# HARRISON

## EDITION 22nd

# RHEUMATOLOGY, TOXICOLOGY AND ENVIRONMENT MEDICINE

# Rheumatology & Immunology

| | |
|---|---|
| Systemic Lupus Erythematosus | Completed |
| Rheumatoid Arthritis | Completed |
| Primary Sjogrens Syndrome | Completed |
| Behcets Disease Relapsing Polychondritis | Completed |
| Inflammatory Myopathies | Completed |
| Systemic Sclerosis | Completed |
| Antiphospholipid Syndrome | Completed |
| Sarcoidosis | Completed |
| IgG4 Related Disease | Completed |
| Clinical Immunology | Completed |

# Systemic Lupus Erythematosus

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## What is new

- What is new in the Harrison's 22nd Edition of internal medicine
- Please go through this class after learning our basic class on the subject
- Consider this as an add on the existing content to the chapter

## Lupus classification

**Type 1 Lupus:**

- Classic immune-mediated features: nephritis, arthritis, vasculitis
- Caused by autoimmune inflammation/organ damage
- Responds to standard immunosuppressive therapy

**Type 2 Lupus:**

- Symptoms: fatigue, diffuse pain, depression, cognitive dysfunction, sleep disturbances, anxiety, brain fog
- Less responsive to immunosuppressive therapy

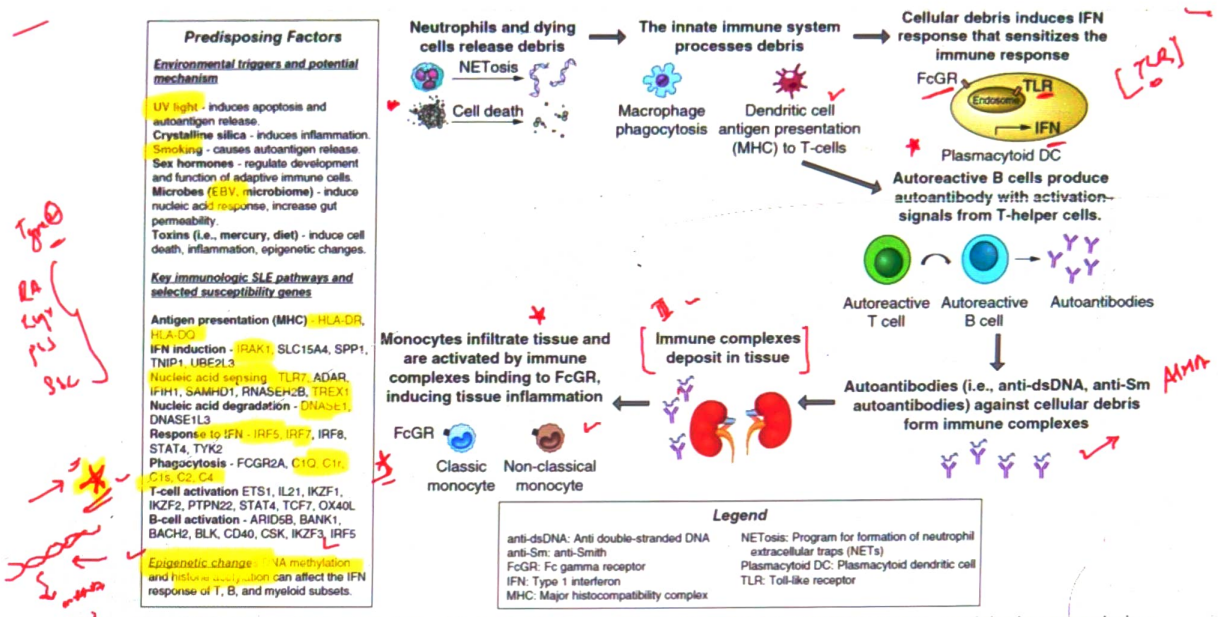



**FIGURE 368-1 Pathogenesis of systemic lupus erythematosus (SLE).** Autoantigens from neutrophil NETosis and cellular turnover overwhelm clearance mechanisms regulated by the innate immune system in SLE. Consequently, these autoantigens accumulate and induce an immune response. Nucleic acid activates TLR signaling in plasmacytoid dendritic cells (DCs), producing type 1 IFN, sensitizing the innate and adaptive immune responses. DCs present autoantigens to autoreactive T cells, leading to B-cell stimulation and the production of immune complexes against these autoantigens. Immune complexes deposit in tissue and induce local immune responses that lead to inflammation and repair and, eventually, fibrosis after recurrent SLE flares. EBV, Epstein-Barr virus.




**FIGURE 368-2 Characteristic musculoskeletal and cutaneous manifestations seen in systemic lupus erythematosus (SLE).** *A.* Jaccoud arthropathy, characterized by chronic, nonerosive, and reversible deviations caused by joint capsule inflammation with subsequent fibrotic retraction and metacarpophalangeal joint subluxation. *B.* Patchy, nonscarring alopecia. *C.* Patchy scarring alopecia. *D.* Patchy alopecia associated with chronic, scarring discoid lupus changes. *E.* Classic photosensitive malar rash. *F.* Subacute cutaneous lupus erythematosus (SCLE) with widespread, nonscarring photosensitive features. *(Panels B–E reproduced with permission from Victoria Werth, MD. Panels A and F reproduced with permission from DoQuyen Huynh, MD.)*

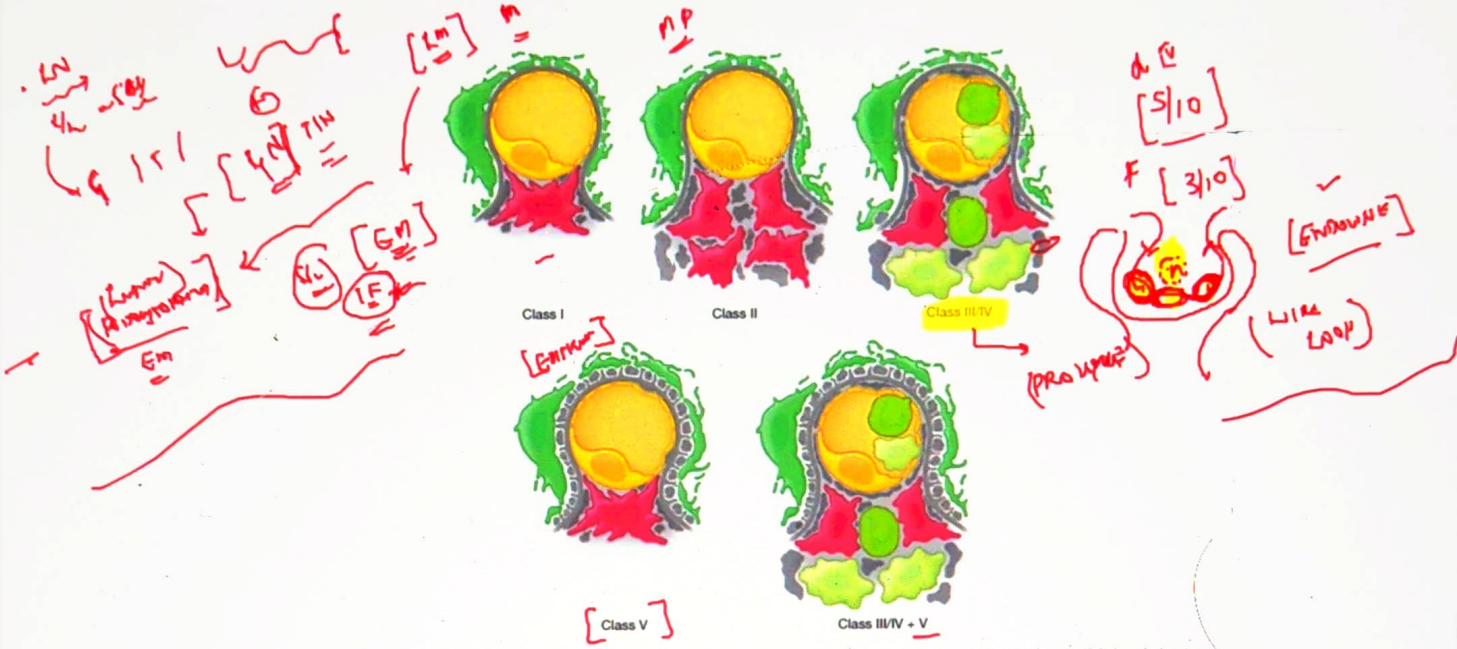



**FIGURE 368-3 Ultrastructural features of lupus glomerulonephritis.** Class I: Mesangial immune deposits (*black*) without mesangial cell (*red*) hypercellularity or leukocyte infiltration. Class II: Mesangial immune deposits with mesangial cell hypercellularity, no leukocyte infiltration. Class III/IV: Subendothelial immune deposits visible by light microscopy, with infiltration of mesangial and capillary leukocytes (dark green neutrophils and light green monocytes/macrophages). Class III/IV + V: Leukocyte infiltration with subepithelial and subendothelial immune deposits. Class V: Subepithelial immune deposits, no leukocyte infiltration. *(Reproduced with permission from IM Bajema et al: Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: Clarification of definitions, and modified National Institutes of Health activity and chronicity indices. Kidney Int 93:789, 2018, Figure 2.)*

**TABLE 368-1 Clinical Manifestations of Systemic Lupus Erythematosus**

| | |
|---|---|
| Constitutional | Fatigue, malaise, fever, weight loss, anorexia |
| Cutaneous | |
| Generalized | Photosensitivity, oral and nasal ulcers, alopecia |
| Acute cutaneous lupus | Malar rash, maculopapular rash, bullous lupus, toxic epidermal necrolysis variant |
| Subacute cutaneous lupus | |
| Chronic forms of cutaneous lupus | Discoid rash, panniculitis, tumid lupus, chilblains, verrucous lupus, cutaneous vasculitis |
| Musculoskeletal | Arthralgia, myalgia, polyarthritis, Jaccoud hand deformity, inflammatory myopathy, avascular necrosis of bone |
| Hematologic | Anemia, leukopenia, lymphopenia, thrombocytopenia, lymphadenopathy, splenomegaly, venous or arterial thrombosis, atypical hemolytic-uremic syndrome |
| Cardiopulmonary | Pleurisy, pericarditis, pleural and pericardial effusions, myocarditis, endocarditis, pneumonitis, coronary artery disease, interstitial fibrosis, pulmonary hypertension, diffuse alveolar hemorrhage, shrinking lung syndrome |
| Vascular | Pulmonary hypertension, stroke, myocardial infarction, peripheral arterial disease, pulmonary embolism, deep vein thrombosis, Raynaud's phenomenon |
| Neurologic | Cognitive dysfunction, mood disorder, depression, headache, seizures, mononeuropathy, polyneuropathy, stroke, transient ischemic attack, psychosis, aseptic meningitis, transverse myelitis |
| Renal | Proteinuria ≥500 mg/24 h, cellular casts, nephrotic syndrome, end-stage renal disease |
| Gastrointestinal | Nausea, abdominal pain, diarrhea, elevated liver enzymes, peritonitis, pancreatitis |
| Ocular | Sicca syndrome, conjunctivitis, episcleritis, scleritis, uveitis, retinal vasculitis |

**TABLE 368-2 Autoantibodies in Systemic Lupus Erythematosus**

| ANTIBODY | PREVALENCE, % | CLINICAL ASSOCIATIONS |
|---|---|---|
| ANA | 95 | Titers of 1:80 or higher are considered positive and are sensitive for SLE but not specific. |
| Anti-dsDNA | 70 | Higher titers are more specific for SLE.<br>Levels correlate with disease activity and nephritis. |
| Anti-Sm | 30 | Most specific autoantibody for SLE and more common in black and Asian patients. |
| Anti-RNP | 25 | Not SLE-specific. Associated with overlap syndromes and increased risk for pulmonary hypertension. Correlates with high interferon gene signature. |
| Anti-Ro (SS-A) | 30 | Not SLE-specific. Associated with sicca syndrome, neonatal lupus, and subacute cutaneous lupus. |
| Anti-La (SS-B) | 20 | Associated with anti-Ro. |
| Antiribosomal P | 15 | May be associated with CNS involvement. Specific for SLE but not sensitive. |
| Antihistone | 70 | Associated with drug-induced lupus. |
| Anti–U1-RNP | 13 | Associated with musculoskeletal and lung impairment. |
| Antiphospholipid<br>*Anticardiolipin*<br>*Anti-$\beta_2$-glycoprotein*<br>*Lupus anticoagulant* | 50 | Arterial or venous thrombosis, pregnancy morbidity and fetal loss, thrombocytopenia. Associated with CNS manifestations, Libman-Sacks endocarditis, hypertension, pulmonary hypertension. |

*Abbreviations:* ANA, antinuclear antibody; CNS, central nervous system; dsDNA, double-stranded DNA; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus; Sm, Smith.

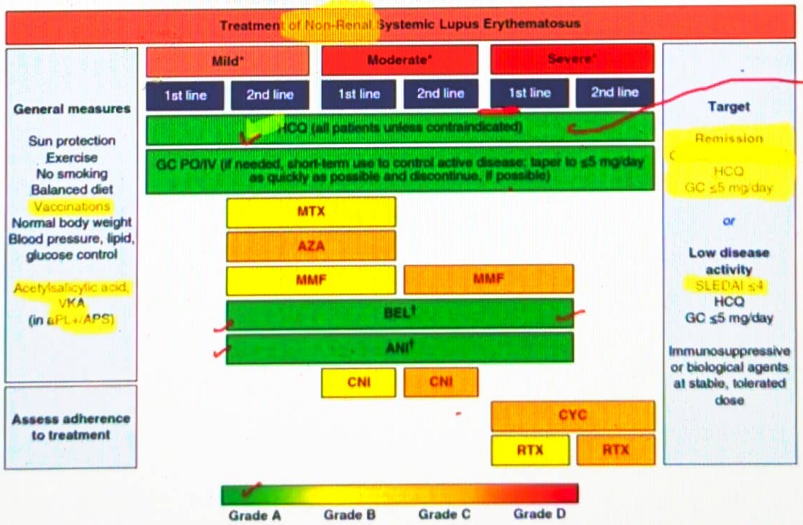



**FIGURE 368-4 Treatment of nonrenal systemic lupus erythematosus (SLE).** Notes: Top-to-bottom sequence does not imply order of preference (e.g., MTX, AZA, and MMF are equal options for second-line therapy in mild disease or first-line therapy in moderate disease). *Mild disease: constitutional symptoms; mild arthritis; rash ≤9% body surface area; platelet count (PLTs) 50–100 × 10⁹/L; SLEDAI ≤6; BILAG C or ≤1 BILAG B manifestation. *Moderate disease: moderate-to-severe arthritis ("rheumatoid arthritis–like"; rash 9–18% body surface area (BSA); PLTs 20–50 × 10⁹/L; serositis; SLEDAI 7–12; ≥2 BILAG B manifestations). *Severe disease: major organ-threatening disease (e.g., cerebritis, myelitis, pneumonitis, mesenteric vasculitis); thrombocytopenia with platelets <20 × 10⁹/L; thrombotic thrombocytopenic purpura–like disease or acute hemophagocytic syndrome; rash >18% BSA; SLEDAI >12; ≥1 BILAG A manifestation. †Recommendation of belimumab and anifrolumab as first-line therapy in severe disease refers to cases of extrarenal SLE with nonmajor organ involvement but extensive disease from skin, joints, and so on. The use of anifrolumab as add-on therapy in severe disease refers mainly to severe skin disease. For patients with severe neuropsychiatric disease, anifrolumab and belimumab are not recommended. ANI, anifrolumab; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; AZA, azathioprine; BEL, belimumab; BILAG, British Isles Lupus Assessment Group; CNI, calcineurin inhibitor; CYC, cyclophosphamide; GC, glucocorticoids; HCQ, hydroxychloroquine; IV, intravenous; MMF, mycophenolate mofetil; MTX, methotrexate; PO, per os; RTX, rituximab; SLEDAI, SLE Disease Activity Index; VKA, vitamin K antagonists. *(Reproduced with permission from A Fanouriakis et al: Ann Rheum Dis 83:15, 2024.)*

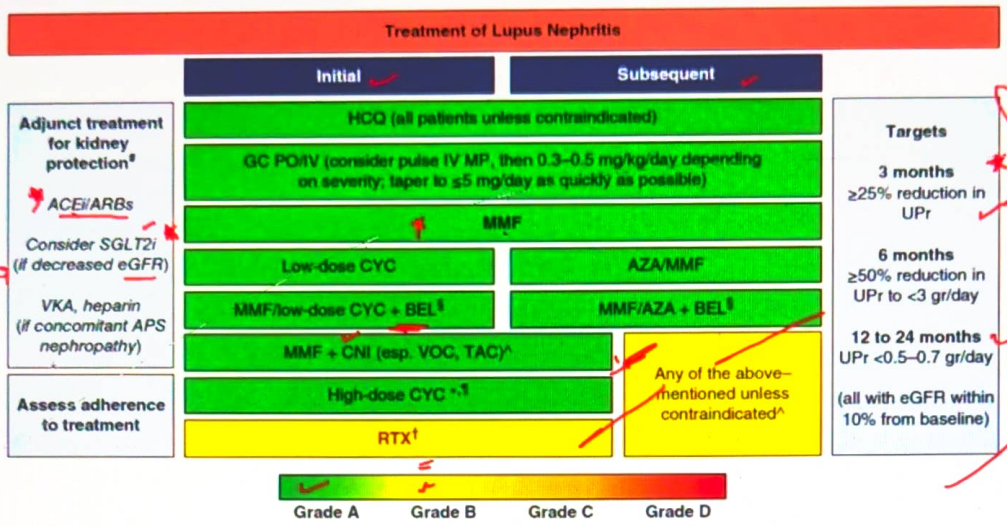



**FIGURE 368-5 Treatment of lupus nephritis.** Notes: Top-to-bottom sequence does not imply order of preference. [#]In addition to general protective measures, as outlined in Figure 368-3. [§]BEL should always be given in combination with MMF or low-dose CYC as initial therapy and with MMF or AZA as maintenance therapy. ^CNIs should be given in combination with MMF. *Particularly recommended in the presence of poor prognostic factors: reduced eGFR, histologic presence of cellular crescents or fibrinoid necrosis, or severe interstitial inflammation. [¶]Extension of high-dose CYC to subsequent phase refers to severe lupus nephritis cases, in which bimonthly or quarterly CYC pulses may be given following 6 monthly pulses. [†]In relapsing/refractory disease, especially after failure of CYC-based regimens. ACEi, angiotensin-converting enzyme inhibitors; APS, antiphospholipid syndrome; ARB, angiotensin receptor blockers; AZA, azathioprine; BEL, belimumab; CNI, calcineurin inhibitor; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; GC, glucocorticoids; HCQ, hydroxychloroquine; IV, intravenous; MMF, mycophenolate mofetil; MP, methylprednisolone; PO, per os; RTX, rituximab; SGLT2i, sodium-glucose cotransporter 2 inhibitors; TAC, tacrolimus; Upr, urine protein; VKA, vitamin K antagonists; VOC, voclosporin. *(Reproduced with permission from A Fanouriakis et al: Ann Rheum Dis 83:15, 2024.)*

# Emerging Therapies in SLE / Lupus Nephritis

- **SGLT2 inhibitors**: Tubular protection; reduce inflammation & fibrosis
- **Obinutuzumab (anti-CD20 mAb)**:
  - Phase 3: efficacy in lupus nephritis
  - Also under study for non-renal SLE
  - Anecdotal use: may outperform rituximab (better CD20 tissue depletion)
- **Deucravacitinib**: Oral Tyk2 inhibitor, Phase 3 trial in SLE
- **Telitacicept**: TACI-Fc fusion protein (targets BLyS & APRIL); approved in China for SLE

# Ongoing & Novel Therapies in SLE

**Telitacicept**: Phase 3 global studies underway

**Litifilimab (anti-BDCA2 mAb):**

- Targets plasmacytoid dendritic cells
- Suppresses type I interferons & proinflammatory cytokines
- Promising late-stage results

**CAR-T (CD19-directed):**

- Achieved remission (per DORIS criteria) in early studies
- Stimulating further trials

**Cell-based therapies (experimental):**

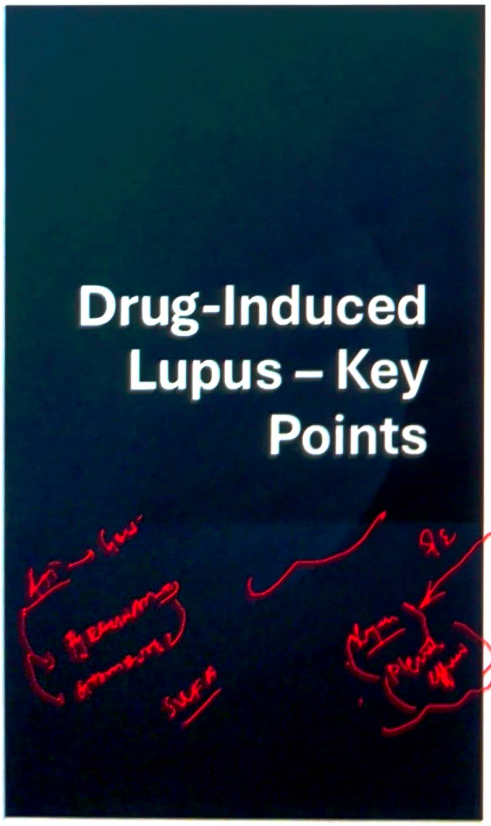
- Allogenic & autologous NK cell–based approaches
- Mesenchymal embryonic stem cell transplantation for severe SLE

# FDA-Approved Therapies for Lupus Nephritis

- **Belimumab** – approved 2020
- **Voclosporin (cyclosporine analogue)** – approved 2021
- Both used **with standard therapy** for active nephritis

# Drug-Induced Lupus (DIL)

- Autoimmune reaction triggered by drug exposure
- Accounts for **6–12%** of lupus cases
- **Symptoms**: fever, rash, arthralgia, myalgia, serositis
- **Antibodies**:
  - Antihistone (common)
  - Anti-dsDNA (less frequent)
- Usually **milder than SLE** → kidneys & brain rarely involved
- Symptoms resolve after stopping the offending drug (within weeks)




- **First drug reported**: Hydralazine (1954)
- **>100 drugs** identified as triggers
- **Highest risk**: Procainamide (up to 30%)
- **Other implicated drugs**:
  - **Antihypertensives**: Hydralazine, methyldopa
  - **Antiarrhythmics**: Procainamide, others
  - **Antibiotics**: Minocycline, isoniazid, rifampin, nitrofurantoin
  - **Antirheumatic**: Sulfasalazine
  - **Anticonvulsants**: Phenytoin, carbamazepine
  - **Antipsychotics**: Chlorpromazine, lithium
  - **Others**: ACE inhibitors, beta blockers, hydrochlorothiazide, propylthiouracil, PPIs, NSAIDs, oral contraceptives
  - **Biologics**: Anti–TNF-α (infliximab, etanercept), IFN-α

## Diagnosis

DIC

- Onset: Weeks to months after drug initiation
- Skin biopsy: Indistinguishable from SLE
- **Labs**:
  - ANA (homogeneous pattern, often appears before symptoms)
  - Anti-histone positive in ~75%
  - Cytopenias: usually mild
  - Other autoantibodies: rarely present (helps distinguish from SLE)

**Q1.**
Which autoantibody is most specific for SLE?
A. Anti-dsDNA
B. Anti-Smith
C. Anti-histone
D. Anti-Ro

✅ **Answer: B. Anti-Smith**

*Explanation*: Anti-dsDNA is sensitive and correlates with nephritis, but **Anti-Smith is most specific**.

- **Q2.**
  Which complement levels are most useful in monitoring SLE disease activity?

A. C1q and C2
B. C3 and C4
C. C5 and C9
D. CH50 only

✅ **Answer: B. C3 and C4**
*Explanation*: Both fall during active disease, especially nephritis

**Q3.**
A 25-year-old woman presents with fever, malar rash, and arthritis. ANA is positive, Anti-dsDNA elevated. Urinalysis shows proteinuria 2 g/day, RBC casts. What is the most likely renal lesion?

A. Minimal change disease
B. Class II mesangial lupus nephritis
C. Class IV diffuse proliferative lupus nephritis
D. Class V membranous lupus nephritis

✅ **Answer: C. Class IV diffuse proliferative lupus nephritis**
*Explanation*: Most severe, commonest cause of nephritic presentation (casts, hematuria, proteinuria)

**Q4.**
Which of the following drugs is **contraindicated in pregnancy** in an SLE patient?
A. Hydroxychloroquine
B. Azathioprine
C. Mycophenolate mofetil
D. Low-dose prednisone

✅ **Answer: C. Mycophenolate mofetil**

*Explanation*: Mycophenolate, methotrexate, and cyclophosphamide = teratogenic; hydroxychloroquine should be continued.

**Q5.**
The presence of which antibody increases the risk of neonatal lupus with congenital heart block?

A. Anti-Smith
B. Anti-dsDNA
C. Anti-Ro (SSA)
D. Anti-histone

✅ **Answer: C. Anti-Ro (SSA)**

*Explanation*: Anti-Ro/SSA and Anti-La/SSB cross placenta → risk of neonatal lupus, CHB.

**Q6.**
Drug-induced lupus (DIL) is most strongly associated with which antibody?

A. Anti-Smith
B. Anti-histone
C. Anti-dsDNA
D. Anti-U1 RNP

✅ **Answer: B. Anti-histone**
*Explanation*: Anti-histone seen in 75–95% of DIL cases.

**Q7.**
Which biologic is FDA-approved for SLE?
A. Rituximab
B. Belimumab
C. Abatacept
D. Tocilizumab

✅ **Answer: B. Belimumab**

*Explanation*: Anti-BLyS monoclonal antibody, approved for SLE and lupus nephritis.

Q8. A 30-year-old woman with known SLE presents with recurrent miscarriages at 12–14 weeks. She is ANA+, Anti-dsDNA–, anticardiolipin antibody +, lupus anticoagulant +.
Which is the best prophylactic therapy during next pregnancy?

A. Warfarin throughout pregnancy
B. Low-dose aspirin + prophylactic low-molecular-weight heparin
C. Prednisolone + azathioprine
D. Hydroxychloroquine alone

☑ **Answer: B. Low-dose aspirin + prophylactic LMWH**

*Explanation*: Standard of care for obstetric APS associated with SLE.

## Rapid fire - SLE

- **2019 EULAR/ACR entry criterion for SLE?**
  → ANA ≥1:80.
- **Most specific antibody for SLE?**
  → Anti-Smith.
- **Antibody most associated with lupus nephritis?**
  → Anti-dsDNA.
- **Class IV lupus nephritis histology?**
  → Diffuse proliferative GN (most severe, commonest).
- **Lupus anticoagulant effect in vitro?**
  → Prolongs aPTT, not corrected by mixing study.

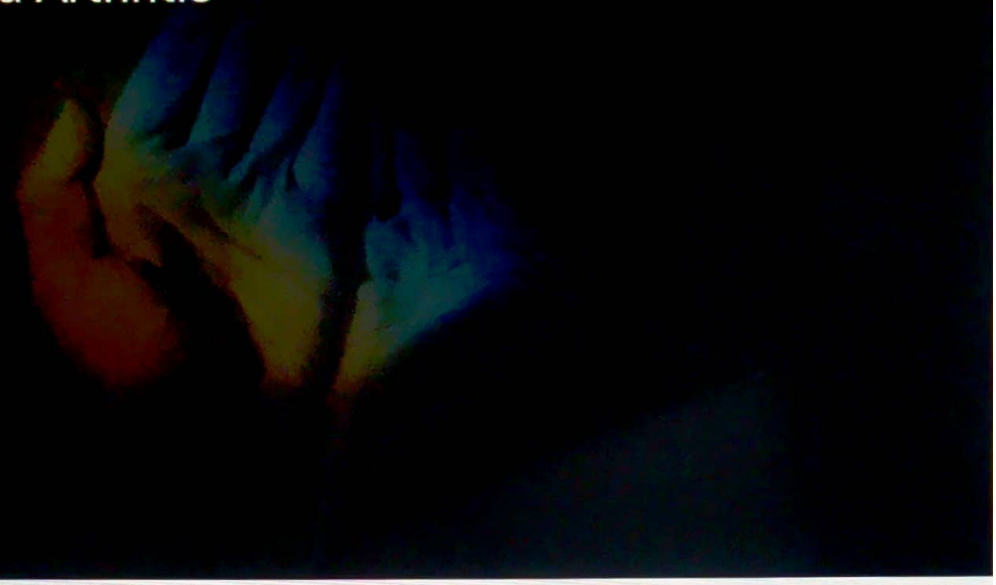
## Rapid Fire Lupus

- **Most common cause of death in long-standing SLE?**
  → Cardiovascular disease (accelerated atherosclerosis).
- **Drug-induced lupus most commonly caused by?**
  → Procainamide > hydralazine.
- **Antibody hallmark of DIL?**
  → Anti-histone.
- **Neonatal lupus antibodies?**
  → Anti-Ro (SSA), Anti-La (SSB).
- **Lupus nephritis treatment induction (Class III/IV)?**
  → High-dose steroids + cyclophosphamide or mycophenolate. + CNI

## Rapid Fire - Lupus

- **FDA-approved biologic for SLE?**
  → Belimumab (anti-BLyS).
- **Drug that must be continued lifelong in SLE (unless contraindicated)?**
  → Hydroxychloroquine.
- **Mortality in early SLE mostly due to?**
  → Infections.
- **Histone antibodies in idiopathic SLE vs DIL?**
  → Seen in both, but **very high prevalence in DIL (>90%)**

# Rheumatoid Arthritis



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# What is new

What is new in the Harrison's 22nd Edition of internal medicine

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Consider this as an add on the existing content to the chapter



**FIGURE 370-1 Metacarpophalangeal joint swelling and subluxation.** *(Reproduced with permission from RP Usatine, MA Smith, EJ Mayeaux: The Color Atlas and Synopsis of Family Medicine, 3rd ed. New York, McGraw Hill, 2019; Fig. 97.5.)*

## Rheumatoid Arthritis – Onset & Early Features

- **Incidence**: rises age 25–55, plateaus → ↓ after 75
- **Presenting symptoms**:
  - Early morning stiffness >1 h (improves with activity)
  - Small joints of hands & feet → earliest involved
- **Patterns**:
  - Monoarticular / oligoarticular (≤4) / polyarticular (>5)
  - Usually symmetric
- **Undifferentiated inflammatory arthritis** → higher risk for RA if:
  - Many tender/swollen joints
  - RF or ACPA positive
  - High disability scores

## Rheumatoid Arthritis – Established Disease

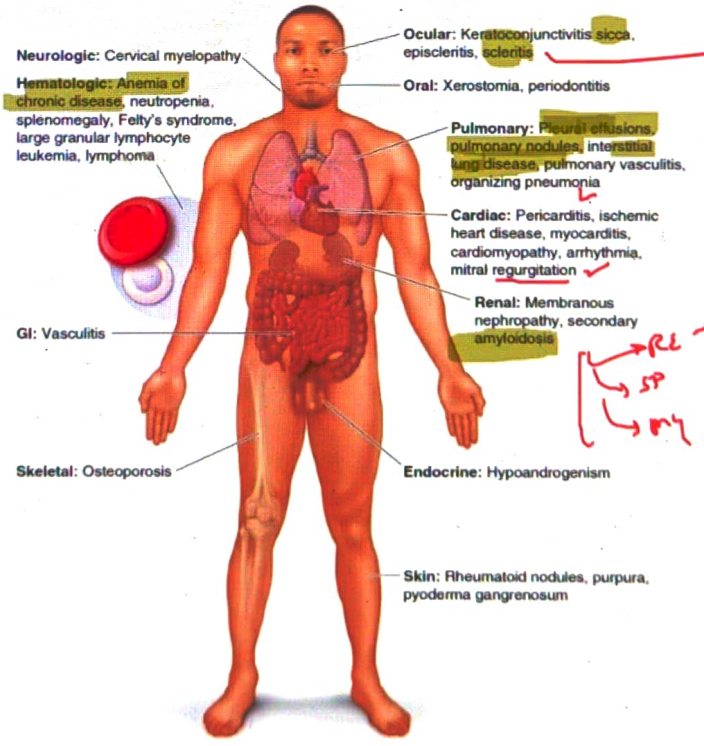
- **Commonly involved joints**: wrists, MCP, PIP
- **Flexor tendon tenosynovitis** → ↓ ROM, weak grip, trigger fingers, possible rupture (esp. flexor pollicis longus)
- **Deformities**:
  - **Ulnar deviation** (MCP subluxation)
  - **Swan-neck** (PIP hyperextension + DIP flexion)
  - **Boutonnière** (PIP flexion + DIP hyperextension)
  - **Z-line deformity** (1st MCP subluxation + 1st IP hyperextension)
  - **Piano-key sign** (ulnar styloid subluxation)

## Rheumatoid Arthritis – Foot & Large Joints

- **MTP joints** → early involvement
- **Chronic ankle/midtarsal disease** → pes planovalgus (flat feet)
- **Large joints** (knees, shoulders) → affected later, often silent for years

# Rheumatoid Arthritis – Cervical Spine Involvement

- **Atlantoaxial subluxation (C1–C2)**
  - Risk: compressive myelopathy, neurologic dysfunction
  - Symptoms: evolve slowly (rarely presenting feature)
  - Prevalence now <10% (declining with modern therapy)
- **Spinal involvement**
  - Rare in thoracic/lumbar spine (vs spondyloarthritides)




2 **Extraarticular manifestations** of rheumatoid arthritis.

## Rheumatoid Arthritis – Extraarticular Manifestations

- Occur in **≤40%** (sometimes before arthritis onset)
- **Risk factors**: smoking, early disability, RF/ACPA positivity
- **Common features**:
  - Subcutaneous nodules
  - Secondary Sjögren's disease
  - Interstitial lung disease (ILD)
  - Pulmonary nodules
  - Anemia of chronic disease
- **Declining incidence**: Felty's syndrome, vasculitis

## Rheumatoid Arthritis – Subcutaneous Nodules

- Seen in **30–40%** of patients
- More common with:
  - High disease activity
  - **Shared epitope (SE)** positivity
  - Positive **RF**
  - Radiographic erosions
- **Prevalence declining** (early aggressive DMARD therapy)

## Rheumatoid Arthritis – Features of Nodules

- **Clinical**: firm, nontender, adherent to periosteum/tendons/bursae
- **Sites**: trauma/pressure areas → forearm, sacrum, Achilles tendon
- **Other locations**: lung, pleura, pericardium, peritoneum
- **Complications**: infection, ulceration, gangrene
- **Methotrexate**: accelerated nodulosis in ~10% with long-term use

# Rheumatoid Arthritis – Pulmonary Manifestations

- **Pleuritis** → most common
  - Symptoms: pleuritic chest pain, dyspnea, pleural rub
  - **Effusion**: exudative, ↑ monocytes/neutrophils
- **Interstitial Lung Disease (ILD)**
  - Symptoms: dry cough, progressive dyspnea
  - **Prevalence**: up to 12% (sometimes precedes joint disease, 3.5%)
  - Risk factors: smoking, high disease activity
  - **Diagnosis**: HRCT (infiltrates, ground-glass opacities)
  - Poor prognosis (but better than idiopathic pulmonary fibrosis)

# Rheumatoid Arthritis – Pulmonary Pathology

- **ILD patterns**:
  - **UIP** → honeycombing (peripheral, lower lungs), progressive scarring
  - **NSIP** → symmetric ground-glass opacities, fine reticulations, volume loss, traction bronchiectasis
  - PFTs: restrictive + ↓ DLCO
- **Pulmonary nodules**
  - Solitary or multiple
  - **Caplan's syndrome**: nodules + pneumoconiosis (silica exposure)
- **Other**: respiratory bronchiolitis, bronchiectasis

# Rheumatoid Arthritis – Cardiac Involvement

- **Pericardium = most frequent site**
  - Clinical pericarditis in **<10%**
  - **Silent pericardial disease** in ~50% (echo/autopsy)
  - Up to **20%** → asymptomatic pericardial effusions (echo)