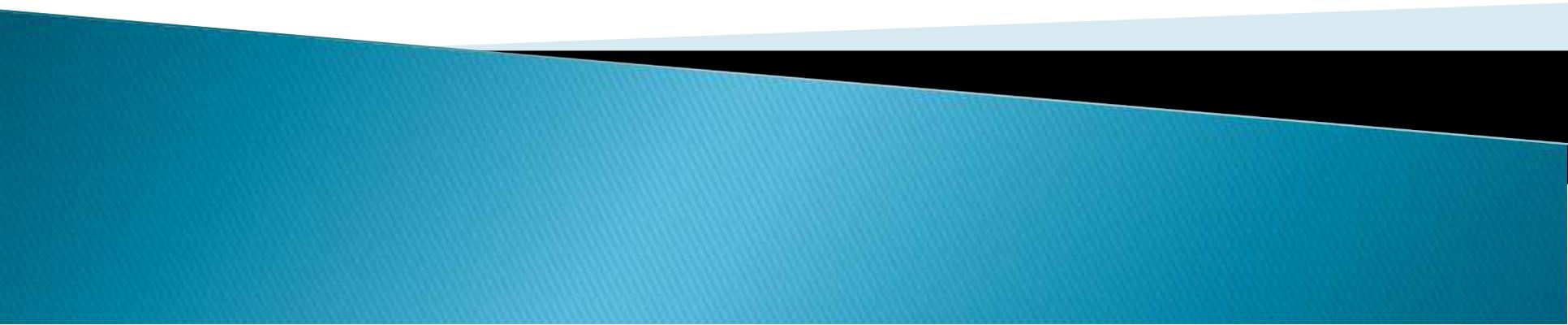
- ▶ One of the inflammatory arthritis.
- ▶ Characterised by a triad:
 - Arthritis
 - Rash Salmon pink colored non-itchy.
 - Fever recurrent
- ▶ Lymph-adenopathy.
- ▶ Hepato-splenomegaly.
- ▶ Pericarditis, myocarditis
- ▶ Leukocytosis, anemia
- ▶ Negative RF, ANA and Anti CCP.
- ▶ High serum Ferritin and high liver enzymes.

Lyme disease

- ▶ Spirochetal bacteria (*B. burgdorferi*)
- ▶ *Borrelia burgdorferi*
- ▶ More in USA northeast
- ▶ ECM (Bull's eye rash) 75%



Acute Rheumatic Fever



Delayed non suppurative
sequele of pharyngeal
infection with group A
streptococcus

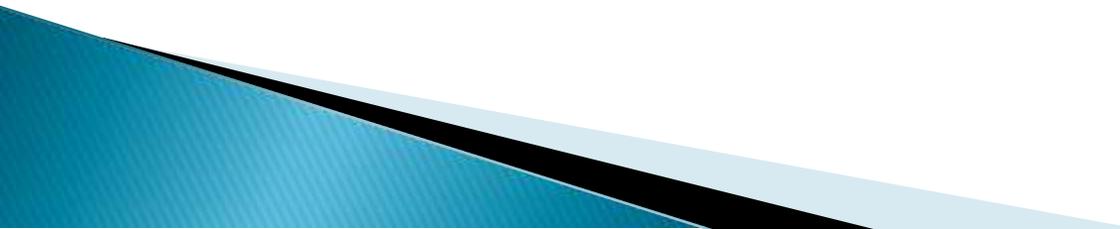


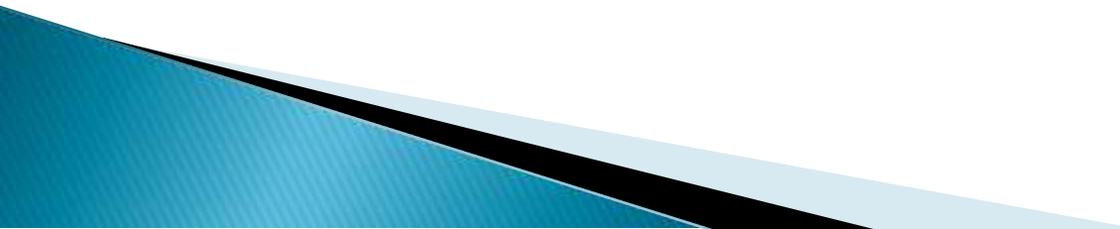
- Latent period 2-4 wks.
- Cardinal manifestations include:
 - Arthritis
 - Carditis
 - Chorea
 - S. C nodules
 - Erythema marginatum

Rheumatogenic strains(3,5,6,14,18,19,24).

Any strep. that can cause a well defined pharyngitis can cause ARF.

Pathogenesis:

- Streptococcus pharyngeal infection.
 - Genetic susceptibility.
- 

- ▶ Strept. Pharyngitis is the **only** strept. infection associated with ARF.
 - ▶ Impetigo:
glomerulonephritis, but almost never ARF.
- 

Bacterial genetic factors are important:
(5 chromosomal patterns of emm
genes)

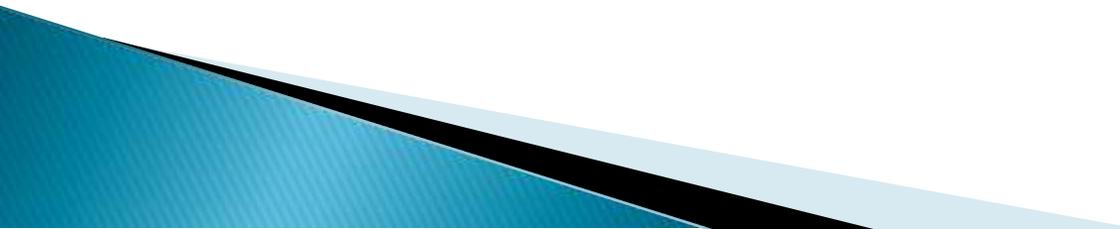
A,B,C strains	pharyngitis
D,E strains	impetigo

Host genetic susceptibility

MHC class 2

HLA DR4

DR2 (Caucasians and blacks with RHD)

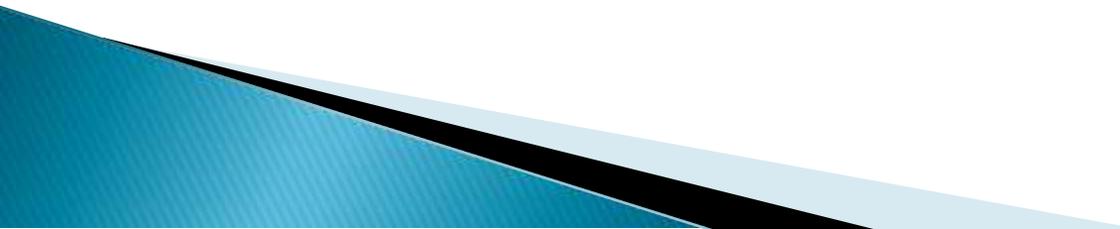


Clinical manifestations:

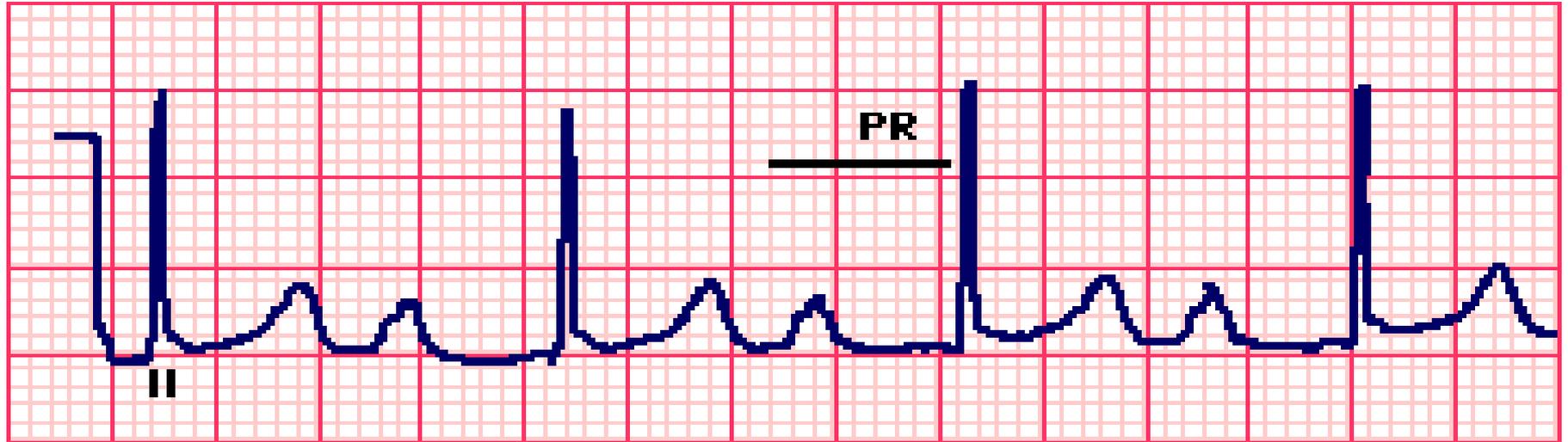
ARTHRITIS:

- Earliest manifestation of ARF
- Migratory
- Large joints(knees, elbows ,ankles,wrists).
- Pain > inflammation signs
- 6-16 joints involved
- Transient for almost 1 wk.
- More common and more severe in teenagers and young adults than in children.
- Synovial fluid :sterile, inflammatory fluid

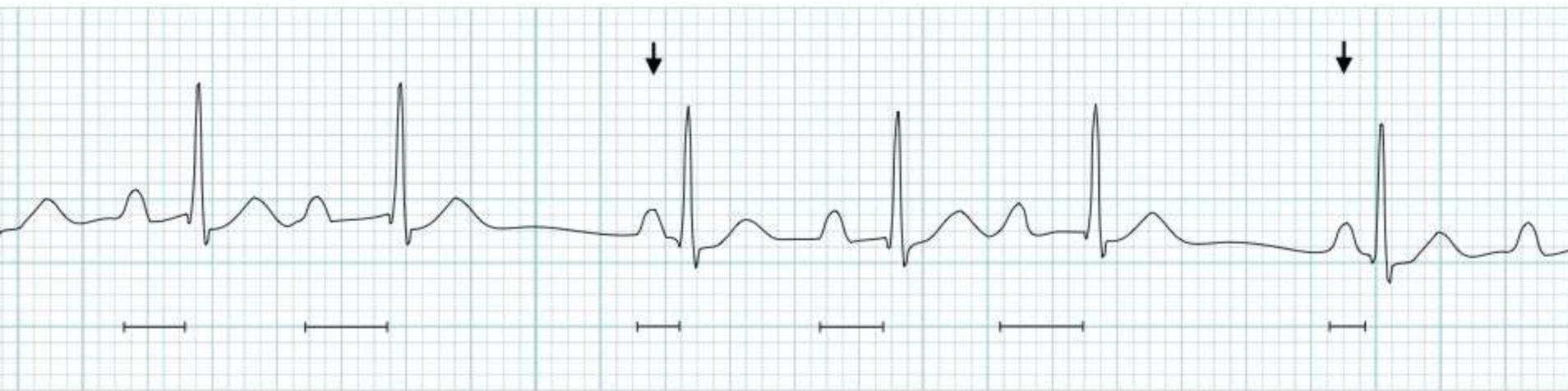
CARDITIS:

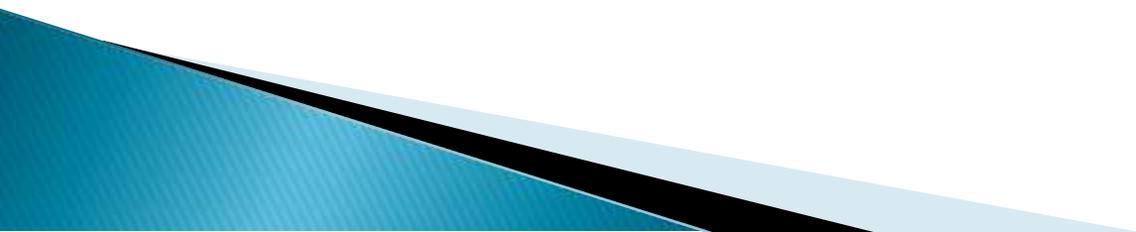
- Pancarditis can occur(pericarditis, myocarditis ,endocarditis.
 - MR IS THE MOST COMMON VALVE LESION AT PRESENTATION.
 - MS,AR,AS CAN OCCUR LATE.
 - MS is a manifestation of late scarring, and calcification of damage.
 - HEART FAILURE IS THE MOST LIFE THREATENING CLINICAL SYNDROME IN ARF
- 

1st degree A-V block

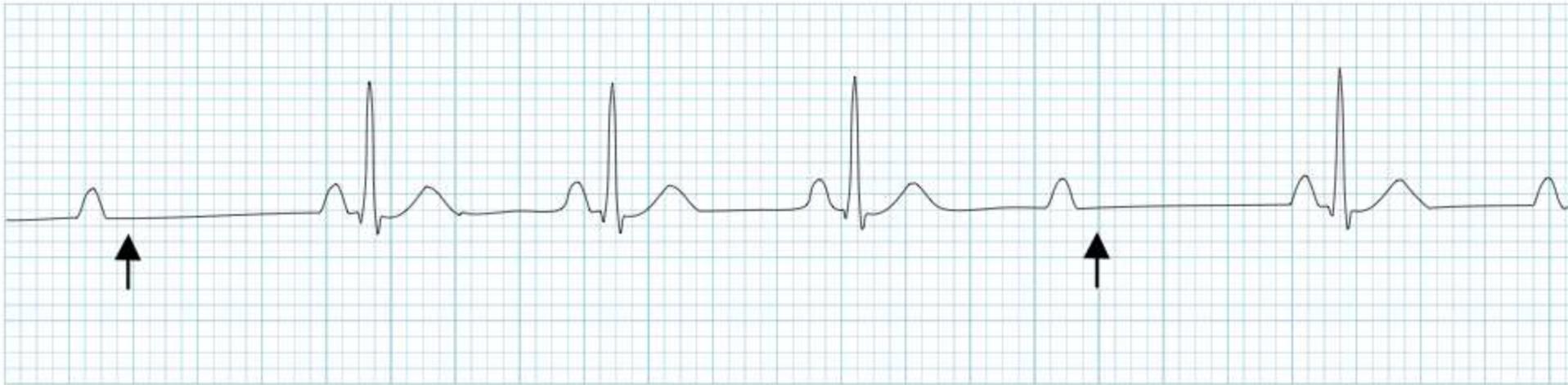


2nd degree A-V block Mobitz I (Wenckebach Phenomenon)

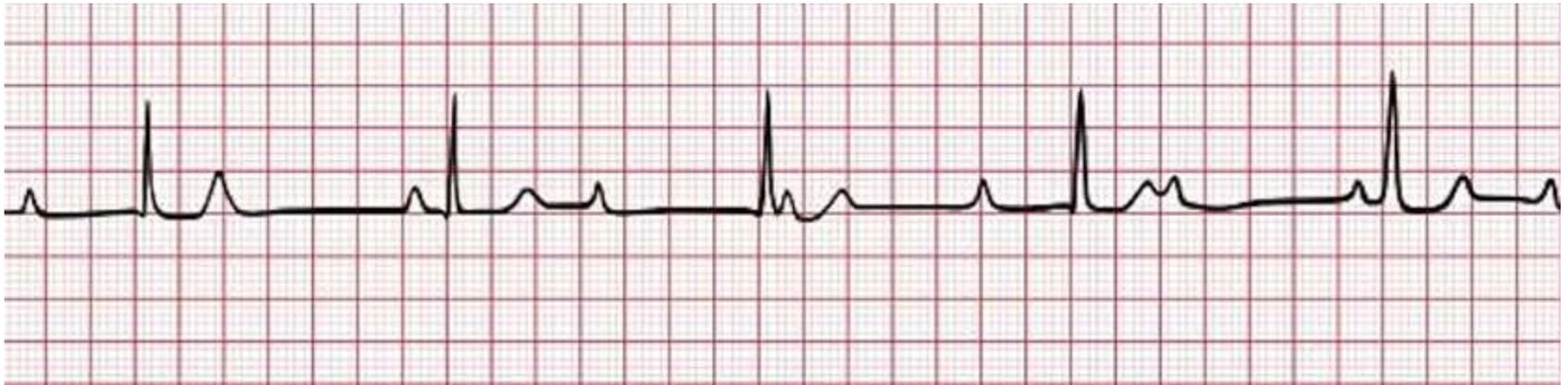


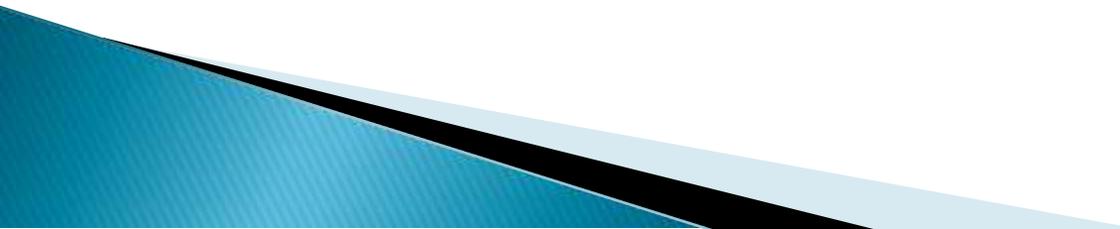


AV Block: 2nd degree, Mobitz II



Third-degree atrioventricular (AV) block

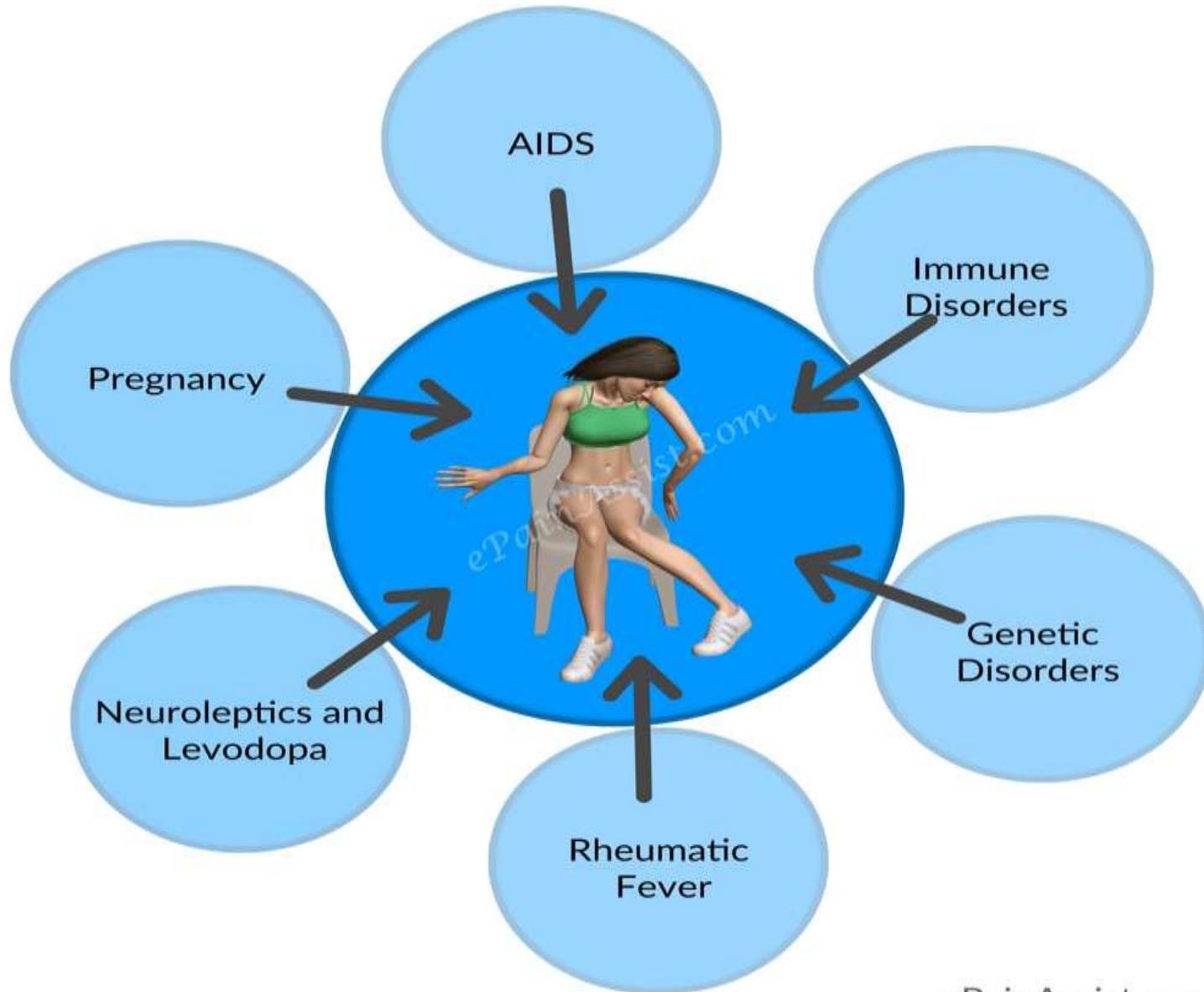


- EKG : may show all degrees of heart blocks.
 - CXR : cardiomegaly.
 - ECHO : acute carditis (most patients with ARF).
 - Anti-Myosin Scintigraphy: 80% sensitivity in detection of carditis.
- 

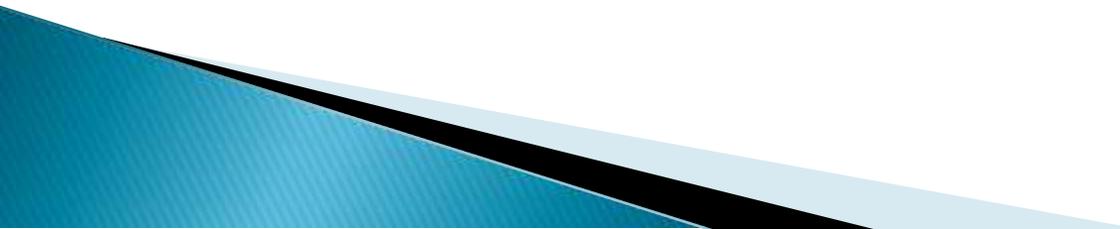
CHOREA

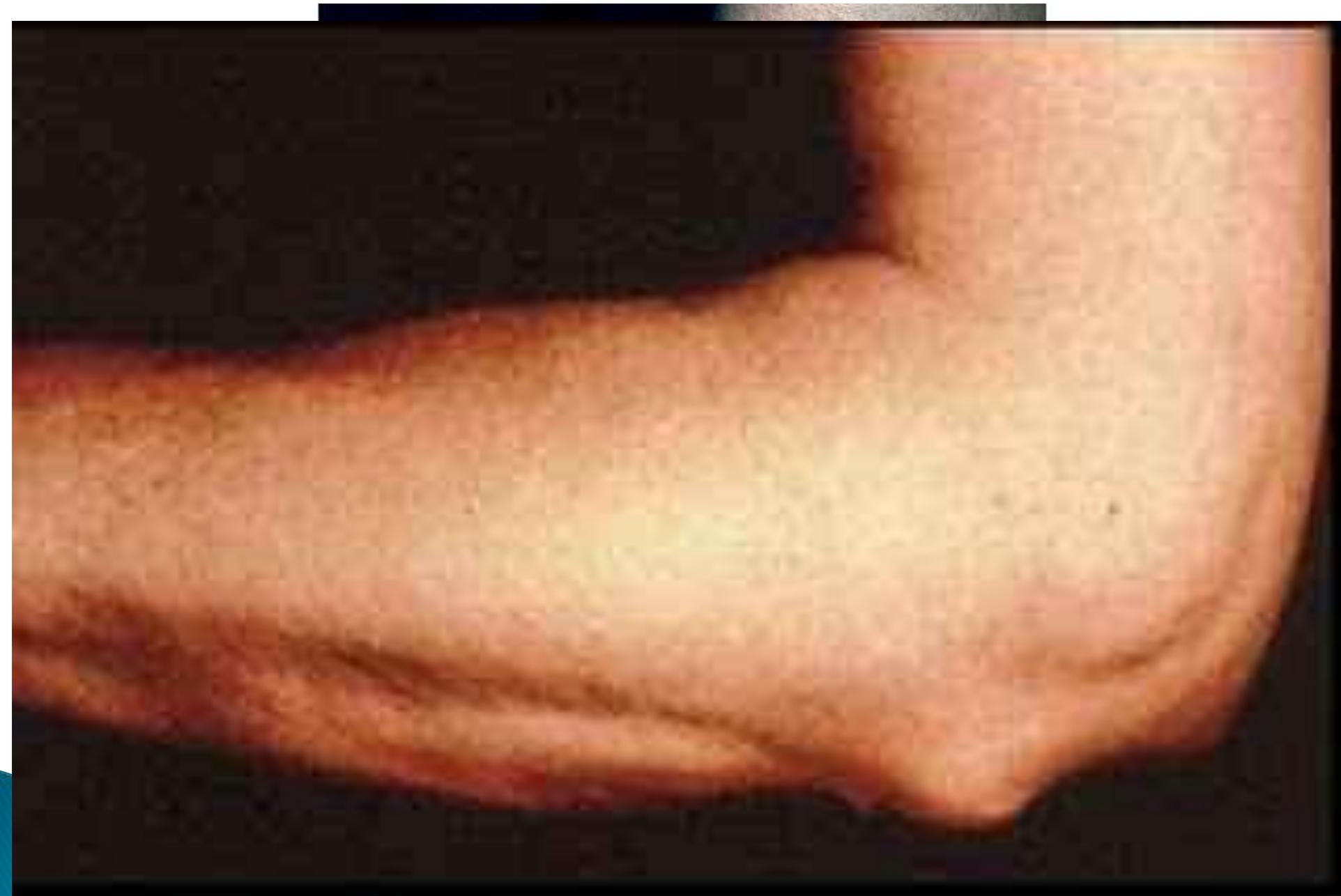
- Sydenhams chorea, chorea minor , st.vitus dance.
- Abrupt ,purposeless, non- rythmic involuntary movements with muscular weakness , and emotional disturbance

What Causes Chorea

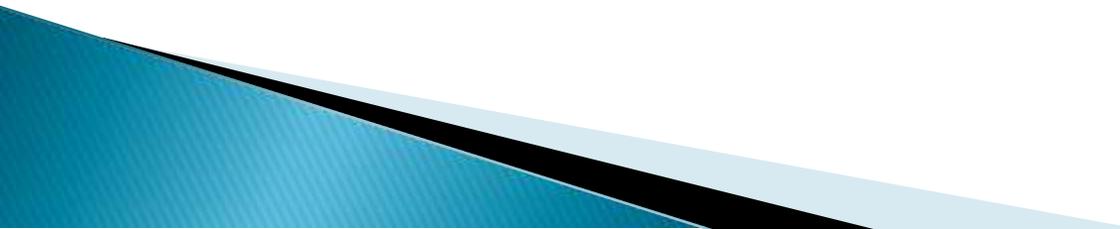


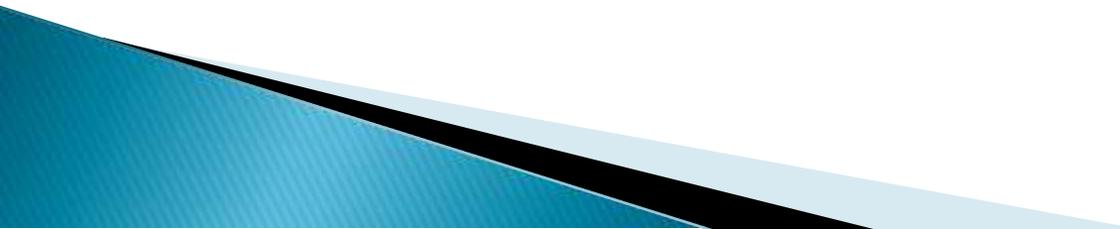
Chorea:

- More on one side .
 - Occasionally unilateral (hemi-chorea).
 - Ceases during sleep .
- 



SUBCUT. NODULES

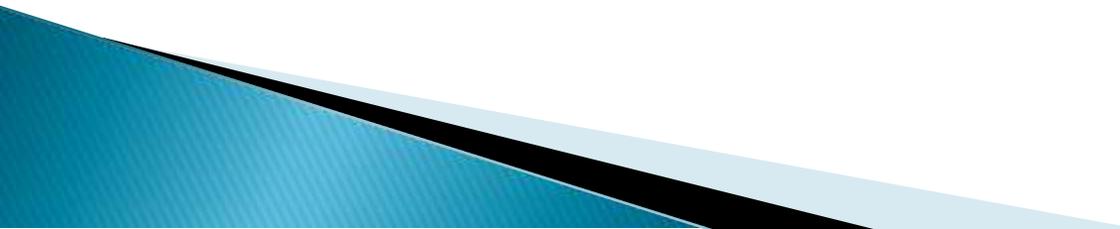
- usually near tendons or over bony surfaces.
 - size :variable few mm.-----2 cm .
 - overlying skin is not inflamed.
 - firm, painless.
 - 3-4 nodules when multiple -symmetrical .
 - last for few weeks, rarely more than one month.
- 

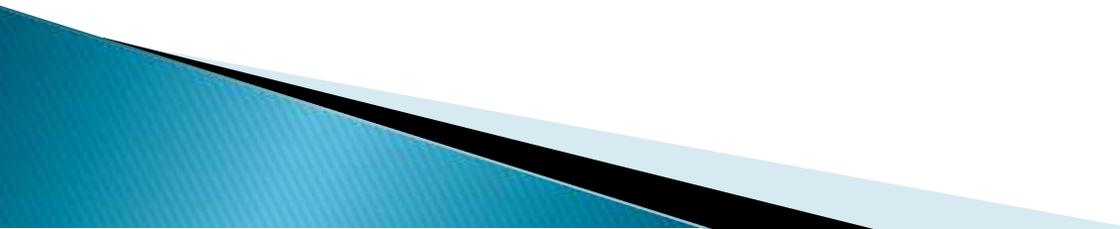
- ▶ Smaller and more short-lived than Rh.A nodules .
 - ▶ ARF nodules are often over the olecranon. Rh.A nodules are often 3–4 cm distally .
 - ▶ Appear after the 1st wk. of the illness .
 - ▶ **Occurs almost always in patients with carditis.**
- 





ERYTHEMA MARGINATUM (erythema annulare)

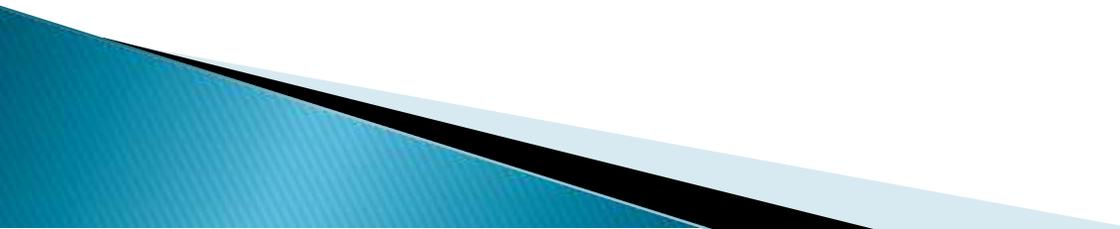
- Occurs early in the disease
 - Evanescent ,non- pruritic ,rash .
 - Pink ,or faintly red .
 - Usually affect trunk ,s.t proximal parts of the limbs but not the face .
 - Spreads centrifugally while center returns to normal .
- 

- outer edge is sharp ,inner edge is diffuse.
 - rapidly disappears in few hours.
 - may be provoked by a hot bath.
 - may persist or recur when all the other manifestations have disappeared.
- 

DIAGNOSIS :

Revised Jones Criteria

Major criteria :

- Carditis
 - Polyarthritits
 - Chorea
 - E. marginatum
 - S.C nodules
- 

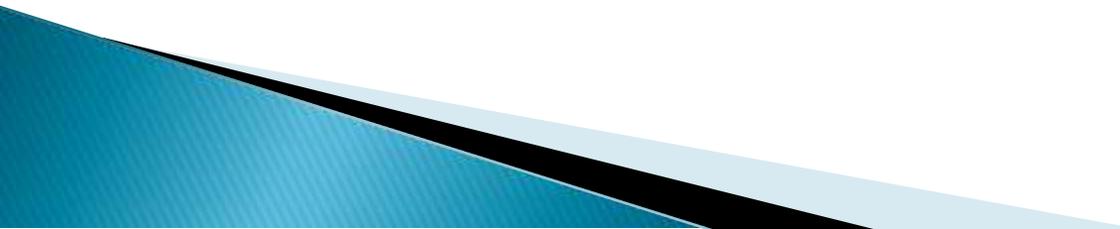
Minor criteria :

- Fever
- Arthralgia
- Previous Rheumatic fever or RHD .

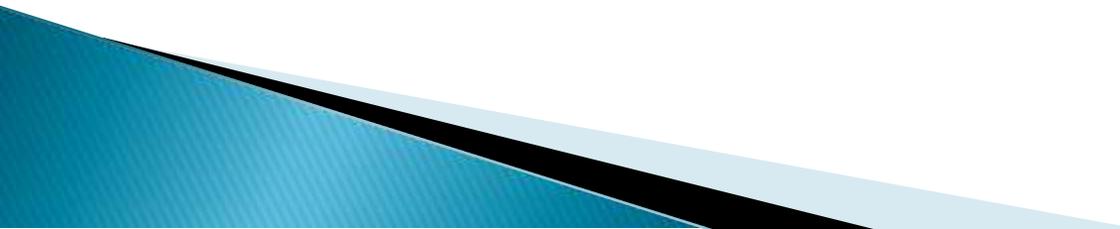
Evidence of strept. Infection :

- high ASOT
- positive throat culture (strept.)
- recent scarlet fever .
- positive direct group A strept. CHO antigen test .

FOR DIAGNOSIS:

- ▶ **2 Major criteria or**
 - ▶ **1 major and 2 minor plus
evidence of recent strept.
infection**
- 

ASOT

- Peak at time of diagnosis 2-4 wks. After pharyngitis .
 - normal value 200-300 todd's units .
 - falls in 6/12 time .
 - indicate true infection rather than a carrier state
 - titers cannot be used as indicators of rheumatic activity.**
- 

Other tests :

ESR

CRP

both are useful for follow up

Symptomatic relief :

arthritis :

ASA or other NSAIDS

- dose: 80–100 mg/kg/day (children)
4–8 gm/day (adults)
- serum level 20–30 mg%
- continue treatment until all the symptoms are relieved and ESR, CRP are back to normal .

rash : transient

no need for treatment

may need antihistamine

Carditis

- ▶ Severe involvement – 3rd degree heart block
 - CHF
 - Cardiomegaly on CXR

You should treat as such.

- ▶ **Steroids :**
conflicting results
2 mg/kg/day for 1–2 wks. Then taper over
the next 2 wks.

Antibiotics :

- should be given for 10 days regardless of the presence or absence of pharyngitis .
- give penicillin V 250 mg 2-3 times/day
500 mg TID (adults)
- Benzathine penicillin:
 - 600,000 units if < 27 kg
 - 1,200,000 units if > 27 kg
- Erythromycin (if allergic to penicillin)
40 mg/kg (max 1000 mg in 2-4 doses)
- Do throat swabs for all contacts ,if positive for beta hemolytic strept. →antibiotics

Antibiotic prophylaxis

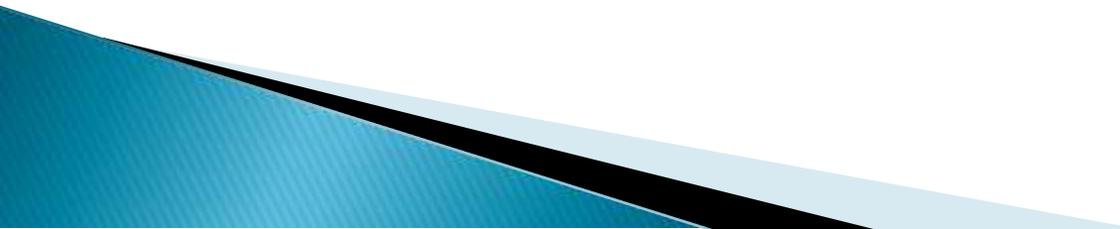
- Aim is to prevent recurrence of ARF (most common in 2 years)
- decrease with age
- penicillin V 400,000 units (250 mg) BID
sulfadiazine 500 mg/day <27 kg
1000 mg/day >27 kg
- classically , benzathine penicillin 1.2 MU Q 4 wks.
- may be more effective q 3 wks

Duration of prophylaxis :

- with evidence of RHD → **INDEFINITELY**
as recurrence may occur in the 5th , or 6th
decade .
- At least 10 years

Future :

strep. Vaccine





Systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus is a **chronic, multisystem, inflammatory, autoimmune disorder** characterized by formation of autoantibodies directed against self-antigens and **immune-complex** formation resulting in damage to essentially any organ.

- SLE affects **primarily women of childbearing age**

- **F > M 10-15:1**

TYPES OF LUPUS

1. Systemic Lupus Erythematosus (SLE):

The symptoms of SLE may be mild or serious. **Although SLE usually first affects people between the ages of 15 and 45.**

2. Discoid Lupus Erythematosus (DLE):

A chronic skin disorder in which a red, raised rash appears on the face, scalp, or elsewhere. The raised areas may become thick and scaly and may cause scarring. The rash may last for days or years and may recur. A small percentage of people with discoid lupus have or develop SLE later.







TYPES OF LUPUS

3. Neonatal Lupus:

- A rare disorder that can occur in newborn babies.
- Mother with positive **anti-Ro (SSA) and anti-La (SSB)** have increased risk.
- **At birth**, the babies have: **skin rash**, **liver problems**, and low blood counts. These symptoms gradually go away over several months.
- In rare cases, babies with neonatal lupus may suffer from complete heart block.

“drug-induced lupus”. The features typically go away completely when the drug is stopped. The kidneys and brain are rarely involved >>>>> **Hydralazine , Procainamide , Quinidine , Methyldopa , Chlorpromazine , Isoniazid .**

Drug-Induced Lupus Erythematosus

- *A lupus erythematosus–like syndrome may develop in patients receiving a variety of drugs, including hydralazine, procainamide, isoniazid, and d-penicillamine, **Many** of these drugs are associated with the development of **ANAs**, but **most patients do not have symptoms of lupus erythematosus.***
- *For example, 80% of patients receiving procainamide test positive for ANAs, but only one third of these manifest clinical symptoms, such as arthralgias, fever, and serositis.*

- **Drug-induced lupus**

(consider before diagnosing native lupus)

- Sex ratios are nearly equal.
- Nephritis and CNS not common.
- No anti- native DNA or hypocomplementemia.
- Resolution on discontinuation of drug.

Drugs associated with lupus erythematosus

- **Definite association**
 - **Chlorpromazine**
 - **Methyldopa**
 - **Hydralazine**
 - **Procainamide**
 - **Isoniazid**
 - **Quinidine**
- **Unlikely Association:**
 - Allopurinol,
 - Penicillin, Chlorthalidone, Phenylbutazone, Gold salts, Reserpine, Griseofulvin, Streptomycin, Methysergide, Tetracyclines, Oral contraceptives
- **Possible Association**
 - **Beta blockers**
 - **Methimazole**
 - **Captopril**
 - **Nitrofurantoin**
 - **Carbamazepine**
 - **Penicillamine**
 - **Cimetidine**
 - **Phenytoin**
 - **Ethosuximide**
 - **Propylthiouracil**
 - **Sulfasalazine**
 - **Levodopa**
 - **Sulfonamides**
 - **Lithium**
 - **Trimethadione**

CLINICAL FEATURES

DERMATOLOGICAL

- Alopecia
- Butterfly rash
- Mucous membrane lesion
- Photosensitivity
- Purpura
- Raynaud's phenomenon
- Urticaria
- Vasculitis



CLINICAL FEATURES

MUSCULOSKELETAL

- Arthralgia
- Arthritis
- Myositis

RENAL

- Casts
- Hematuria
- Nephrotic syndrome
- Proteinuria

HEMATOLOGIC

- Anemia
- Leukopenia
- Thrombocytopenia

CLINICAL FEATURES

CARDIAC

- Endocarditis
- Myocarditis
- Pericarditis

CONSTITUTIONAL

- Fatigue
- Fever
- Weight loss

GASTROINTESTINAL

- Abdominal pain
- Nausea & vomiting

CLINICAL FEATURES

NEUROPSYCHIATRIC

- Cranial neuropathies
- Organic brain syndrome
- Peripheral neuropathies
- Psychosis
- Seizures
- Transverse myelitis

PULMONARY

- Pleurisy
- Pulmonary hypertension
- Pulmonary parenchyma

CLINICAL FEATURES

RETICULOENDOTHELIAL

- Hepatomegaly
- Lymphadenopathy
- Splenomegaly

Clinical presentation varies in different patients & the disease activity varies over time in a single patient

1. Majority of patients have **arthralgia of the hand**
2. Compared with adults, **children have a higher incidence of malar rash, anemia, leukopenia, neurologic & renal involvement**









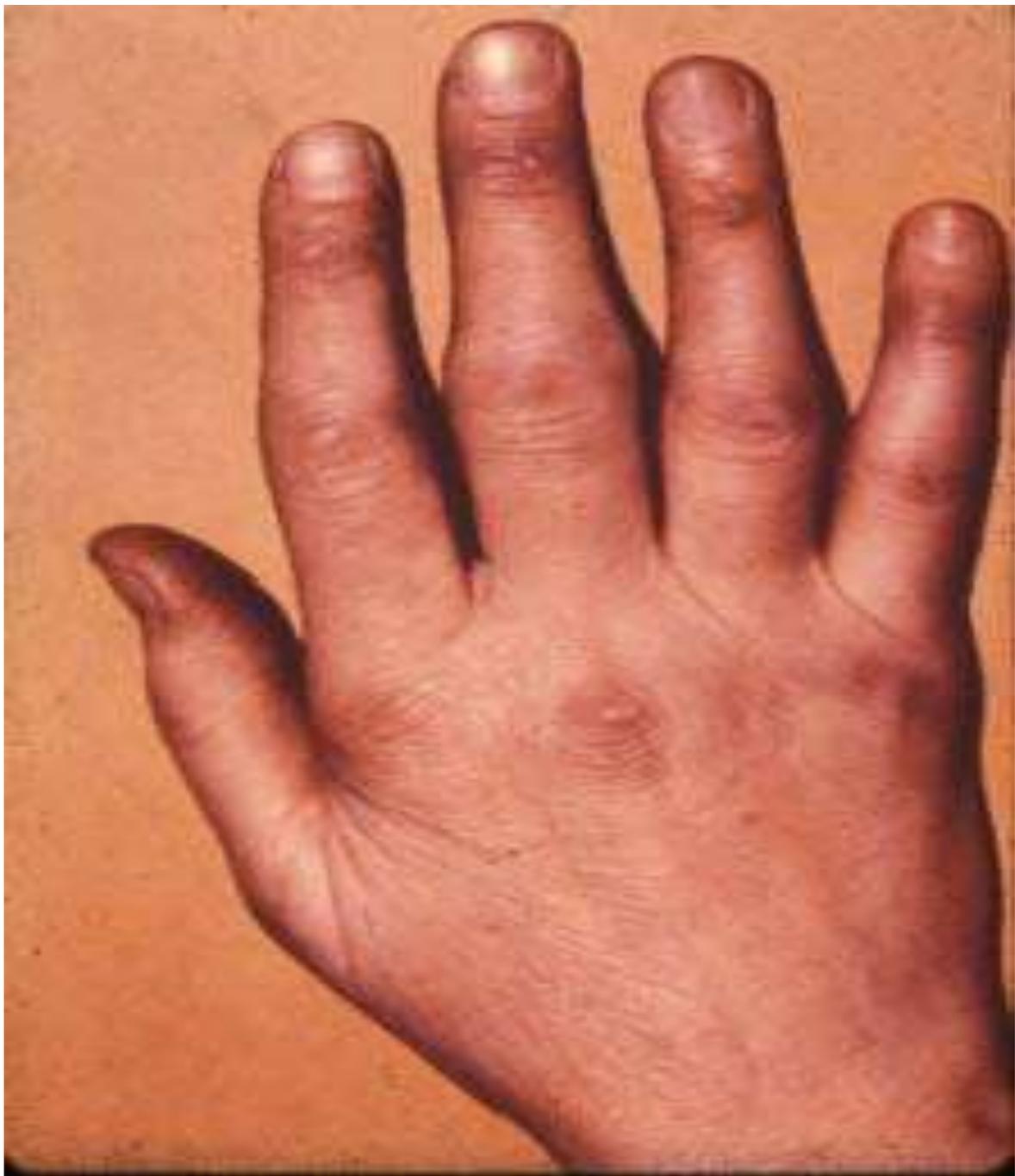










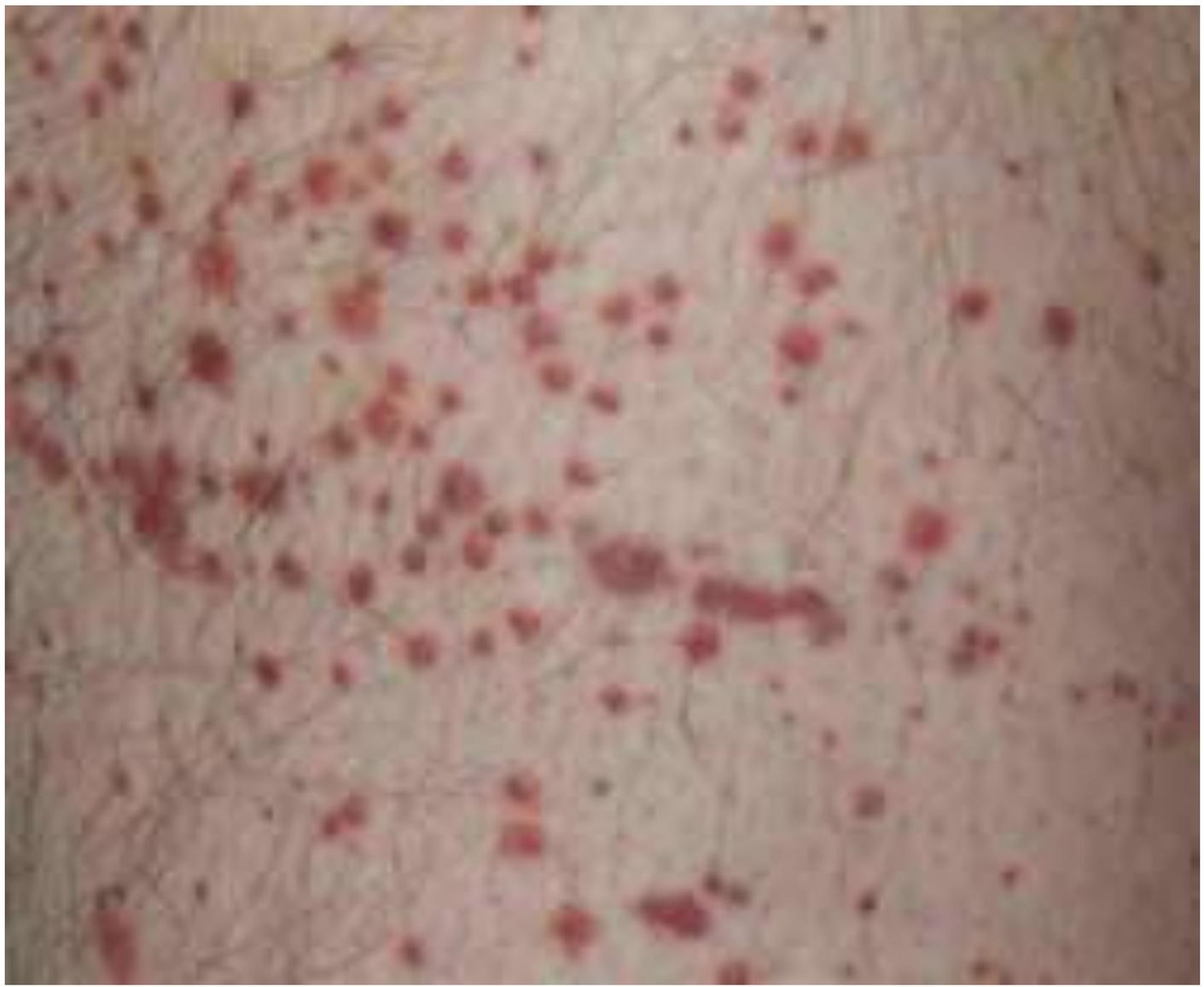




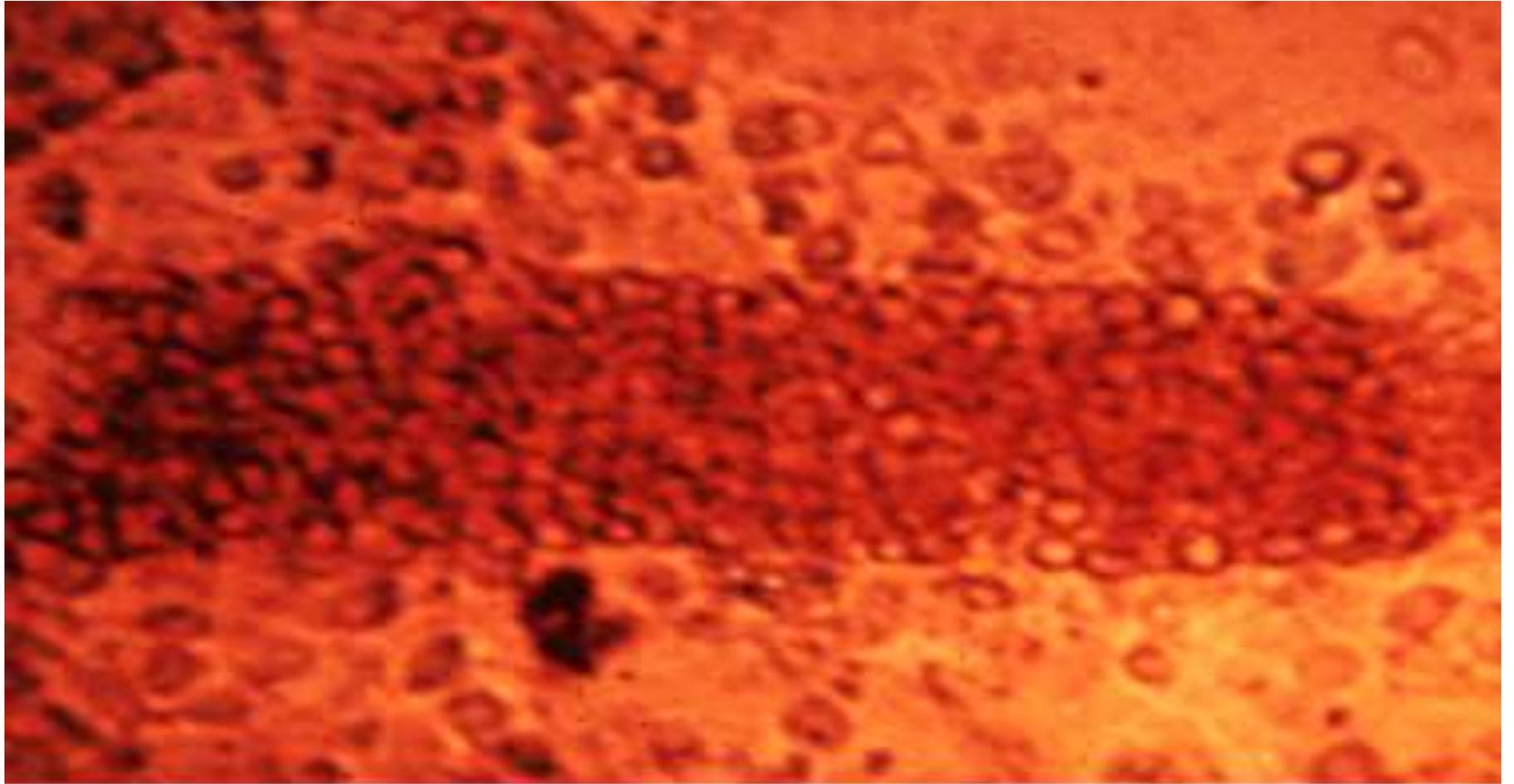




2







Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion <i>OR</i> b) Pericarditis--documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	a) Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed <i>OR</i> b) Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed

8. Neurological disorder	a) Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance OR b) Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematological disorder	a) Hemolytic anemia--with reticulocytosis OR b) Leucopenia--less than 4,000/mm³ total on 2 or more occasions OR c) Lymphopenia--less than 1,500/mm³ on 2 or more occasions OR d) Thrombocytopenia--less than 100,000/mm³ in the absence of offending drugs
10. Immunological disorder	a) "Positive finding of antiphospholipid antibodies based on 1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2) a positive test result for lupus anticoagulant using a standard method, or 3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by <i>Treponema pallidum</i> immobilization or fluorescent treponemal antibody absorption test." Standard methods should be used in testing for the presence of b) Anti-DNA: antibody to native DNA in abnormal titer OR c) Anti-Sm: presence of antibody to Sm nuclear antigen OR d) False positive serologic test for syphilis known to be positive for at least 6 months and confirmed by <i>Treponema pallidum</i> immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

The revised criteria for the classification of systemic lupus erythematosus

1. Serositis
2. Oral Ulcers
3. Arthritis
4. Photosensitivity
5. Blood disorders:
 - Hemolytic anemia
 - Leukopenia
(Lymphopenia)
 - Thrombocytopenia
6. Renal disorders
7. ANA positive
8. Immunologic abnormalities:
 - Anti-ds- DNA
 - Anti- Sm
 - Antiphospholipid
 - False +ve VDRL
9. Neurologic abnormalities
10. Malar rash
11. Discoid rash – rimmed with scaling, follicular plugging

New SLICC criteria

- **Classify a patient as having SLE if:**
- **A. The patient has biopsy-proven lupus nephritis with ANA or anti-dsDNA OR the patient satisfies four of the criteria, including at least one clinical and one immunologic criterion.**
- **B. Clinical Criteria**
- **1. Acute or subacute cutaneous lupus**
- **2. Chronic cutaneous lupus**
- **3. Oral/Nasal ulcers**
- **4. Nonscarring alopecia**
- **5. Inflammatory synovitis with physician-observed swelling of two or more joints OR tender joints with morning stiffness**
- **6. Serositis**
- **7. Renal: Urine protein/creatinine (or 24 hr urine protein) representing at least 500 mg of protein/24 hr or red blood cell casts**
- **8. Neurologic: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, cerebritis (acute confusional state)**
- **9. Hemolytic anemia**
- **10. Leukopenia ($<4000/\text{mm}^3$ at least once)**
- **OR**
- **Lymphopenia ($<1000/\text{mm}^3$ at least once)**
- **11. Thrombocytopenia ($<100,000/\text{mm}^3$) at least once**

Immunologic Criteria

- 1. ANA above laboratory reference range
- 2. Anti-dsDNA above laboratory reference range (except ELISA: twice above laboratory reference range)
- 3. Anti-Sm
- 4. Antiphospholipid antibody
- lupus anticoagulant
- false-positive test for syphilis
- anticardiolipin—at least twice normal or medium-high titer
- anti-b2 glycoprotein 1
- 5. Low complement
- low C3
- low C4
- low CH50
- 6. Direct Coombs test in absence of hemolytic anemia.

Renal Findings In SLE

Most common cause of morbidity & mortality

- Lupus nephritis affects up to 50% of SLE patients.
- The principal mechanism of injury is **immune complex deposition** in the glomeruli, tubular or peritubular capillary basement membranes, or larger blood vessels.
- A variety of clinical findings may point toward renal involvement, including hematuria, red cell casts, proteinuria, and in some cases the classic nephrotic syndrome

Normal Microscopy



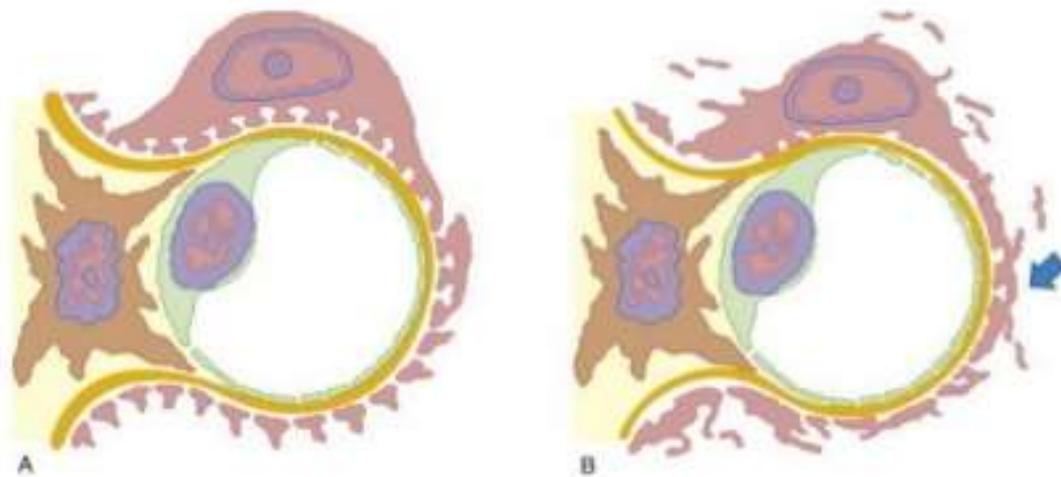
Minimal change disease

Loss of foot process - EM

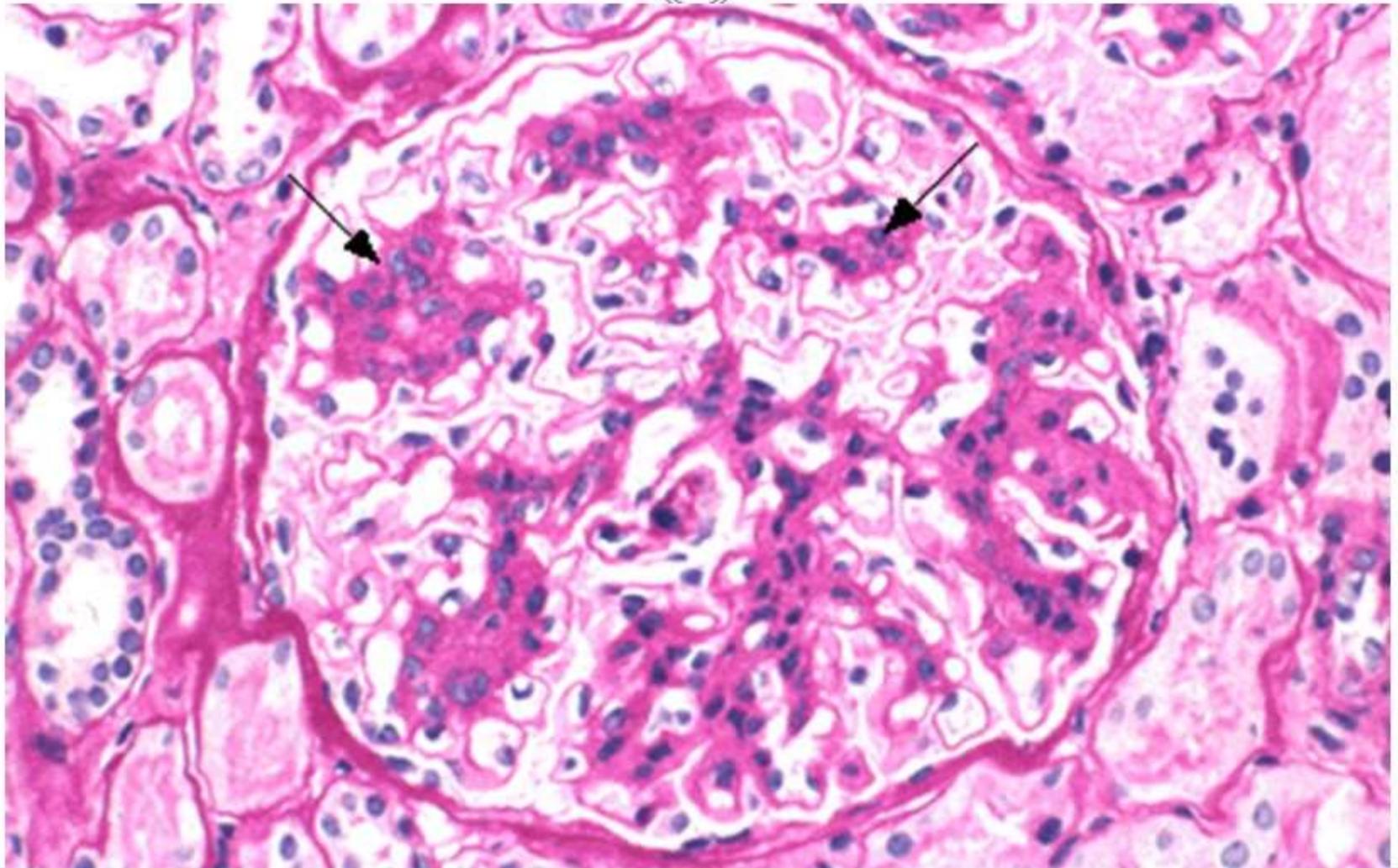


Pathology: Foot Process Effacement

- FIGURE 31-3 Diagrams depicting the ultrastructural features of a normal glomerular capillary loop (A) and a capillary loop with features of minimal change glomerulopathy (B). The latter has effacement of epithelial foot processes (arrow) and microvillous projections of epithelial cytoplasm.

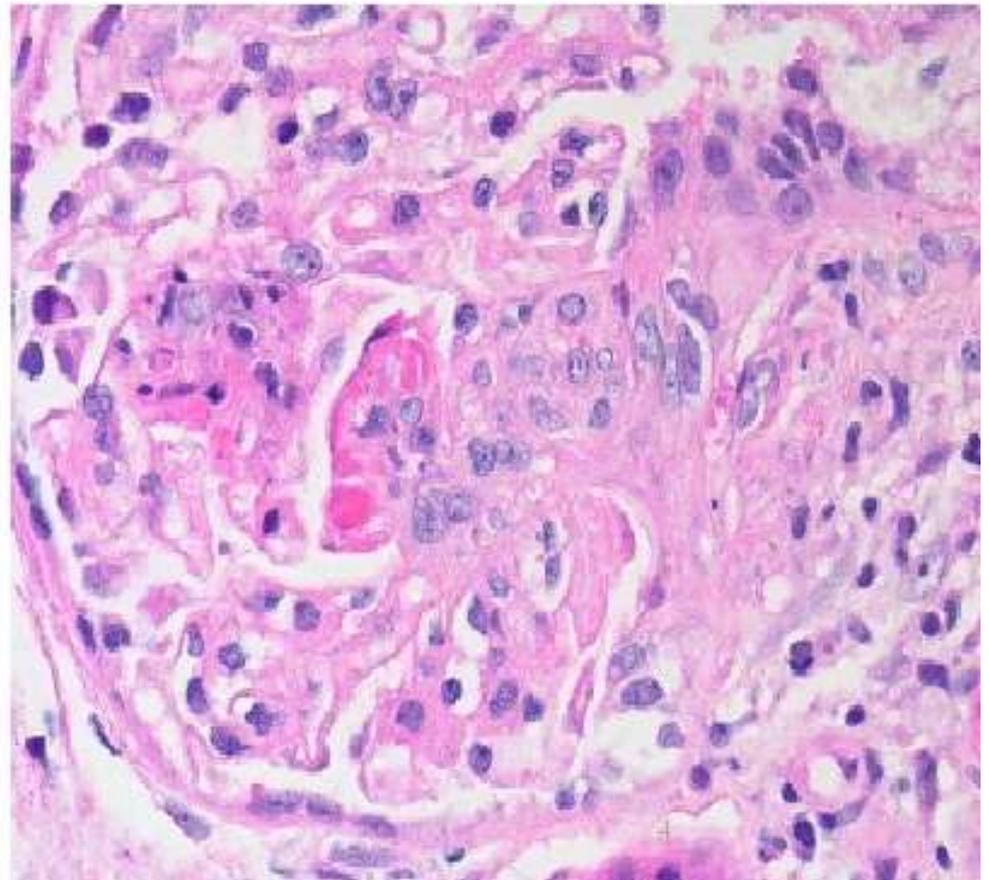


Mesangial proliferative glomerulonephritis

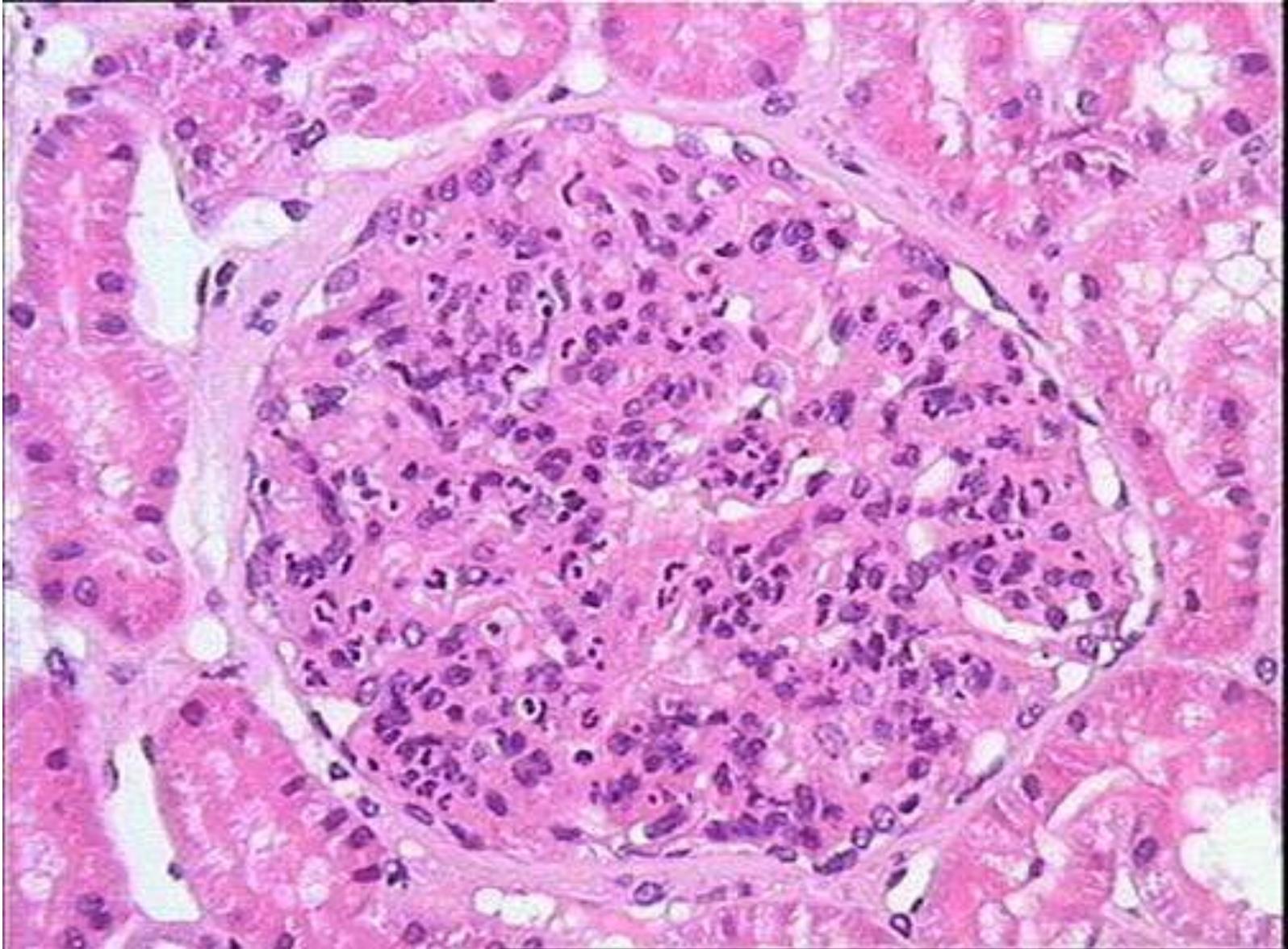


CLASS 3: Focal proliferative glomerulonephritis

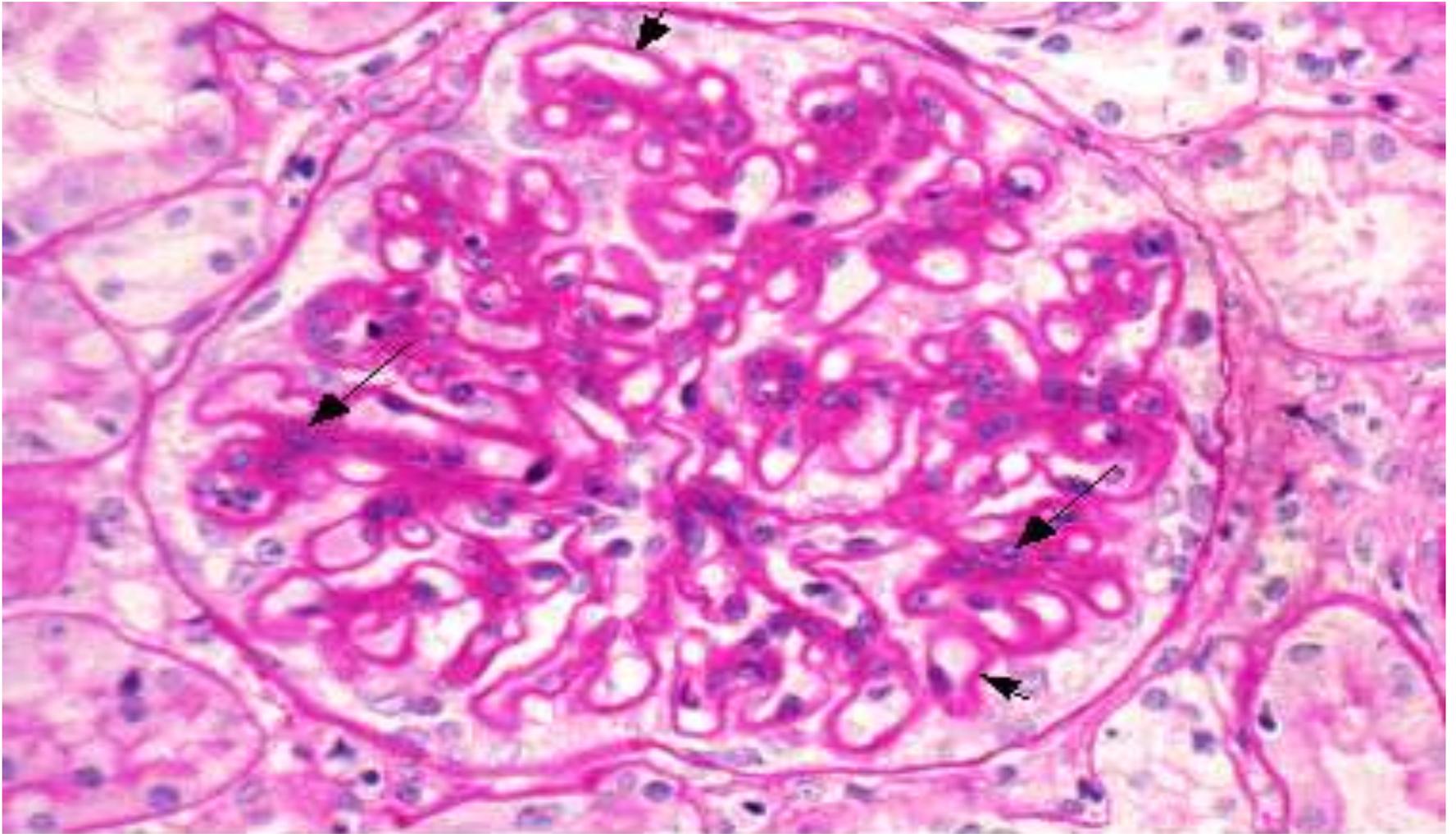
- **Focal and segmental** proliferation of endothelial and mesangial cells
- Neutrophil infiltration
- Fibrinoid necrosis
- Capillary thrombosis



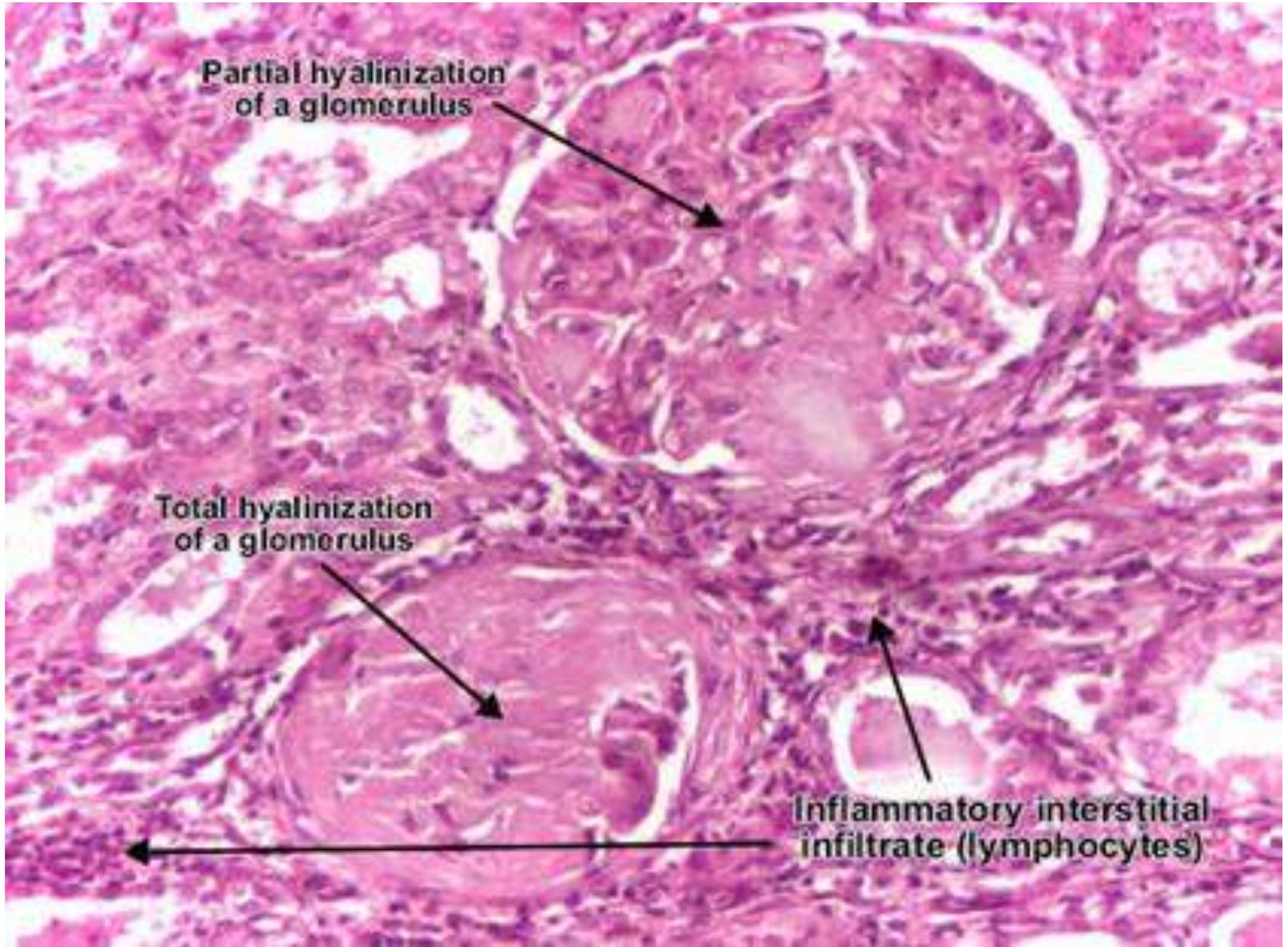
Diffuse proliferative GN



Membranous GN



Sclerosing GN



• **AETIOLOGY:**

– **Genetic predisposition :**

- **Concordance rate in monozygotic twins is 25-70%.**
- **If a mother has SLE, her daughter's risk of developing the disease is 1:40, and her son's risk is 1:250.**
- **HLA-DR2 and HLA-DR3 and other HLA genes occur more often in SLE than in the general population.**

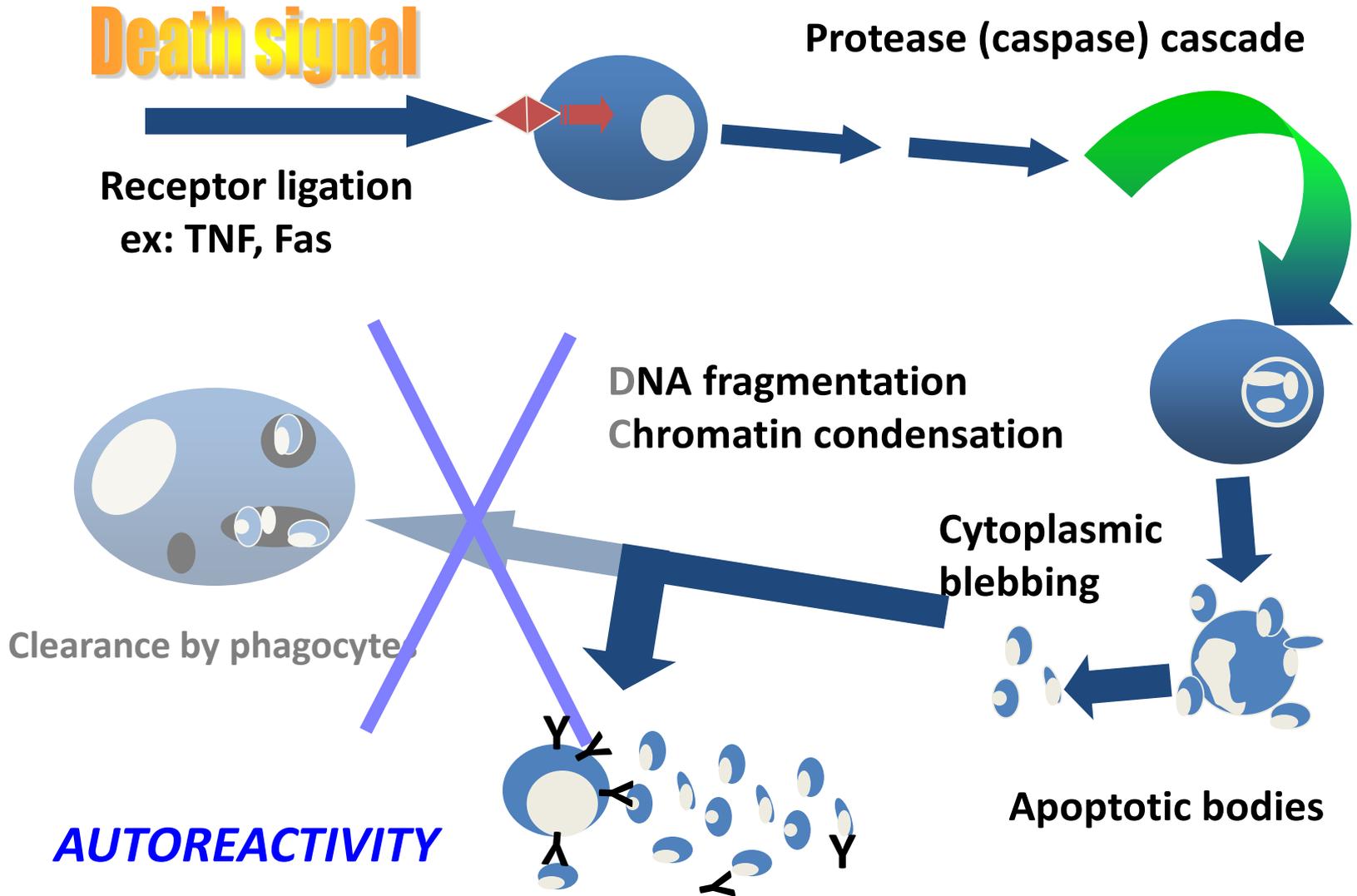
AETIOLOGY(cont.):

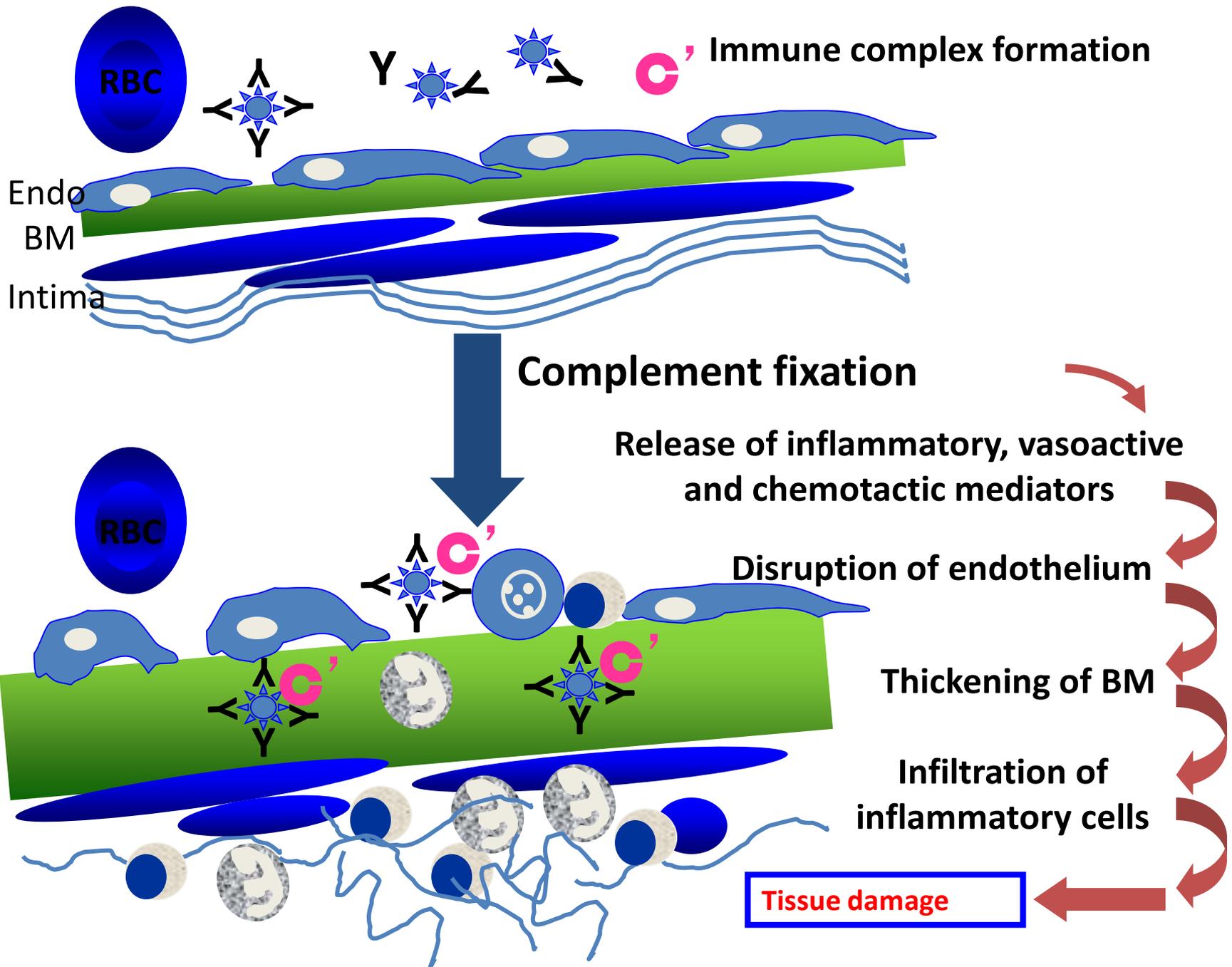
- Hormonal factors:
 - F:M ratio of prevalence in different age groups:
 - In adults, F:M ratio is 10-15:1
 - In older, the ratio is approximately 8:1 .
 - Higher prevalence in men with Klinefelter disease.

AETIOLOGY(cont.):

- Environmental:
 - worldwide variability of prevalence the disease (blacks in Africa and US)
 - Influence of environmental factors on the course of the disease, eg:
 - ultraviolet light
 - viruses
 - Drugs, cause or exacerbate
 - silica dust.
 - cigarette smoking.

APOPTOSIS





MANAGEMENT

MONITORING

Monitoring during clinic visit should include:

1. History-taking
2. Physical exam
3. Lab tests
4. Complete blood count (CBC)
5. Creatinine measurement
6. Urinalysis

MANAGEMENT

MONITORING

Results of lab tests that may precede a disease flare:

1. Decrease in serum complement levels
2. Increase in anti-double stranded antibodies(dsDNA)
3. Increase in erythrocyte sedimentation rate (ESR)
4. Decrease in hemoglobin level, leukocyte or platelet counts
5. Increase in creatine phosphokinase (CPK) levels
6. Appearance of microscopic hematuria or proteinuria

TREATMENT

GOALS OF THERAPY:

- **Control disease manifestation**
- **Allow PATIENT to have a good quality of life without major exacerbations**
- **Prevent serious organ damage that adversely affects function or lifespan**
- **Prevent adverse effects of the drugs used**

TREATMENT (cont.):

- **GENERAL CONSIDERATIONS :**

- Prevention:**

- Avoid UV light and sun (sun screening).
 - Anti malarials to prevent relapses.
 - Treat hypertension and dyslipidemias
 - Avoid smoking
 - Treat infection aggressively.
 - Vaccination.

TREATMENT

1- CORTICOSTEROIDS

Oral corticosteroids

- 1- Patients w/ mild SLE *do not normally* require use of systemic corticosteroids
- 2- High-dose corticosteroids are necessary for refractory manifestations of SLE & for severe organ systems' manifestations especially CNS, renal & hematologic manifestations

Topical corticosteroids

- Helpful for discoid lesions especially on the scalp
- Use a less potent steroid on the face because it is more prone to atrophy

Parenteral corticosteroids

- combination with immunosuppressive therapy is recommended for Class III and IV SLE patients with confirmed glomerulonephritis

TREATMENT

2-HYDROXYCHLOROQUINE

- Used for skin & joint manifestations
- Also used for preventing flares & other constitutional symptoms
- Recommended as background treatment for Class III and IV SLE patients with nephritis

TREATMENT

3-IMMUNOSUPPRESSANTS

- In the treatment of severe CNS & severe glomerulonephritis, thrombocytopenia & hemolytic anemia, high dose glucocorticoids & immunosuppressants are used
 - Concomitant use with corticosteroids allows lower doses of immunosuppressants
1. **Azathioprine**
 2. **Belimumab**
 3. **Cyclophosphamide**
 4. **IV Immune Globulin (IVIg)**
 5. **Methotrexate**

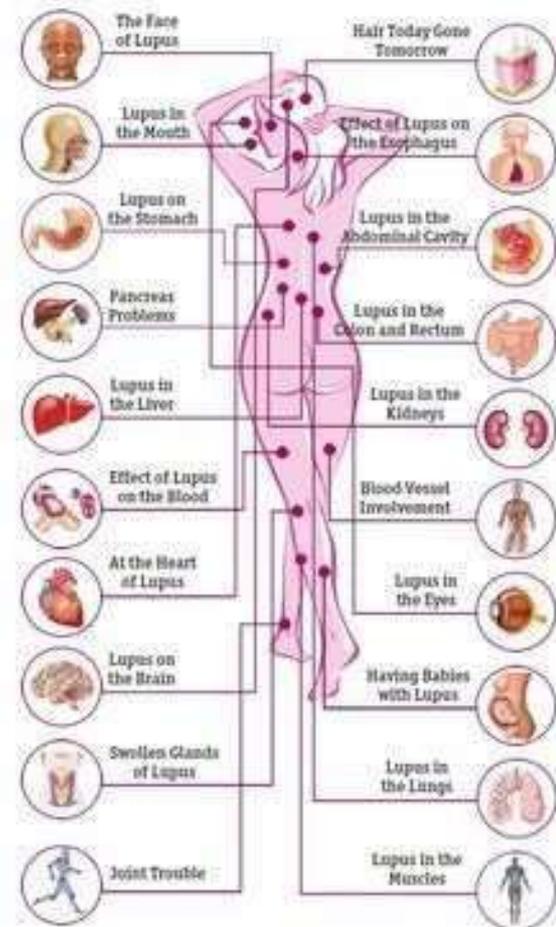
- Antimalarial Drugs
 - Hydroxychloroquine (Plaquenil), chloroquinone (Aralen)
 - Reduces inflammation, protects against organ damage
 - Used for skin symptoms, joint pain
- DMARDs (disease-modifying antirheumatic drugs)
 - Belimumab (Benlysta).
 - Rituximab (Rituxan)
Suppress B cell development, block B cell stimulation.

(Bartels et al. 2014; Schur et al. 2014; Shiel et al. 2014)

COMPLICATIONS

Some degree of long term and often permanent organ dysfunction from either SLE or its treatment has been found in 88% of patients.

1. Hypertension
2. Growth retardation
3. Chronic pulmonary impairment
4. Ocular abnormalities
5. Permanent renal damage
6. Neuropsychiatric symptoms
7. Musculoskeletal damage
8. Gonadal impairment



Mortality/Morbidity:

- **Improved survival rate**
 - **10-year survival rate now 90% .**

Despite that, death rate still 3 times higher than general population.

Causes of Death:

- **Active SLE (26 %)**
 - **Infection (25 %)**
 - **Thromboses (26%)**
 - **Miscellaneous**
- Risk of death due to SLE is highest in the first five years.

Special Concerns:

- **Pregnancy:**

- **Fertility rates are similar to general population.**
- **Higher rates of abortion, premature labor, and intrauterine death
esp. with APS.**
- **Control for at least 6 months prior to conception .**
- **SLE can flare postpartum.**
- **Neonatal lupus in the babies of mothers with anti-SSA/Ro.**

PROGNOSIS

- *Unpredictable course*
- *The outcome has improved significantly, and an approximately 90% 5-year and 80% 10-year survival can be expected*
- *Most SLE patients die from renal failure and infection, probably related to therapy which suppresses immune system*
- *Recommend smoking cessation, yearly flu shots, pneumovax q5years*

THANK YOU