

The Clinical Approach to Rheumatic Patients

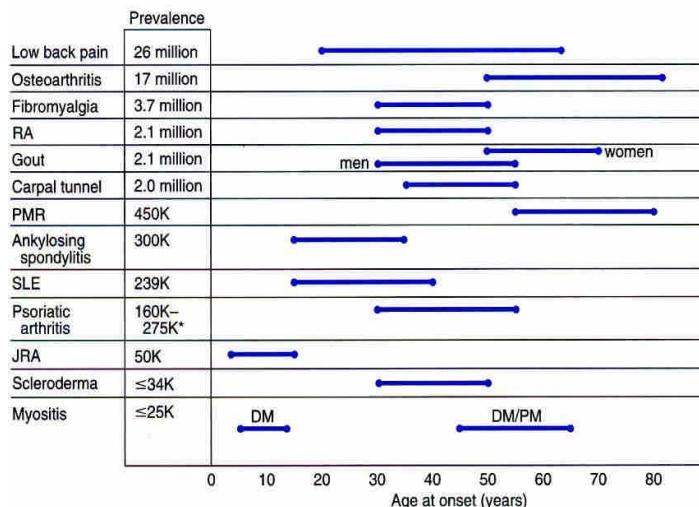
- **Recognize the urgent rheumatological conditions: "Red Flag" symptoms and signs. One should not miss diagnoses because delayed recognition may cause permanent disability and death.**
 1. Infection (septic arthritis, sepsis, osteomyelitis, necrotizing fasciitis)
 2. Acute crystal-induced arthritis (e.g. gout)
 3. Systemic vasculitis and arterial thrombosis
 4. Acute myelopathy and spinal cord compression
 5. Fracture, anterior compartment syndrome, tumor
- **Initial approach:** thorough history taking and physical examination.
- **The goals of the initial encounter are to determine whether the musculoskeletal complaint is :**
 1. Articular or nonarticular disorders
 2. Inflammatory or non-inflammatory arthritis
 3. Acute or chronic arthritis
 4. The distribution of complaint: localized or widespread, symmetric or asymmetric.

(A) History taking

A thorough history taking is most important part of the practice of all kinds of medicine. Providing information on the pathologic process, it is also most important skill needed in rheumatology for clinical diagnosis, disease activity evaluation, and differential diagnosis.

1. Joint pain
 - (a) **Character of pain (what):** For example, vascular origin causes throbbing pain. Describe the subjective quality and quantity of pain.
 - (b) **Location (where):** **upper limb** involvement in RA; **lower limb** involvement in spondyloarthropathy and gout; **Involvement of the axial skeleton** in osteoarthritis and ankylosing spondylitis, and infrequent in RA (except the cervical spine)
 - (c) **When and why:** use-related pain in OA and spinal stenosis (extending the spine while walking downhill for spinal stenosis); peri-articular problems usually are induced by a specific type of activity; constant severe pain may indicate a bone disorder; pain caused by inflammation is usually worse at the end of the day with stiffness.
 - (d) **Swelling and prolonged morning stiffness (> 1 hour):** indicating inflammatory arthritis.
 - (e) **Duration of arthritis:** **brief arthritis** (palindromic rheumatism, crystal- induced arthritis) or **sustained (chronic) arthritis** (more than 6 weeks for RA).
 - (f) **Number of joint involvement:** monoarthritis, oligoarthritis (2-4 joints), polyarthritis (more than 4 joints), see below for differential diagnosis.
 - (g) **Distribution of arthritis:** **symmetric** for RA and SLE; **asymmetric** and additive for spondyloarthropathy.
 - (h) **Chronology:** Onset (Abrupt or indolent); evolution (acute, chronic or intermittent).
2. Symptoms of connective tissue diseases: oral ulcer, hair loss, skin rash, arthralgia, and seizure for SLE; dry eye and dry mouth for Sjögren's syndrome; proximal muscle weakness for polymyositis.
3. Drug history: including previous and current drug intake, medication compliance, and history of alternative or complimentary medicines; a clear drug history is important for evaluation of disease activity and therapeutic decision; the flare of rheumatic diseases is frequently caused by interruption of medication after seeking alternative therapy.
4. The review of systems:
 - (1) Very helpful for differential diagnosis of many rheumatic diseases due to the association of specific presentation patterns with different diseases; some presentations are even parts of classification criteria of diseases.
 - (2) Presence of any constitutional features: **Fever, anorexia, weight loss, weakness** and **fatigue** are generally associated with the active inflammation process; fatigue is an important feature of most generalized rheumatic diseases and may be a good indicator of disease activity of RA and SLE; fever in SLE patients may indicate disease flare or infection; weakness is also present with polymyositis.
 - (3) Asking systemic symptoms at present and in the past: (a) **Photosensitivity and hair loss** in SLE. (b) **Skin rash** in SLE, psoriatic arthropathy, dermatomyositis, erythema nodosum and hypersensitivity. (c) **Mucosal (Oral and genital) ulcers** in SLE, spondyloarthropathy (painless ulcer), and Behçet's disease (painful ulcer). (d) **Raynaud's phenomenon** in SLE, scleroderma, MCTD. (e) **Heel pain** (pain of Achilles tendon) for spondyloarthropathy. (f) Preceding **diarrhea** or **UTI symptoms** for Reiter's syndrome. (g) **Eye inflammation**

also occurs in Behçet's disease, sarcoidosis. (h) ***Emotional liability*** and any ***neuropsychiatric disturbance*** in SLE. (i) Symptoms of ***nervous systems*** in Lyme disease, SLE, vasculitis and Behçet's disease.



5. Age and gender: Gout and hyperuricemia rarely happen in young female before menopause.
6. History of infection: arthritis associated with viral infection (e.g. hepatitis viral infection mimicking RA, but not lasting more than 3 weeks); Lyme disease with skin lesion after recent travel; reactive arthritis followed by UTI after sexual exposure; the possibility of HIV infection; any history suggesting infective endocarditis which can mimic SLE; throat symptoms for rheumatic fever; **Try to identify any sign of infection in immunocompromised patients with rheumatic diseases.**
7. Past history of other systemic diseases: Increased incidence of hyperuricemia and gouty arthritis in the elderly with heart failure treated with diuretic; increase in the possibility of infective arthritis in DM patients; asthma and chronic sinusitis for Churg-Strauss syndrome and Wegener's granulomatosis, respectively.
8. Family history: heritable HLA-B27 gene in family member with spondyloarthropathy; family aggregation in connective tissue diseases and rheumatoid arthritis.
9. Other important history: social and occupational history; heavy smoking history for Buerger's disease and Raynaud's phenomenon; alcohol intake for gout attack; history suggesting extra-articular manifestations

Age	Young: SLE, rheumatic fever, Reiter's syndrome Middle age: fibromyalgia, RA Elderly: OA, polymyalgia rheumatica
Sex	Men: gout, AS, Reiter's syndrome Women: SLE, RA, fibromyalgia
Race	Whites: polymyalgia rheumatica, giant cell arteritis, Wegener's granulomatosis Blacks: sarcoidosis, SLE
Familial aggregation	AS, gout, RA, SLE, Heberden's node of OA
Chronology	<p>(a) Onset</p> <ul style="list-style-type: none"> • Abrupt: septic arthritis, gout • Indolently: OA, RA, fibromyalgia <p>(b) Evolution</p> <ul style="list-style-type: none"> • Acute (last less than 6 weeks): septic arthritis • Chronic (more than 6 weeks): OA, RA • Intermittent: gout • Migratory: rheumatic fever, gonococcal or viral arthritis • Additive: RA, Reiter's syndrome <p>(c) Causes</p> <ul style="list-style-type: none"> • Acute or intermittent: infectious, crystal-induced, reactive • Chronic: non-inflammatory, immune-related arthritis

(B) Physical Examination

1. General physical examination: thorough physical examination is absolutely important for differential diagnosis. Some common clinical signs in rheumatic diseases includes anemia (represent chronic inflammation)

- (1) Skin lesions: psoriatic skin lesion, nail hyperkeratosis.
- (2) Neurological examination

2. Musculoskeletal examination:

(1) Identify any joint abnormality

- (a) Inspection: (i) Swelling: could be caused by intra-articular effusion, synovial thickening or peri-articular soft tissue inflammation (bursitis or tendonitis). (ii) Skin redness (diffuse in synovitis, whereas possibly focal redness in spondyloarthropathy). (iii) Deformity. (iv) Observing posture, the stance and gait from the front, the behind and the lateral side.
- (b) Palpation: (i) Warmth: usually indicates for inflammatory arthritis. (ii) Tenderness: location of tenderness determines the pathologic site is intra-articular or peri-articular (such as enthesitis). (iii) Swelling with synovial effusion: bulge sign at knee; differential diagnosis from synovial hypertrophy or bony hypertrophy. (iv) **Joint crepitus**: fine crepitus indicated roughening of cartilage in chronic inflammatory arthritis, whereas coarse crepitus can be caused by OA or inflammatory arthritis. DD from sound caused by slipping of tendon over bone, such as tendon friction rub in scleroderma. (v) Bursal effusion: overlie bony prominences and are fluctuant with sharply defined border. (vi) **Joint stability**: palpation and application of manual stress to reveal ligament deficiency, Subluxation and dislocation.
- (c) Movement: passive and active movement, and against resistance; identify any limitation of motion.
- (d) The nature of joint abnormality: (i) **Deformity**: long-standing or aggressive pathologic process; ligamentous destruction, soft tissue contracture, bony enlargement, ankylosis, erosive disease, or subluxation. (ii) **Contracture**: antecedent synovial inflammation or trauma.
- (e) Examination of each joint: (i) **Hand and foot joints**: flexion (make a fist) and finger extension (prayer sign); “squeeze test” to elicit tenderness in inflammatory arthritis; identifying “sausage digit”, deformity, and nodule; examining muscle power. (ii) **Wrist**: flexion and extension (normal 60-90°); crepitus over carpometacarpal joint of the thumb in OA; swelling due to tenosynovitis; synovitis palpable over the dorsal surface. (iii) **Elbow** flexion (normal 145°) and extension. (iv) **Shoulder**: elevation, abduction/lateral rotation (hands behind head), extension/internal rotation (hands behind back), glenohumeral external rotation, glenohumeral abduction, glenohumeral flexion, palpation of acromoclavicular and glenohumeral joints. (v) **TM joint**: mouth opening (measure the distance between tips of upper and lower incisor teeth) and side-to-side movement of jaw. (vi) **Cervical spine**: right and left rotation, flexion and extension, and right and left lateral flexion. (vii) **Dorsal spine**: right and left rotation, Occiput-wall distance (for ankylosing spondylitis). (viii) **Lumbar spine**: flexion and lateral movement and overall spinal movement; Schober's test and finger-floor distance in ankylosing spondylitis), right and left flexion, lumbar extension; test for Sciatica (SLRT, Straight leg raise test); test for cruralgia (femoral nerve stretch test). (ix) **Hip**: check flexion, extension, abduction, adduction, internal and external rotations, and circumduction; Patrick's test for hip lesions or sacroiliitis, tenderness for trochanter bursitis. (x) **Knee**: bulge sign for synovial effusion as small as 4-8 ml; localized tenderness for bursitis or enthesitis; identify Baker's cyst from behind; valgus and varus stress and drawer test for ligamentous instability. (xi) **Ankle**: palpate fullness over the anterior and anterolateral aspects for effusion; DD synovitis from tenosynovitis

(3) Other maneuvers for non-articular abnormalities

- (a) Carpal tunnel syndrome: Median nerve irritability may be demonstrated by (1) Tinel's sign, which involves tapping over the palmar aspect of the carpal tunnel, or (2) Phalen's maneuver, which requires flexion of the wrist causing increased pressure within the carpal tunnel.
- (b) Trigger points associated with fibromyalgia.
- (c) Examine muscle power.

(C) Approach to Arthritis

◆ **Classification of arthritis**

- (1) **Acute or chronic**: duration less or more than **6 weeks**.
- (2) **Adult or juvenile arthritis**: **16 years old**
- (3) **Monoarthritis, oligoarthritis** (involving 2, 3 or 4 joints), or **polyarthritis** (5 or more than 5 joints).
- (4) **Inflammatory or non-inflammatory**
- (5) **Symmetric or asymmetric** polyarthritis

1. Distinguish between articular and non-articular problems

* Pain from monoarticular structures may mimic true articular pain.

<i>Articular structures</i>	<i>Non-articular (Periarticular)</i>
Synovium, synovial fluid, articular cartilage, intra-articular ligaments, joint capsule, and juxta-articular bone	Supportive extra-articular ligaments, tendons, bursae, muscle, fascia, bone, nerve, and overlying skin
<ul style="list-style-type: none"> ▪ Deep or diffuse joint pain ▪ Limited range of motion on active and passive movement ▪ Swelling caused by synovial proliferation or effusion or bony enlargement. ▪ Crepitus, instability, locking, or deformity 	<ul style="list-style-type: none"> ▪ Painful on active but not passive range of motion. ▪ Point or focal tenderness in regions distinct from articular structures. ▪ Physical findings remote from the joint capsule ▪ Seldom demonstrate crepitus, instability, deformity, or swelling.

Non-articular causes: *tendinitis, bursitis, fibromyalgia, myalgia*.

2. Distinguish between inflammatory and non-inflammatory arthritis

- (1) **Causes of Inflammatory disorder:** **Infection** (Neisseria gonorrhoea or Mycobacterium tuberculosis); **Crystal-induced** (gout or pseudogout); **Immune-related:** RA, SLE; **Reactive** (rheumatic fever, Reiter's syndrome); **Idiopathic.**
- (2) **Causes of non-inflammatory disorder:** **Trauma** (rotator cuff tear); **Ineffective repair** (OA); **Cellular overgrowth** (pigmented villonodular synovitis); **Pain amplification** (fibromyalgia).

	<i>Inflammatory disorders</i>	<i>Non-inflammatory disorders</i>
<i>Joint stiffness and pain</i>	<i>Morning stiffness (last more than 60 min)</i> <i>Precipitated by prolonged rest</i> <i>Improve with activity and anti -inflammatory medications</i>	<i>Intermittent stiffness (lasts less than 60 min)</i> <i>Precipitated by brief periods of rest</i> <i>Exacerbated by activity</i>
<i>Inflammatory signs</i>	<i>Redness, warmth, pain, and swelling of painful joints</i>	<i>No inflammatory signs</i>
<i>Constitutional symptoms</i>	<i>Prolonged morning stiffness, fatigue, fever, weight loss.</i>	<i>No constitutional symptoms</i>
<i>Laboratory abnormality</i>	<i>Elevated ESR and/or CRP ; thrombocytosis; anemia of chronic disease; hypoalbuminemia</i>	<i>Normal laboratory test</i>

3. Distinguish between monoarthritis, oligoarthritis, and polyarthritis

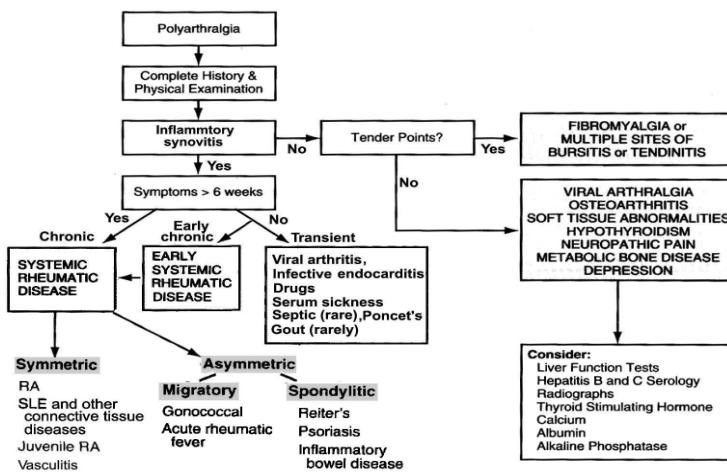
<A> Monoarthritis

1. **Acute monoarthritis:** the common causes are non-inflammatory causes (Bursitis, Tendinitis), Septic arthritis, Gout, Pseudogout (CPPD deposition), Hemarthrosis, or acute presentation of seronegative spondyloarthropathy (e.g. Reiter syndrome or reactive arthritis)
2. **Subacute or chronic monoarthritis:** the common causes TB arthritis, Osteoarthritis, Trauma, Juvenile chronic arthritis, Malignancy, rarely Rheumatoid arthritis (usually polyarthritis)
3. **Duration of arthritis:** spontaneous remission in several days suggests palindromic rheumatism; crystal-induced arthritis usually last for about one week. The duration of arthritis in reactive arthritis varies from weeks to months.
4. Initial evaluation with **radiography** and **joint ultrasonography** is convenient and useful for differential diagnosis. May also require **synovial fluid aspiration** and examination, including identification of **crystals** by polarizing microscopy and **bacterial cultures**. **Arthroscopy** and **synovial biopsy** may be needed for subacute/chronic monoarthritis.

 Oligoarthritis and polyarthritis

1. Non-inflammatory: osteoarthritis, tendon-itis, bursitis, hypertrophic osteoarthro- pathy, and fibromyalgia.
2. Inflammatory: Spondyloarthropathy, RA, connective tissue diseases, viral infection, JRA, drug-induced arthritis; Lyme disease; vasculitis; infective endocarditis; un- commonly crystal-induced arthritis and septic arthritis (which usually involve one joint).
3. Other clinical features may help further differential diagnosis (see table on the right side).
4. Polyarthritis can be **sustained, chronic (more than 6 week, e.g. RA and SLE)** or **brief, transient** (e.g. hepatitis virus- induced arthritis for 3 weeks). The flow chart on the next page may be useful for differential diagnosis of some common causes of polyarthritis. Check textbook for other uncommon causes.

Acute monoarthritis		SELECTED CAUSES OF CHRONIC MONOARTHRITIS	
Infectious		Infectious arthritis	
Bacterial		Mycobacterial, fungal, bacterial, viral, Lyme disease	
Neisserial (may be preceded by transient polyarticular disease)		Inflammatory arthritis	
Mycobacterial		Crystal induced	
Virus	Lyme disease	Monoarticular RA	
Crystal induced	Gout	EOPA-JCA	
	CPPD (pseudogout type)	Seronegative spondyloarthropathies (ankylosing spondylitis, reactive arthritis, inflammatory bowel disease arthritis, undifferentiated)	
	Hydroxyapatite (acute calcific periarthritis)	Psoriatic arthropathy	
Traumatic		Foreign body synovitis (e.g. plant thorn synovitis)	
Palindromic rheumatism		Sarcoidosis	
Psoriatic arthropathy			
Reactive arthritis			
Bacterial endocarditis			
Major Diagnostic Features of Joint Disorders		Noninflammatory arthritis	
Mode of onset : acute or insidious		Osteoarthritis	
Duration of symptoms		Internal derangement	
Self-limiting or chronic		Osteonecrosis	
Number of affected joints		Synovial osteochondromatosis	
Monoarthritis, oligoarthritis, or polyarthritis		Reflex sympathetic dystrophy	
Distribution of joint involvement		Hemarthrosis (e.g. coagulopathy, anticoagulants)	
Symmetric or asymmetric		Neuropathic (Charcot's joint)	
Localization of affected joints		Stress fracture	
Axial or peripheral, or both		Transient regional osteoporosis	
Sequence of involvement		Juvenile osteochondroses	
Additive, intermittent or migratory			
Local pattern of involvement (in individual joints)			
		Tumors	
		Pigmented villonodular synovitis (PVNS)	
		Lipoma arborescens	
		Synovial metastasis from solid tumors	
		Synovial sarcoma	
Undiagnosed			
		EOPA-JCA = Early onset pauciarticular juvenile chronic arthritis	



4. Distinguish between symmetric and asymmetric polyarthritis

- Basically, arthritis is symmetric for RA and asymmetric for spondyloarthropathy. But early RA could have asymmetric arthritis, which progresses into symmetric pattern (So, it may takes some time to have a clue about the diagnosis).
- The following table may be useful in making differential diagnosis for common rheumatic diseases.

CHARACTERISTIC DISTRIBUTION OF JOINT INVOLVEMENT						
Diagnosis	Symmetry	Number of joints involved*	Large/small joints	Peripheral/central distribution	Upper/lower limb	Predilection
Rheumatoid arthritis	Symmetrical	Mono/oligo/polyarthritis	Large/small	Peripheral	Upper/lower	MCPs, PIPs, MTPs, DIPs
Ankylosing spondylitis				Central		Sacroiliac joints, hip, shoulder
Psoriatic arthritis	Asymmetrical	Polyarthritis	Large/small	Peripheral	Upper/lower	DIPs, sacroiliac joints
Reactive arthritis	Asymmetrical	Oligo/polyarthritis	Large	Peripheral	Lower	Sacroiliac joints, DIPs (toes)
Gout	Asymmetrical	Mono/oligoarthritis	Large/small	Peripheral	Lower > upper	1st MTP, knee, hip

(D) Specific organ involvement in rheumatic diseases

<1> Cutaneous lesions in rheumatic diseases

- The skin is the most accessible organ and often provides valuable diagnostic clues leading to a specific diagnosis or limiting the list of possible diagnosis. Conversely, unrelated skin lesions may occasionally mislead the clinician.

- **Exanthem:** diffuse rash with fever and systemic symptoms; Still's disease, SLE, Lyme disease, rheumatic fever; DD from viral infection, drug eruption, allergic reaction, angioimmunoblastic lymphadenopathy, and meningococcemia.
- **Annular lesions:** skin lesions in which the central portion has a distinctive appearance compared with the border; occurs in rheumatic fever, SCLE and Lyme disease (erythema migrans).
- **Papulosquamous lesions:** (1) psoriatic arthritis (DIP joint synovitis; erythematous scaling plaques over extensor surfaces of elbows and knees, the scalp, ears and presacral area; nail pitting) (2) Reiter's syndrome (keratoderma blennorrhagica) (3) Lupus erythematosus (subacute and discoid) (4) DD from Lichen planus and pityriasis rosea.
- **Nontender cutaneous and subcutaneous nodule:** (1) **Rheumatoid nodule** (firm, flesh colored, and movable or fixed), (2) **Rheumatic fever** (firm lesions in areas of pressure, usually less than 1cm and shorter-lived with the average duration of 4-6 days, and rarely longer than 1 month). (3) **Crystal deposition diseases** (asymmetry, DIP joint involvement, involvement of the helix of the ear, origin at the joint margin, yellow appearance, overlying erythema).

Types of Cutaneous Lesions Observed in Rheumatic Disorders

Disorder	Lesion type	Macules/papules	Palpnodular	Vesicular/bullous	Pustular	Ulcerating	Patchy/purpura
Primary immune disease							
Systemic lupus erythematosus	•	•	•		•		•
Scleroderma		•			•		
Dermatomyositis	•	•			•		•
Rheumatoid arthritis		•			•		•
Still's disease	•						
Sjögren's syndrome					•	•	
Erythema nodosum		•					
Pyoderma gangrenosum		•		•	•		
Sarcoid	•	•					
Inflammatory bowel disease	•	•	•	•	•		•
Psoriatic arthritis	•			•			
Reiter's syndrome	•			•			
Behçet's syndrome	•	•	•	•	•		•
Multicentric reticulohistiocytosis	•	•					
Serum sickness	•						•
Neutrophilic dermatoses	•	•	•	•	•		
Kawasaki disease	•			•			
Necrotizing venulitis	•	•	•		•		•
Polyarteritis nodosa	•	•	•		•		•
Wegener's granulomatosis	•	•	•		•		•
Lymphomatoid granulomatosis	•	•			•		
Infections							
Neisserial infections		•		•	•	•	
Rheumatic fever		•	•				
Subacute bacterial endocarditis			•				
Hydradenitis suppurativa/acne conglobata			•		•		
Syphilis		•	•		•	•	
Lyme disease		•			•		
Rickettsial infections		•					•
Viral infections		•		•	•		
Fungal infections			•			•	
Mycobacterial infections			•			•	
Other conditions							
Diabetes mellitus			•	•	•	•	
Thyroid disease		•	•	•	•	•	
Hyperlipidemia (Type II)			•				
Crystal disease			•				
Neoplasms	•	•			•		•

- **Red and tender subcutaneous nodules:** (1) **Panniculitis, arteritis, atypical infections and metastatic tumor.** (2) **Erythema nodosum** (lesions are red or violet subcutaneous nodules, 1-5cm in diameter, without associated epidermal abnormalities with the pathological finding of septal panniculitis without vasculitis; pretibial locations and resolve spontaneously over several weeks without ulceration or scarring; accompanied by acute polyarthralgia or arthritis; occur in sarcoidosis, or inflammatory bowel disease, Behçet's disease, the effects of drugs (sulfa, birth control pills), pregnancy and infections.
- **Nonpalpable purpura:** thrombocytopenia; primary amyloidosis; reduced integrity of supportive connective tissue in corticosteroid therapy; and vessel thrombosis or nonseptic emboli such as thrombotic thrombocytopenic purpura, antiphospholipid syndrome, cholesterol emboli and infective endocarditis.
- **Palpable purpura:** (1) **Vasculitis:** usually over the buttock or lower extremities; leukocytoclastic vasculitis or necrotizing vasculitis with hemorrhage and infarction. (2) Other causes: ecthyma gangrenosum (Gram-negative bacterial infection with erythematous wheals or papules with irregular areas of purpura followed by necrosis and ulceration).
- **Pustular skin lesions:** pustular vasculitis, Sweet's syndrome (acute febrile neutrophilic dermatosis), Behçet's syndrome, inflammatory bowel disease (bowel-associated dermatosis-arthritis syndrome with episodic painful cutaneous pustules on a purpuric base), pustular psoriasis, keratoderma blennorrhagica (in soles and palms), disseminated pustular lesions (meningococcemia, disseminated herpes viral infections, and reactions to drugs).
- **Vesicle eruptions in SLE:** (1) Generalized bullous eruption: in normal appearing or erythematous skin; pemphigoid-like, not pruritic; DD from pemphigus or pemphigoid, dermatitis herpetiformis (pruritic), necrotizing vasculitis, ecthyma gangrenosum and DIC, erythema multiforme, varicella or herpes viral infections. (2) Blistering in areas of photosensitive dermatitis; DD from the rash of porphyria cutanea tarda.
- **Ulcers of lower extremity:** vasculitis, pyoderma gangrenosum (in RA, inflammatory bowel disease, Behçet's syndrome, Wegener's granulomatosis, or paraproteinemia patients), pressure sores, infection and vascular insufficiency.
- **Painful oral ulcers:** round to oval ulcers with discrete borders predominantly on mucosa in **Behçet's disease** or **Crohn's disease**; recurrent intraoral **herpes** which tend to be present upon the hard palate and gingiva. DD from

erythema multiforme.

- **Painless oral ulcers:** commonly located upon the palate or dorsum of the tongue with irregular border in **Reiter's syndrome**; usually painless or slight painful in **SLE**.
- **Periungual telangiectases** and **mat telangiectases** (broad, oval or polygonal macules 2-7mm in diameter and found on the face, mucous membranes and hands) in **scleroderma**.

<2> Cardiac involvement

- **Pericarditis:** **SLE** (25% at some time during the course; possibly large pericardial effusions with or without symptoms); common in **Still's disease**; less frequently in **RA** and **scleroderma**. Tamponade or constrictive pericarditis are uncommon, but RA with positive RA factor and extraarticular manifestation is at risk of developing chronic constrictive pericarditis.
- Constrictive pericarditis with mild dyspnea in RA.
- **Infective endocarditis:** (1) Higher incidence in SLE patients. (2) Can also be seen in patients with AS (aortitis and aortic insufficiency) and RA. (3) Antibiotic prophylaxis is suggested.
- Increased risk for coronary artery disease: autoimmune diseases (especially SLE) treated with steroid.
- Echocardiography: (1) most useful for detecting pericarditis with pericardial effusion, (2) not useful for determining the thickness of the pericardium (CT scan or MRI are useful) for constrictive pericarditis or chronic symptomatic pericarditis.(3) Detecting valvular vegetation and disorders. (4) Pulmonary artery pressures for pulmonary hypertension can be estimated.
- Nonspecific ST-T changes on EKG can be seen in rheumatic diseases. Standard exercise ECG testing has a lower sensitivity and specificity in patients with rheumatic diseases.
- Rheumatic Fever:

<3> Pulmonary involvement in rheumatic diseases

- **Pleuritis:** usually moderate and intermittent pain of pleurisy; localized or migratory; **SLE** (usually small and resolve with either corticosteroid treatment or the passage of time); **pulmonary embolism** (with dyspnea) in antiphospholipid syndrome; **RA** (20%; most mild pleuritic pain, usually early in the course); **Still's disease** (during the acute, toxic phase); **vasculitis** (especially Wegener's granulomatosis); occasionally in **scleroderma**; DD from **infection**.
- **Dyspnea:** (1) May be due to lung disease, heart disease, **severe anemia** (e.g. hemolytic anemia), muscle weakness or severe deconditioning in the rheumatic diseases. (2) **SLE:** probably diaphragmatic weakness, interstitial pneumonitis, pulmonary fibrosis, pulmonary hypertension (associated with Raynaud's phenomenon or thrombosis in **antiphospholipid syndrome**), pulmonary hemorrhage (3) **RA:** Dyspnea is an indication of serious underlying disease; caused by large pleural effusions or rheumatoid lung disease (inflammatory interstitial infiltrate or progressive pulmonary fibrosis (10% of seropositive RA)).(4) **Scleroderma:** interstitial pneumonitis and pulmonary fibrosis (diffuse type), pulmonary hypertension (limited type); dyspnea due to aspiration. (5) **Polymyositis and dermatomyositis:** weakness of the chest wall and diaphragm (restrictive lung disease); pulmonary fibrosis (with anti-Jo-1). (6) **Sjögren's syndrome:** due to recurrent pulmonary infections.
- Hemoptysis: **Small-vessel Vasculitis** (Wegener's granulomatosis, microscopic polyangiitis, CSS), alveolar hemorrhage in SLE; **infections**
- Tests: **Pulmonary function test** (most commonly restrictive lung disease; reduced vital capacity, and reduced

FREQUENCY OF CARDIAC COMPLICATIONS OF RHEUMATOLOGIC DISEASES		
Disease	Complication	Frequency
Systemic lupus erythematosus	Pericarditis Leaflet fibrosis Libman-Sacks vegetations Mild valve regurgitation Coronary occlusion Myocarditis, cardiomyopathy Pulmonary hypertension	++++ ++++ +++ +++ +++ ++ ++
Rheumatoid arthritis	Leaflet fibrosis Pericardial effusion Coronary occlusion Myocarditis/cardiomyopathy Valve granulomas Mild valve disease	++++ ++++ ++++ ++ + +
Ankylosing spondylitis	Aortic valve disease Subaortic bump Conduction system disease Coronary occlusion Pericarditis Myocarditis/cardiomyopathy Mild aortic regurgitation	++++ +++ +++ +++ ++ ++ ++
Systemic sclerosis	Myocarditis/cardiomyopathy Pulmonary hypertension Pericarditis Coronary occlusion Valve disease	+++ +++ ++ ++ ++
Polymyositis/ dermatomyositis	Myocarditis/cardiomyopathy Pericarditis Pulmonary hypertension	+++ +++ +

FREQUENCY OF PULMONARY COMPLICATIONS OF RHEUMATOLOGIC DISEASES		
Disease	Complication	Frequency
Systemic lupus erythematosus	Pleural effusion Fibrosing alveolitis Acute alveolitis Pulmonary hemorrhage Pulmonary vasculitis	++++ +++ + + +
Rheumatoid arthritis	Pleural effusion Fibrosing alveolitis Necrobiotic nodules Obliterative bronchiolitis Pulmonary vasculitis	+++ +++ + + +
Ankylosing spondylitis	Fibrosing alveolitis	++
Systemic sclerosis	Fibrosing alveolitis	++++
Polymyositis/dermatomyositis	Fibrosing alveolitis	++

- carbon dioxide diffusing capacity (DLCO), and **arterial blood gas** for occasionally hypoxia.
- Pleural effusion: (1) SLE: exudative with lymphocytosis, normal glucose and a low C3 and C4 (compared with blood levels), positive ANA and anti-ds DNA. (2) Rheumatoid arthritis: exudative and serosanguineous with high neutrophil counts ($>200/\text{mm}^3$), high LDH level, low glucose, and low C3 and C4 levels. (3) Bacterial culture and for possible infection.
 - Pleural biopsy can also be useful in patients with RA if nodules are seen.
 - Lung biopsy is rarely indicated.

<4> GI disorders/complication in rheumatic diseases

- Inflammatory joint disease associated with gut: Inflammatory bowel diseases, SLE, systemic vasculitis, scleroderma, amyloidosis, intestinal bypass surgery and in celiac disease, Whipple's disease, and NSAIDs.
- Major symptoms: diarrhea, abdominal pain, and blood loss.
- Distribution of the joint inflammation can be useful to aid differential diagnosis of inflammatory arthritis associated with abdominal symptoms: **peripheral joint involvement** (monoarticular, oligoarticular and polyarticular; with or without tendinitis; see the table below) and **axial inflammation**.
- Abdominal symptoms with monoarthritis, oligoarthritis or axial involvement:** the major cause is HLA-B27-associated spondyloarthropathy (Crohn's disease, ulcerative colitis, enterogenic reactive arthritis and undifferentiated spondyloarthropathy) with asymmetric arthritis of lower limbs and enthesitis.

THE GUT AND ARTHRITIS					
DISORDERS WITH MONOARTICULAR OR PAUCArtICULAR JOINT INVOLVEMENT AND ABDOMINAL SYMPTOMS					
Diagnosis	Abdominal symptoms	General symptoms	Extra-articular features	Relationship between abdominal symptoms and arthritis	
				Onset	Course
Crohn's disease	Diarrhea Abdominal pain Fistulae	Weight loss Ill-being Fever	Erythema nodosum Clubbing Uveitis, conjunctivitis	Usually before arthritis, sometimes coincident or postdated	Flares rarely coincide
Ulcerative colitis	Diarrhea Blood loss	Rare	Erythema nodosum Uveitis	Before arthritis, frequently coincident	Flares directly related
Enterogenic reactive arthritis	Diarrhea Vomiting	Spiking fever Ill-being Dehydration	Uveitis Urethritis	1–4 weeks before arthritis	Longer arthritis duration
Undifferentiated spondyloarthropathies	Rare diarrhea	None	Uveitis Erythema nodosum Urethritis	Arthritis before abdominal symptoms 'subclinical' gut inflammation	Related
DISORDERS WITH POLYARTICULAR JOINT INVOLVEMENT AND ABDOMINAL SYMPTOMS					
Diagnosis	Abdominal symptoms	General symptoms	Extra-articular features	Relationship between abdominal symptoms to arthritis	
Whipple's disease	Diarrhea (steatorrhea) Abdominal pain	Fever Weight loss Lymphadenopathy	Neurologic Dermatologic	Onset	Different
Blind loop syndrome	Abdominal pain Diarrhea	Fever Weight loss	Erythema nodosum Vesicopustulæ Urticaria	Onset	2–30 months after surgery
Celiac disease	Absent in 50% Abdominal pain Steatorrhea	Malaise Weight loss	Osteomalacia	Relationship unknown	
Vasculitic syndromes Henoch-Schönlein (leukocytoclastic vasculitis) Rheumatoid arthritis Systemic lupus erythematosus Polyarteritis nodosa	Abdominal pain Intestinal bleeding Perforation	Disease-related	Purpura Disease-related	No direct relationship	
Scleroderma	Obstipation Abdominal cramps	Disease-related	Disease-related	No direct relationship	

- Abdominal symptoms with polyarthritis:** abdominal symptoms are not prominent in rheumatic diseases with polyarthritis, and they frequently appear as a complication.
 - Vasculitis: the gut is not primarily involved; inflammation of the abdominal (usually mesenteric) arteries and secondary vasculitic lesions in gut mucosal and submucosal layers may arise. For example, GI features of polyarteritis nodosa include abdominal pain, nausea, vomiting, diarrhea, bleeding, ulceration, infarction, and GI perforation; and saccular or fusiform aneurysms and narrowing of abdominal arteries on angiography are of diagnostic importance.
 - Rheumatoid Arthritis: vasculitis (with this complication have high rheumatoid factor titers) causes infarction of intestinal arteries, resulting in abdominal pain, intestinal bleeding or perforation.
 - SLE: abdominal pain and nausea are more common and less often by diarrhea; mainly caused by mesenteric arteritis; perforations may occur.
 - Scleroderma: motility dysfunction of the entire gastrointestinal tract; pseudodiverticula of colon.
 - Behçet's disease: diarrhea and abdominal pain; intestinal ulceration, bleeding and more rarely perforation.
 - Whipple's Disease: probably a form of enterogenic reactive arthritis caused by the infection of a gram-positive

- actinomycete, *Tropheryma whipplii*, which can be stained by PAS and resides in macrophages of the small intestine and in the mesenteric nodes; weight loss, fever, lymphadenopathy, abdominal pain with diarrhea and steatorrhea; non-erosive, symmetric, migratory polyarthritis (transient or chronic, not correlate with GI symptoms). Responds very well to antibiotic treatment, usually with tetracyclines, which have to be continued for more than one year.
- (g) Blind loop syndrome: dermatitis (erythema nodosum, vesicopustular eruptions and urticaria) and non-erosive, symmetric, migratory polyarthritis (frequently over knees and hand joints, may become chronic) in 20%-50% of patients 2-30 months after intestinal bypass surgery, which will resolve after surgical reanastomosis.
- (h) Celiac Disease (gluten-sensitivity enteropathy): associated with abnormal intestinal permeability; mainly polyarticular and symmetric, involving predominantly the large joints, hips, knees and shoulders with negative radiographic changes; striking response of joint manifestations to a gluten-free diet.
6. Long-term NSAID use increases the relative risk for gastric ulcer to 5 and for duodenal ulcer to 1.1, with a combined prevalence of 10-20%

<5> Renal disorders and rheumatic diseases

1. SLE and vasculitis frequently involve kidney,
2. Henoch-Schönlein purpura: nephritis is a source of major morbidity and an important cause of end-stage renal failure in children.
3. Relapsing polychondritis: often crescentic glomerulonephritis, but inconstant. The role of immunosuppressive therapy is unclear.
4. Scleroderma: renal vasoconstriction with diminished renal blood flow and increased filtration fraction is a very early manifestation of scleroderma.
5. Reactive amyloid A is the most important renal complication arising from rheumatologic conditions. It may follow **any inflammatory condition except SLE (and ulcerative colitis)**, but is **particularly common in RA**. It may also complicate **ankylosing spondylitis**. Once amyloid has been deposited within the kidney it does not regress.
6. Crystal-induced arthritis in uremia: (1) **Gouty nephropathy** accounts for 0.5-1.0% of chronic renal insufficiency. (2) Gout rarely attacks in patients with chronic renal failure. **Pseudogout** is more common in patients with chronic or end-stage renal failure (secondary hyperparathyroidism) than in those with true gout. (3) **Periarticular hydroxyapatite deposits** mimics arthritis.
7. Sjögren's syndrome: rarely renal tubular acidosis of minor clinical importance.
8. IgA nephropathy in ankylosing spondylitis. Membranous nephropathy and various forms of nephritis in association with psoriasis.
9. The glomerular lesion in mixed connective tissue disease is usually not severe.
10. Behcet's disease with nephritis is infrequent.
11. Medication and kidney disease: (1) NSAID: nephrotoxicity. Opiate-based preparations such as codeine and its relatives are safe analgesics, but have no anti-inflammatory actions. (2) Penicillamine can induce membranous nephropathy.
12. Septic arthritis is common in patients with end-stage renal disease, and may occur in almost any site. *Staphylococcus aureus* most common. Other causes of joint swelling with effusion in uremic patients: hemarthrosis and β 2-microglobulin arthropathy (non-inflammatory, associated with carpal tunnel symptoms).

<6> Ocular manifestations in rheumatic diseases

Ocular Disorders and Their Frequently Associated Rheumatic Diseases	
Ocular Disorder	Rheumatic Disease
Dry eyes (sicca syndrome)	Rheumatoid arthritis; Primary Sjögren's syndrome; Systemic lupus erythematosus; Scleroderma
Uveitis	
Acute anterior uveitis	Spondyloarthropathies; Inflammatory bowel disease; Behcet's disease
Chronic anterior uveitis	Inflammatory bowel disease; Relapsing polychondritis
Panuveitis	Behcet's disease
Scleritis	Rheumatoid arthritis; Inflammatory bowel disease; Vasculitis, especially Wegener's granulomatosis; Relapsing polychondritis
Keratitis	
Non-necrotizing corneal melt	Sjögren's syndrome; Rheumatoid arthritis
Necrotizing keratitis	Rheumatoid arthritis; Vasculitis
Retinal vasculopathy	
Microvasculopathy	Systemic lupus erythematosus
Diffuse vaso-occlusive disease	Systemic lupus erythematosus; Behcet's disease; Antiphospholipid antibody syndrome
Optic nerve disease	
Ischemic optic neuropathy	Vasculitis, especially giant cell arteritis

<7> Nervous system and muscle involvement in rheumatic diseases

1. Neuropathy: two common causes are **ischemia secondary to vasculitis** and localized **nerve entrapment**.
2. Muscle weakness may be proximal, distal or local:
 - (a) Proximal weakness: usually presents with lower limb symptoms such as difficulty with walking, running,

climbing steps or rising from a low seat; common in ***inflammatory myopathies, metabolic and endocrine myopathies, corticosteroid myopathy and some forms of muscular dystrophy.***

- (b) Distal: predominantly distal muscle wasting and weakness suggests ***peripheral neuropathy or motor neuron disease.***
- (c) Local: wrist drop or foot drop in peripheral neuropathy.
3. Upper motor neuron lesion: increased muscle tone and fasciculation.
4. Many patients with chronic arthritis complain of lethargy or fatigue, muscle wasting or weakness, loss of fine function or coordination and paresthesia or numbness. These symptoms may represent the constitutional effects of chronic inflammatory disease or indicate specific myopathic or neuropathic complications.
5. Patients with chronic rheumatic disease may have associated anemia, cardiac or pulmonary disease, loss of physical fitness or even malnutrition, depression or anxiety, which may account for fatigue or subjective weakness.
6. The weakness of peripheral neuropathy induced by vasculitis may be sudden in onset, reaching maximal severity over hours or days. The weakness of an entrapment neuropathy or a compressive myopathy is usually more gradual, progressing over months or years.
7. Weakness associated with inflammatory muscle disease may present acutely over a number of days, but patients would more usually notice weakness over a period of weeks or months. Inflammatory muscle disease may also progress more insidiously over months or even years.
8. Disorders of the cranial nerves, particularly ophthalmoplegias and involvement of V and VII, are well recognized complications of SLE, systemic sclerosis, mixed connective tissue disease and Sjögren's syndrome.
9. Approach:
- (a) Drug history: NSAIDs (case reports of reversible peripheral neuropathy); excessive intake of colchicine (severe neuropathy and myopathy); Chloroquine (reversible polyneuropathy and myopathy); gold salts (peripheral polyneuropathy and myokymia); D-Penicillamine (polymyositis, dermatomyositis and myasthenia gravis); corticosteroid myopathy (uncommon for less than prednisolone 20mg daily).
- (b) Muscles should be examined for evidence of wasting or hypertrophy, abnormal movement, flaccidity or spasticity, weakness and tenderness.
- (c) Laboratory tests: full blood count and eosinophil count, ESR, CRP, liver function tests, electrolytes, renal function tests, CPK, LDH, chest radiographs, pulmonary function tests, electrocardiograph and thyroid function tests. Measurements of cryoglobulins, antineutrophil cytoplasmic antibodies (ANCA) and hepatitis surface B antigen are required in patients with suggested vasculitis.

Laboratory Investigations for Rheumatic Diseases

- Autoimmune disorders are characterized by the autoantibodies, which can be divided two major groups.

-- **Organ-specific autoantibodies**

1. Anti-thyroglobulin Ab for thyroiditis
2. Anti-islet cell Ab for DM

-- **Organ non-specific autoantibodies**

1. ANA (Anti-Nuclear Antibody)
2. Anti-ds DNA
3. Anti-ENA antibody (anti-Extractable Nuclear Antigen antibody)
 - d. ANCA (Anti-Neutrophile Cytoplasmic Antibody)
4. Rheumatoid factor (RF)
5. Anti-cardiolipin antibody

(1) Autoantibodies

1. Antinuclear antibody (ANA)

- Method: Hep-2 cells or Hep-2000 cells (Hep-2 cells containing transfected gene for the expression of Ro antigen) for indirect immunofluorescence
- Negative** : Normal titer less than 1:40 dilution
- Positive**: see the table below for disease associated with positive ANA; medications associated with positive ANA includes:

Phenytoin	Ethosuximide	Primidone
Methyldopa	Hydralazine	Penecillin
Carbamazepine	Procainamide	Thiazides
Griseofulvin	Chlorpromazine	

Antinuclear Antibody Test	
Condition	Sensitivity (%)*
Drug-induced lupus	100
Systemic lupus erythematosus	99
Scleroderma	97
Sjögren's syndrome	96
Mixed connective tissue disease	93
Polymyositis and dermatomyositis	78
Rheumatoid arthritis	40
Systemic vasculitis	15
Healthy old age	5

*—Percentage of patients with a positive test.

Conditions Associated with positive ANA		
1. Rheumatic diseases		6. Pulmonary diseases
Systemic lupus erythematosus		Idiopathic pulmonary fibrosis Asbestos-induced fibrosis Primary pulmonary hypertension
Polymyositis		
Sjögren's syndrome		
Scleroderma		
Vasculitis		
Rheumatoid arthritis		
	2. Normal, healthy individuals	
	Females > males, prevalence increases with age	
	Relatives of patients with rheumatic diseases	
	? Pregnant females	
		7. Malignancies
		Lymphoma Leukemia
		Melanoma
		Solid tumors (ovary, breast, lung, kidney)
	3. Drug-induced	8. Hematologic disorders
		Idiopathic thrombocytopenic purpura Autoimmune hemolytic anemia
	4. Hepatic diseases	
	Chronic active hepatitis	9. Miscellaneous
	Primary biliary cirrhosis	Endocrine disorders (type I diabetes mellitus, Graves' disease)
	Alcoholic liver disease	Neurologic diseases (multiple sclerosis)
		End-stage renal failure
		After organ transplantation
	5. Chronic infections	

Patterns:

- (1) **Rim (peripheral) pattern**: most specific for SLE
- (2) **Homogenous**: specific for SLE
- (3) **Speckled pattern**: most common, less specific; associated diseases include SLE, MCTD, scleroderma, Sjögren's syndrome
- (4) **Nucleolar Pattern**: scleroderma
- (5) **Diffuse pattern**: non-specific
- (6) **Centromere pattern**: scleroderma

Interpretation:

- (1) Low Positive (<= 1:80): less likely to be significant.
- (2) High Positive (>= 1:160): significant.
- (3) SLE-specific patterns: a peripheral or rim pattern is highly specific and is suggestive of autoantibodies against double-stranded (native) DNA.
- (4) CREST Syndrome and scleroderma-specific Patterns: Nucleolar and centromere pattern
- (5) Non-specific Patterns: speckled and diffuse pattern

Antinuclear antibody specificities in different diseases						
Antibody	Pattern on IF	SLE	PM/DM	Sjogren's syndrome	Systemic sclerosis	MCTD
DsDNA	Homogenous/rim	70-80	<5	<5	<5	<5
Histones	Homogenous	70	<5	<5	<5	<5
Sm	Speckled	30-50	<5	<5	<5	<5
U1RNP	Speckled	40	<5	5	10	100
SS-A/Ro	Speckled	30	<5	60	<5	<5
SS-B/La	Speckled	10	<5	60	<5	<5
Scl-70	Fine speckled	<5	<5	<5	40-60	<5
Nucleolar	Nucleolar	<5	10	<5	45	<5
Centromere	Centromere	<5	<5	<5	40 (70 in limited SSC)	<5

All values are expressed as %, SSc-systemic sclerosis, MCTD - mixed connective tissue diseases, PM/DM - polymyositis/dermatomyositis, dsDNA - double stranded DNA, Sm-Smith.

2. Autoantibodies to specific autoantigens

- Detection of antibodies to specific autoantigens is helpful for clinical diagnosis and the evaluation of disease activity and severity (organ involvement) in connective tissue diseases.
- SLE:** anti-Sm (highly specific); anti-ds DNA (associated with lupus nephritis and lupus CNS Involvement); anti-ribosomal P (associated with psychosis).
- MCTD:** high titer of anti-U1 RNP
- Scleroderma:** Anti-centromere and anti-scl-70 kinetochore (anti-topoisomerase I)
- Polymyositis and dermatomyositis:** anti-Jo-1, anti-SRP, anti-Mi-2.
- Anti-histone, anti-ss DNA, anti-Ro, anti-La are relatively non-specific, although anti-Ro and anti-La are associated with **Sjögren's syndrome**.

DIAGNOSTIC CHARACTERISTICS OF THE ANTNUCLEAR ANTIBODIES

Specificity	ANA Pattern	Primary Rheumatic Disease Associations
Nuclear		
Chromatin-associated antigens		
dsDNA	Rim, homogeneous	SLE
ssDNA	Undetectable	SLE, DILE, RA
Histones		
H1, H2A, H2B, H3, H4	Homogeneous, rim	SLE, DILE, RA, PBC, Scl
H3	Large speckles	SLE, UCTD
Ku	Diffuse-speckled nuclear/nucleolar*	SLE, PM/Scl overlap
PCNA/Ga/LE-4	Nuclear or nucleolar speckles*	SLE
Spliceosomal components	Speckled	
Sm		SLE
U1 snRNP		SLE, MCTD
U2 snRNP		SLE, MCTD, overlap
U4/U6 snRNP		SS, Scl
U5 snRNP		SLE, MCTD
U7 snRNP		SLE
U11 snRNP		Scl
Other ribonucleoproteins		
Ro(SS-A)	Speckled or negative†	SS, SCLE, NLE, SLE, PBC, Scl
La(SS-B/Ha)	Speckled	SS, SCLE, NLE, SLE
Mi-2	Homogeneous	DM
p80-coilin	Speckled	SS
MA-1	Speckled*	SS
Nucleolar		
RNA polymerases	Punctate	
RNAP I	Nucleolar	Scl
RNAP II	Nuclear or nucleolar‡	Scl, SLE, overlap
RNAP III	Nuclear or nucleolar‡	Scl
Ribosomal RNP	Nucleolar, cytoplasmic	SLE
Topoisomerase I (Scl-70)	Diffuse, grainy nuclear or nucleolar spots	Scl
U3 snoRNP (fibrillarin)	Clumpy	Scl
Th snoRNP (RNase MRP)	Diffuse with sparse nuclear spots	Scl
NOR 90 (hUBF)	10-20 discrete nuclear spots*	Scl
PM-Scl (PM-1)	Homogeneous nuclear or nucleolar	PM, DM, Scl, overlap
Cytoplasmic		
tRNA synthetases		
tRNA ^{Asn} (Jo-1)	Diffuse	PM, DM
tRNA TM (PL-7)	Diffuse	PM, DM
tRNA ^{Ala} (PL-12)	Diffuse	PM, DM
tRNA ^{Gln} (Ej)	Diffuse	PM, DM
tRNA ^{Leu} (OJ)	Diffuse	PM, DM
Signal recognition particle (SRP)	?	PM
KJ	?	Myositis
Elongation factor 1α (Fer)	?	Myositis
tRNA ^{Ser} (Mas)	?	Myositis

*Cell cycle dependent.

†In cell studies, Ro RNP associates with cytoplasmic fractions (see O'Brien CA, Wolin SL: Genes Dev 8:2891, 1994).

‡May also stain nucleoli because of an association with antibodies to RNA polymerase I.

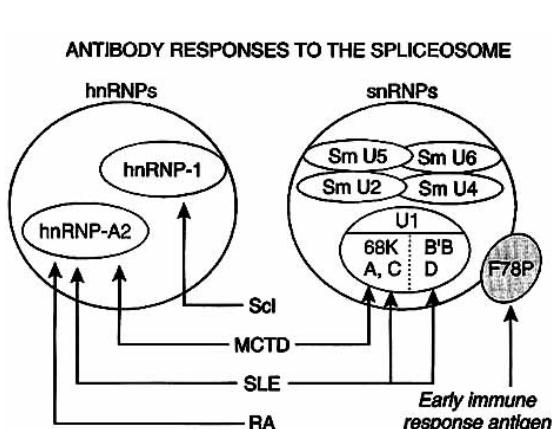
Abbreviations: ANA, antinuclear antibody; C, complement fixation; DIF, direct immunofluorescence; DILE, drug-induced lupus erythematosus; DM, dermatomyositis; ELISA, enzyme-linked immunosorbent assay; Farr, Farr radioimmunoassay; IB, immunoblot; ID, immunodiffusion; IPP, immunoprecipitation; MCTD, mixed connective tissue disease; NLE, necrotal lupus erythematosus; overlap, overlap syndrome; PBC, primary biliary cirrhosis; PM, polymyositis; RA, rheumatoid arthritis; RIA, radioimmunoassay; Scl, systemic sclerosis; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; UCTD, undifferentiated connective tissue disease.

● **Anti-ds DNA antibody**

- (1) Method for the detection of native, double-stranded DNA: Farr radioimmunoassay; *Crithidia luciliae* test; ELISA method, and Uni-CAP method
- (2) Specific to SLE (95 %)
- (3) Fluctuate with disease activity

● **Anti-ENA antibody**

- (1) Indications for anti-ENA testing: positive ANA; for the diagnosis of connective tissue diseases; or predicting clinical manifestation
- (2) Disease association
 - a. RNP: 30-40 % in SLE; high titer is indicative of MCTD; Generally associated with Raynaud's phenomenon
 - b. Sm: specific for SLE; seen in 30-40% of SLE patients
 - c. Ro (SSA) and La (SSB): associated with Sjogren's syndrome and SLE; in pregnancy, maternal SSA is associated with neonatal lupus and congenital heart block (esp. ant-52 Kd Ro antibody)
 - d. Centromere: limited type scleroderma; associated with pulmonary hypertension
 - e. Scl-70: diffuse type scleroderma; associated with interstitial lung involvement
 - f. Jo-1 and other antisynthetases: Polymyositis and dermatomyositis; associated with pulmonary involvement



Conditions associated with a positive Rheumatoid factor test

Rheumatic conditions (prevalence)

- Rheumatoid arthritis (50 to 90%)
- Systemic lupus erythematosus (15 to 35%)
- Sjögren's syndrome (75 to 95%)
- Systemic sclerosis (20 to 30%)
- Cryoglobulinemia (40 to 100%)
- Mixed connective tissue disease (50 to 60%)

Nonrheumatic conditions

- Aging
- Infection: bacterial endocarditis, liver disease, tuberculosis, syphilis, viral infections (especially mumps, rubella and influenza), parasitic diseases
- Pulmonary disease: sarcoidosis, interstitial pulmonary fibrosis, silicosis, asbestosis
- Miscellaneous diseases: primary biliary cirrhosis, malignancy (especially leukemia and colon cancer)

3. Rheumatoid factor

- Autoantibodies (IgG, IgM or IgA) reactive with the Fc portion of IgG.
- About 5% of the general population will have positive tests for rheumatoid factor and ANAs, yet only 1% or 0.04% will have RA or SLE, respectively.
- IgM rheumatoid factor** is found in **80% of patients with RA**. Low titers in chronic infections (tuberculosis, leprosy); other autoimmune diseases (SLE, Sjögren's syndrome); or chronic pulmonary, hepatic, or renal diseases.

4. Anti-phospholipid antibodies

- Polyclonal and poly-specific antibodies against phospholipid and its associated proteins
- Tests for detecting the presence of anti-phospholipid antibodies
 - (1) Anti-cardiolipin antibody: can be measured by ELISA for IgG and IgM isotypes
 - (2) Lupus anticoagulant
 - (3) False positive VDRL
 - (4) Prolonged aPTT test (cannot be corrected by normal serum when patient's and normal sera are mixed at the ratio of 1:1)
 - (5) Anti-β2 glycoprotein antibody

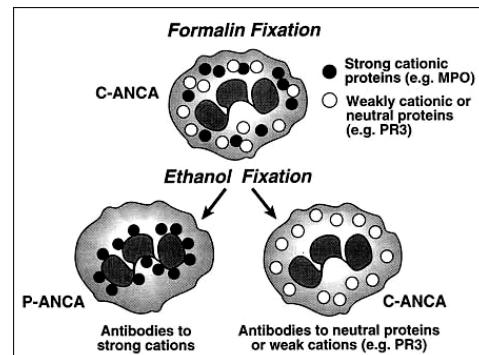
Autoantibodies Detected in Patients with Connective Tissue Diseases

Autoantibody	Disease (frequency of autoantibody)	Comments
RF	Rheumatoid arthritis (80%), other connective tissue diseases (see Table 1)	Sensitive but not specific for rheumatoid arthritis; correlates with prognosis of disease severity (not disease activity)
ANA	Systemic lupus erythematosus (99%), drug-induced lupus (100%), other connective tissue diseases (see Table 2)	Sensitive but not specific for connective tissue diseases; correlates poorly with disease activity
Anti-dsDNA	Systemic lupus erythematosus (60%)	Specific but not sensitive for systemic lupus erythematosus; correlates with lupus nephritis and disease activity
Anti-ssDNA	Infrequent	Nonspecific and of little clinical utility
Anti-histone	Drug-induced lupus (90%), systemic lupus erythematosus (50%)	Sensitive but not specific for drug-induced lupus
Anti-Sm	Systemic lupus erythematosus (20 to 30%)	Specific but not sensitive for systemic lupus erythematosus
Anti-U1 snRNP	Systemic lupus erythematosus (30 to 40%), mixed connective tissue disease (100%)	Associated with disease activity in systemic lupus erythematosus
Anti-Ro (anti-SS-A)	Sjögren's syndrome (75%), systemic lupus erythematosus (40%)	Associated with photosensitive skin rash, pulmonary disease and lymphopenia in systemic lupus erythematosus
Anti-La (anti-SS-B)	Sjögren's syndrome (40%), systemic lupus erythematosus (10 to 15%)	Associated with late-onset systemic lupus erythematosus, secondary Sjögren's syndrome and neonatal lupus syndrome
Anti-ribosome	Systemic lupus erythematosus (10 to 20%)	Highly specific but not sensitive for systemic lupus erythematosus; associated with lupus psychosis
Anti-centromere	Scleroderma (22 to 36%)	Associated with CREST syndrome and Raynaud's phenomenon
Anti-topoisomerase I (anti-Scl-70)	Scleroderma (22 to 40%)	Highly specific but not sensitive for scleroderma
Anti-Jo1	Polymyositis and dermatomyositis (30%)	Associated with pulmonary fibrosis and Raynaud's phenomenon
c-ANCA	Wegener's granulomatosis (>90%)	Highly specific and sensitive for Wegener's granulomatosis; correlates with disease activity
p-ANCA	Wegener's granulomatosis (10%), microscopic polyangiitis, glomerulonephritis	Sensitivity and specificity quite low in Wegener's granulomatosis

RF = rheumatoid factor; ANA = antinuclear antibody; anti-dsDNA = anti-double-stranded DNA; anti-ssDNA = anti-single-stranded DNA; anti-Sm = anti-Smith; anti-U1 snRNP = autoantibodies against small nuclear ribonucleoprotein U1; CREST = calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasias; c-ANCA = cytoplasmic antineutrophil cytoplasmic antibodies; p-ANCA = perinuclear antineutrophil cytoplasmic antibodies.

5. Anti-neutrophil cytoplasmic antibody (ANCA)

- Detected by indirect immunofluorescence (IIF) or antigen specific ELISA:
 - (1) IIF: typical c-ANCA, p-ANCA, atypical c-ANCA and atypical ANCA.
 - (2) ELISA: PR3-ANCA (specific to proteinase 3); MPO-ANCA (specific to myeloperoxidase); ANCA to other neutrophil cytoplasmic antigens (BPI, Cathepsin G); commercially available for PR3 and MPO now.
 - (3) Both IIF and ELISA for PR3-ANCA/ MPO-ANCA should be performed for each patient.
- c-ANCA (usually PR3-ANCA) and p-ANCA (usually MPO-ANCA) are useful in the diagnosis of small-vessel vasculitis and primary pauciimmune crescentic glomerulonephritis.



Antigen specificity		Associated diseases
c-ANCA	Proteinase 3 (PR3) (>95%) Rarely myeloperoxidase (MPO)	Wegener's granulomatosis and microscopic polyangiitis
p-ANCA	Myeloperoxidase, lactoferrin, elastase, cathepsin G, and other proteins Rarely PR3	Present in microscopic polyangiitis, pauciimmune crescentic GN and Churg-Strauss syndrome. Can be present in other autoimmune diseases and infections.

Disease	Immunofluorescence ANCA (Frequency)	Molecular Targets
Wegener's granulomatosis	C-ANCA (75-80 %) P-ANCA (10-15 %) Negative (5-10%)	PR3 MPO
Microscopic polyangiitis/ rapidly progressive glomerulonephritis	C-ANCA (25-35 %) P-ANCA (50-60 %) Negative (5-10 %)	PR3 MPO
Churg-Strauss syndrome	C-ANCA (25-30 %) P-ANCA (25-30 %) Negative (40-50 %)	PR3 MPO
Drug-induced vasculitis/ lupus	P-ANCA (?)	MPO, EL (PR3, CG, AZ, LF)
RA / Felty's syndrome	P-ANCA (30-70 %) A-ANCA	LF (MPO, LZ, many unknown)
SLE	P-ANCA (20-30 %) A-ANCA (10-15 %)	LF
Ulcerative colitis / sclerosing cholangitis	P-ANCA (40-70%) A-ANCA	LF, histone 1 (CG, MPO, BPI, many unknown)
Chronic infections	P-ANCA (?), C-ANCA, A-ANCA	BPI (LF, MPO)

* PR3 : proteinase 3, MPO : myeloperoxidase, EL : elastase , CG : cathepsin G, AZ : azurocidin
 LF:lacinferrin, LZ : lysozyme, BPI : bacterial permeability-increasing protein.

6. Anti-CCP (Cyclic Citrullinated Peptide) antibody

- High titer of anti-CCP antibody is more specific for rheumatoid arthritis; low titers for other autoimmune diseases
- Around 30% of rheumatoid arthritis patients still have negative for anti-CCP antibody

(2) HLA typing

- Detection method: serotyping and genotyping
- Disease association:

Disease	HLA association	Remarks
SLE	DR2 and DR3	↑Susceptibility
Rheumatoid arthritis	DR4	↑Susceptibility
	DRB1 *0401 and 0404	↑Susceptibility
	DRB1 *04 and 04 alleles with LLEQRRAA or LLEQKRAA	↑Susceptibility
Ankylosing spondylitis	HLA-B27	↑Susceptibility (RR=90)
	HLA B27 and B60	↑ additional risk
Reiter's syndrome	HLA B27	↑Susceptibility (RR=41)
Psoriatic arthritis	HLA B27	↑Susceptibility (RR=10)
Enteropathic arthritis	HLA B27	↑Susceptibility (RR=10)
Polyarticular juvenile RA	HLA DR4	↑Susceptibility
Pauciarticular juvenile RA	HLA DR5, DR8 and DP2.1	↑Susceptibility
Sjögren's syndrome	HLA DR3	↑Susceptibility
Behçet's disease	HLA B51	↑Susceptibility

(3) Acute phase reactants

1. Positive acute phase reactants:
 - (1) Mild elevation: ceruloplasmin, C3, C4
 - (2) Moderate elevation: α 1-protease inhibitor, haptoglobin, fibrinogen
 - (3) Marked elevation: CRP, serum amyloid A protein (CRP rises in 24 hours).
2. Negative acute phase reactants: albumin, transferrin
3. In most rheumatic disease, CRP level is in the range between 10 and 100 $\mu\text{g}/\text{ml}$. However, the level can be much higher in crystal-induced arthritis and Still's disease.
4. In SLE patients, CRP can be increased when active arthritis or serositis is present. Otherwise, infection should always be ruled out first in SLE patients with elevated CRP levels, especially when the SLE activity is not increased.
5. Persistent elevation in CRP is a poor prognostic factor for RA.
6. Advantage over ESR: rapid rise and fall, not affected by other factors (see below).

(4) Synovial fluid analysis

1. Synovial fluid analysis is a simple, cheap and accurate test, allows distinction between inflammatory and noninflammatory conditions, and provides direct proof of crystal arthropathy, infection and hemarthrosis, especially in patients with monoarthritis.
2. Biochemical analysis is less well studied and therefore is not informative.
3. Check the **appearance** (pale yellow and clear for normal fluid), **viscosity**, **cell count** and wet preparation for identifying crystals by polarizing microscopy. For example, bloody synovial fluid may indicate trauma, hemarthrosis, pigmented villonodular synovitis (PVNS) or malignancy.
4. If **infective arthritis** is suspected, perform bacterial staining, bacterial culture. Immunosuppressed patients have an increasing incidence of nonsuppurative infectious arthritis, particularly caused by mycobacteria and fungi.
5. Cell count and differential classification
 - (1) **Normal synovial fluid contains <200 cells/mm³ (lymphocyte dominant)**: Greater than 2000 cells/mm³ indicates inflammatory joint disease. Cell counts in excess of 25,000 cells/mm³ are found in three clinical conditions: rheumatoid arthritis, septic arthritis and reactive arthritis. Greater than 100,000 cells/mm³ strongly suggests septic arthritis.
 - (2) **Neutrophils predominate in all inflammatory arthropathies** and in **intra-articular hemorrhage** (commonly represent 60-80% of cells).
 - (3) Septic arthritis: the only disorder with neutrophils > 95% nucleated cells.
 - (4) The presence of small lymphocytes in the synovial fluid of RA is indicative of a better long-term prognosis in RA.
6. The presence of others cells in the synovial fluid may be useful, but not absolutely necessary for differential diagnosis.
 - (1) Plasma cells, rare in synovial fluid, are usually indicative of RA.
 - (2) **Ragocytes**: (a) Cells characterized by the presence of cytoplasmic refractile granules, which are larger than conventional granulocyte granules. (b) Present in all inflammatory arthropathies. However, ragocytes rarely account for > 50% of all nucleated cells with the exception of RA, septic arthritis, gout and pseudogout. (c) Ragocyte count > 95% is diagnostic of septic arthritis.
 - (3) Macrophages are the predominant cell in viral arthritis, acute monocytic arthritis and, with appropriate intracytoplasmic inclusions, pigmented villonodular synovitis (PVNS) and prosthetic debris-induced arthropathy.

Systemic Lupus Erythematosus

(A) Classification criteria

REVISED CRITERIA FOR THE CLASSIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the 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 a physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	(a) Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion or (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 quantification not performed or (b) Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic 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. Hematologic disorder	(a) Hemolytic anemia—with reticulocytosis or (b) Leukopenia—less than 4,000/mm ³ total on two or more occasions or (c) Lymphopenia—less than 1500/mm ³ on two or more occasions or (d) Thrombocytopenia—less than 100,000/mm ³ in the absence of offending drugs
10. Immunologic disorder	(a) Anti-phospholipid antibody (anti-cardiolipin, lupus anticoagulant or false positive serologic test for syphilis) or (b) Anti-DNA; antibody to native DNA in abnormal titer or (c) Anti-Sm: presence of antibody to Sm nuclear antigen
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

(B) Epidemiology and Pathogenesis

1. A disease of unknown etiology in which tissues are damaged by pathogenic autoantibodies and immune complexes.
2. Female:male = 9:1 at the child-bearing age; female:male = 3:1 in pre- and postmenopausal years.
3. More common at the child-bearing age, and in Blacks and Hispanic and Asian populations; the prevalence in Taiwan is about 1/2000.
4. **Genetic predisposition:** increased concordance for disease in monozygotic (24% to 58%) compared with dizygotic (0 to 6%) twins; family aggregation (a 10% to 15% frequency of patients with more than one affected family member); increased susceptibility in C4A deficiency.
5. Other factors that influence susceptibility: **Environmental factors** (UV-B light and sometimes UV-A light definitely can cause flare; other possible factors include sprouts, chemicals, infection); **sex hormones**.

(C) Clinical manifestations

- ◆ Clinical presentation and severity vary from mild and intermittent to persistent and fulminant. Exacerbations can intersperse with periods of relative quiescence.
- ◆ Constitutional symptoms: fatigue, malaise, fever, anorexia, and weight loss

<1> Musculoskeletal Manifestations

1. **Arthralgia and arthritis:** almost all patients experience arthralgia and myalgia with intermittent arthritis (frequently in hand joints and knees). **Deforming non-erosive arthritis (Jaccoud's arthritis) is unusual. Bone erosions are very rare.**
2. Tenosynovitis, bursitis and tendon nodule are not uncommon.
3. **Myopathy:** can be inflammatory (during periods of active disease), or secondary to treatment (hypokalemia or glucocorticoid myopathy).
4. **Osteonecrosis:** a common cause of hip, knee, or shoulder pain in patients receiving glucocorticoids.

<2> Cutaneous Manifestations

1. Acute skin lesions: (a) Malar ("butterfly") rash or rash over sun-exposed areas (nasolabial folds are not involved): flat or raised photosensitive dermatitis; not scarring, atrophic or sclerotic; **usually indicating disease flare.** (2) Generalized erythema and bullous lesions are uncommon.
2. **Subacute cutaneous lupus erythematosus (SCLE):** a distinct subset with recurring extensive dermatitis,

- which is photosensitive and may be annular or papulosquamous psoriasiform lesions over the arms, trunk, and face with hypopigmentation, but without scar; arthritis and fatigue are common; CNS and renal involvement are rare; most patients have anti-Ro.
3. Chronic skin lesions: **discoid LE** (DLE) (circular lesion with an erythematous raised rim, scaliness, follicular plugging, and telangiectasia over the scalp, ears, face, and sun-exposed areas of the arms, back, and chest).
 4. Hair loss of scalp: usually patchy but can be extensive; hair can regrows except in lesions of DLE.
 5. **Vasculitis**: present with purpura, subcutaneous nodules, nail fold infarcts, ulcers, vasculitic urticaria, panniculitis, and gangrene of digits. The pathology usually show leukocytoclastic angiitis
 6. Pathology: degeneration of the basal layer of the epidermis, disruption of the dermal-epidermal junction (DEJ), and mononuclear infiltrates around vessels and appendages in the upper dermis. Deposits of immunoglobulin and complement are seen in the DEJ in 80% to 100% of lesional skin and 50% of nonlesional skin in active SLE.

<3> Renal Manifestations

1. One-half of lupus patients have clinical nephritis, defined by proteinuria. Urinalysis shows hematuria, cylindruria, and proteinuria.
2. Pathology: (1) Location of immune deposits, histologic pattern of renal damage, and **activity** (severity score) and **chronicity** (reversibility score) of lesions are all useful in predicting prognosis and selecting appropriate treatment. (2) Classification: see the table below.
3. Most patients with mesangial or mild focal proliferative nephritis maintain good renal function. Diffuse proliferative nephritis develop renal failure if untreated
4. Because severe nephritis requires aggressive immunosuppression with high-dose glucocorticoids and cytotoxic drugs and mild lesions do not, renal biopsy may provide information that affects therapy.
5. Patients with rapidly deteriorating renal function and active urine sediment require prompt, aggressive therapy; biopsy is not necessary unless they fail to respond.
6. Patients with a slow rise in serum creatinine to 3 mg/dl may show a high proportion of sclerotic glomeruli on biopsy. They are unlikely to respond to immunosuppressive therapies
7. High risks for severe nephritis: persistently abnormal urinalyses, high titers of anti-dsDNA, and/or hypocomplementemia.
8. 10% of patients with lupus nephritis develop **distal renal tubular acidosis** with hyperkalemia (esp. when using potassium-sparing diuretic)—Tx: diet control, fludrocortisone.

*Frequency of systemic lupus erythematosus manifestations**

Manifestations	Onset (376)*	Anytime (750)*
Constitutional	53%	77%
Arthritis	44%	63%
Arthralgia	77%	85%
Skin	53%	78%
Mucous membranes	21%	52%
Pleurisy	16%	30%
Lung	7%	14%
Pericarditis	13%	23%
Myocarditis	1%	3%
Raynaud's	33%	60%
Thrombophlebitis	2%	6%
Vasculitis	23%	56%
Renal	38%	74%
Nephrotic syndrome	5%	11%
Azotemia	3%	8%
Central nervous system	24%	54%
Cytoid bodies	2%	3%
Gastrointestinal	18%	45%
Pancreatitis	1%	2%
Lymphadenopathy	16%	32%
Myositis	3%	3%

WORLD HEALTH ORGANIZATION CLASSIFICATION OF LUPUS NEPHRITIS

Class of Patient	Renal Histology	Clinical Presentation	Prognosis	Treatment
I. Normal	Normal	No abnormalities	Excellent	—
II. <i>Mesangial lupus nephritis</i>	Mesangial hypertrophy; mesangial immune deposits	Up to 25% no abnormalities; transient minimal proteinuria and/or hematuria; decreased C3, C4; and elevated anti-DNA in one third	Good	Steroid (rarely add cytotoxic agent)
III. <i>Focal proliferative lupus nephritis</i>	Both mesangial and endothelial proliferation; immune deposition along capillaries and narrowing of the capillary lumens; fewer than 50% glomeruli involved	Mild proteinuria (<1 g/24 hr) and hematuria; nephrotic syndrome in 20%; decreased C3 and C4 and elevated anti-DNA in 80%	Moderate	Steroid and cytotoxic agent
IV. <i>Diffuse proliferative lupus nephritis</i>	More than 50% glomeruli involved; subendothelial immune deposits; cell proliferation resulting in crescents; hematoxylin bodies present	Moderate to heavy proteinuria, hematuria with red blood cell casts, mild to severe renal insufficiency; hypertension common; decreased C3 and C4; increased anti-DNA in all	Poor	Steroid and cytotoxic agent
V. <i>Membranous glomerulonephritis</i>	Subepithelial granular immune deposits	Nephrotic range proteinuria in two thirds of patients; microscopic hematuria; hypertension; C3, C4; and anti-DNA normal	Moderate	Steroid and cytotoxic agent or No treatment
VI. <i>Sclerosing</i>	Focal segmental and global glomerular sclerosis; fibrous crescents and vascular sclerosis	Severe renal insufficiency	Poor	No treatment

<4> Nervous System involvement in SLE

1. Any region of nerve system can be involved. May be single or multiple lesion; often occur when SLE is active in other organ systems.
2. Depression and anxiety are usually related to being chronically ill and not to active SLE.
3. Laboratory diagnosis of lupus CNS involvement can be difficult; abnormal EEG in about 70% of patients, but non-specific; CSF shows elevated protein levels (50% of patients), increased mononuclear cells (30%), oligoclonal bands, increased immunoglobulin synthesis, and antineuronal antibodies and low complement levels, compared with serum complement levels.
4. Lumbar puncture whenever CNS symptoms could result from infection, especially in immunosuppressed patients.
5. CT scan for focal neurologic deficits, less helpful in cases with diffuse manifestations. MRI is the most sensitive radiographic technique to detect changes of SLE, but the changes are often nonspecific.
6. Laboratory measures of disease activity often do not correlate with neurologic manifestations. Neurologic problems (with the exception of deficits resulting from large infarcts) usually improve with immunosuppressive therapy and/or time; recurrences are seen in approximately one-third of patients.

<5> Vascular System

1. Antiphospholipid syndrome: **thrombosis** in arteries and veins of any size. Therefore, anticoagulation is more appropriate than immunosuppression in some patients.
2. Vasculitis may cause ischemic change (e.g. ischemic bowel disease).
3. Degenerative vascular changes with cardiovascular disease: Causes include years of exposure of blood vessels to circulating immune complexes, hyperlipidemia from glucocorticoid therapy predispose to degenerative coronary artery disease in lupus patients.

<6> Hematologic Manifestation

1. **Anemia** of chronic disease: in most patients when lupus is active.
2. **Hemolytic anemia**: positive Coombs' tests; it is usually responsive to high-dose glucocorticoids; resistant cases may respond to Danazol, plasma exchange or splenectomy.
3. **Leukopenia** (usually **lymphopenia**) is common but is rarely associated with recurrent infections and does not require treatment.
4. Mild **thrombocytopenia** is common; severe thrombocytopenia with bleeding and purpura occurs in 5 percent of patients and should be treated with high-dose glucocorticoids. Short-term improvement can be achieved by administration of intravenous gamma globulin. If the platelet count fails to reach acceptable levels in 2 weeks, addition of cytotoxic drugs and/or splenectomy should be considered.
5. Antiphospholipid syndrome (prolonged PTT, false positive VDRL, anti-cardiolipin antibody, or lupus anticoagulant) with thrombosis, recurrent fetal loss, thrombocytopenia and valvular heart disease

<7> Cardiac involvement

1. Pericarditis is the most frequent feature of cardiac involvement. Large pericardial effusion, tamponade, and constrictive pericarditis are rare.
2. Myocarditis can cause arrhythmias, sudden death, and/or heart failure.
3. **Valvular heart disease**: small vegetations (Libman-Sacks endocarditis) seen almost exclusively on the mitral and aortic valves, either on the atrial or great vessel side rather than on the ventricular side; leaflet thickening resulting in mild valve regurgitation, but rarely stenosis; may be a source of cerebral emboli; this syndrome is probably associated with antiphospholipid antibodies.
4. Coronary artery disease: (1) Coronary vasculitis and antiphospholipid syndrome can cause myocardial infarction. Anti-inflammatory therapy is recommended for coronary vasculitis. *Corticosteroid is contraindicated in the presence of frank myocardial infarction because of wound-healing retardation and the potential for ventricular rupture.* (2) **Premature coronary artery disease**: is now one of main causes of mortality in long-standing lupus patients.
5. Arrhythmias and conduction disturbances can be isolated events or in association with myopericarditis, and they may resolve with steroid therapy. Otherwise pacemaker may be indicated.

<8> Pulmonary involvement

1. **Pleuritis** and pleural effusions with pleurisy are common.
2. **Lupus pneumonitis**: fever, dyspnea, and cough; fleeting infiltrates and areas of plate-like telecasts on chest x-ray; may mimic pneumonia. It responds to steroid rapidly. However, it should be distinguished from **infection, the most common cause of pulmonary infiltrates in lupus patients**.
3. **Interstitial pneumonitis**: leading to **fibrosis** occasionally. The inflammatory phase may respond to treatment, but the fibrosis does not.
4. **Pulmonary hypertension** is uncommon. **Pulmonary embolism** can occur in lupus patients with antiphospholipid syndrome.

5. **Diffuse alveolar hemorrhage** is an infrequent pulmonary manifestation with high mortality.
6. Initial presentation with pericarditis and pleuritis is not uncommon in elderly-onset SLE.

<8> Gastrointestinal System

1. Nausea, diarrhea, and vague discomfort are common GI symptoms.
2. **Lupus peritonitis**: cause abdominal pain; rule out other surgical conditions; lupus peritonitis usually causes minimal to moderate amount of ascites. Massive ascites may be caused by other conditions or the presence of severe hypoalbuminemia.
3. **Intestinal vasculitis**: cause **ischemic bowel disease, which may be rapidly identified by CT scan**; the most dangerous manifestation with **acute crampy abdominal pain**, vomiting, and diarrhea; perforation and intestinal gangrene can occur; pseudoobstruction.
4. Steroid therapy is useful for all these GI syndromes, except the motility disorders similar to that in scleroderma.
5. Acute pancreatitis can occur and may be severe, resulting from active SLE or from therapy with steroid or azathioprine. Elevated amylase levels may reflect pancreatitis, salivary gland inflammation, or macroamylasemia.
6. Elevated GOT and GPT levels are common in patients with active SLE but are not associated with significant hepatic damage; they will return to be normal when the disease is treated.

<9> Ocular Manifestation

1. Retinal vasculitis is a serious manifestation; blindness can develop over a few days, and aggressive immunosuppression should be instituted.
2. Examination shows areas of sheathed, narrow retinal arterioles and cytoid bodies (white exudates) adjacent to vessels. Other ocular abnormalities include conjunctivitis, episcleritis, optic neuritis, and the sicca syndrome.

(D) Laboratory tests and investigations

1. ANAs: (a) the best screening test (> 95% of lupus patients will be positive); (b) High ANA titer supports the diagnosis of SLE but is not specific (ANA occur in some normal individuals, usually in low titer, and the frequency increases with aging); (c) A negative ANA test makes the diagnosis unlikely but not impossible.
2. Anti-ds DNA and to Sm are relatively specific for SLE.
3. **High anti-dsDNA level and low C3 and C4 levels** usually reflect disease activity, especially in patients with **nephritis**. Total functional hemolytic complement (CH50) level is a sensitive measure of complement activation but is also most subject to laboratory error.
4. Determining the complete auto- antibody profile (ANA-8 profile in our hospital) of each patient may help predict clinical subsets and in differential diagnosis (see the table above).
5. Renal function: urinalysis for proteinuria, hematuria and casts; 24-hour daily protein loss; BUN, creatinine and CCr.
6. Hematologic abnormalities: anemia (usually normochromic normocytic but occasionally hemolytic), leukopenia, lymphopenia, and thrombocytopenia.
7. ESR correlates with disease activity in some patients. CRP is usually not increased in active lupus without infection, except in lupus patients with active arthritis or serositis).
8. Antiphospholipid antibodies: PT, PTT, VDRL, lupus anti-coagulant and anti-cardiolipin for diagnosing SLE and when antiphospholipid syndrome is suspected. Check d-Dimer and perform angiography, MRA and MRV when thrombosis is suspected.
9. Analysis of pleural effusion or ascites to distinguish infection from disease flare: biochemistry tests (high protein and normal sugar levels in pleural effusion); C3 and C4 levels much lower than serum levels; positive ANA and anti-ds DNA antibody, especially at high titer; also do microbial cultures.
10. CSF analysis for lupus CNS involvement: increased cell count, high protein level, and normal sugar level; low C3 and C4; high immunoglobulin index; positive ANA and anti-ds DNA antibody, especially at high titer.

(E) Differential diagnosis

1. Some disorders may be confused with SLE (some diseases may even fulfils four of classification criteria are not SLE – criteria-positive non-SLE, e.g. **infective endocarditis**)
2. **It may take several years for a patient to fulfill criteria.** Therefore, it is difficult to classify early SLE that is confined to a few organ systems.
3. Many autoimmune disorders have **overlapping features** of connective tissue diseases, so that exact classification may be difficult. For example, mixed connective tissue disease (MCTD) has features of SLE, polymyositis, and scleroderma, accompanied by high titers of anti-U1 RNP antibodies.
4. **Drug-induced lupus:**
 - (1) Procainamide (most frequent), hydralazine, isoniazid, chlorpromazine, D-penicillamine, practolol, methyldopa, quinidine, and possibly hydantoin, ethosuximide and oral contraceptives. **But, most lupus-inducing drugs can be used safely in patients with idiopathic SLE.**
 - (2) Induction of ANA (mainly anti-histone antibody): procainamide (50% to 75% of individuals in a few months); hydralazine (25% to 30% of individuals).

- (3) Lupus-like symptoms (arthralgias, polyarthritis and pleuropericarditis) were found in 10% to 30% of ANA-positive individuals. ***Renal and CNS involvements and the presence of anti-ds DNA and hypocomplementemia are rare.*** Anemia, leukopenia, thrombocytopenia, anti-phospholipid antibody, rheumatoid factors, cryoglobulinemia, and positive Coombs' tests can occur.
- (4) Treatment: (i) Withdrawal of the offending drug (most patients improve in a few weeks) (ii) A short course (2 to 10 weeks) of glucocorticoids is indicated for severe case. Symptoms rarely persist more than 6 months; ANA may persist for years.

(F) **Treatment:** There is no cure for SLE. Complete remission is rare.

1. Treatment for patients with mild disease activity

- (1) NSAIDs without steroid may be enough for mild disease without life-threatening manifestations (arthralgias, arthritis, myalgias, fever, fatigue, and mild serositis).
- (2) **Skin lesions:** (a) May respond to antimalarials (hydroxychloroquine at doses of 400 mg/daily) in a few weeks. Side effects are uncommon and include retinal toxicity, rash, myopathy, and neuropathy. Retinal toxicity is related to cumulative dose. (b) Sunscreens. (c) Topical or intra-lesional steroid.
- (3) **Systemic steroid with low to moderate doses (prednisolone 0.25 to 0.5 mg/kg/day)** should be given for patients unresponsive to these conservative measures.
- (4) **Antimalarials:** only **Hydroxychloroquine** is available. Because of satisfactory drug safety of hydroxychloroquine, it is advised to maintain this drug during the periods of active or inactive disease activity.

2. Treatment for patients with severely disabling manifestations

- (1) **High doses of steroid (prednisolone 1 to 2 mg/kg/day)** in divided doses every 8 to 12 h for lupus nephritis with normal renal function, hemolytic anemia, vasculitis, refractory thrombocytopenia, CNS involvement, and lupus pneumonitis. After the disease is controlled, therapy should be consolidated to one morning dose. Ideally, patients should be slowly converted to alternate-day therapy with a single morning dose of short-acting glucocorticoid (prednisolone, prednisolone, methylprednisolone) to minimize side effects.
- (2) **Hydroxychloroquine**
- (3) **Steroid pulse therapy:** Methylprednisolone 1000 mg/day intravenously for 3 days for proliferative lupus nephritis, myelopathy, severe CNS involvement with confusional state, alveolar hemorrhage (can also be treated with plasma exchange and cyclophosphamide) and optic neuritis. Disease flares are probably controlled more rapidly by this approach, but it is unclear whether long-term outcome is changed.
- (4) **Immunosuppressive drugs:** include **cyclophosphamide, mycophenolate, cyclosporine, azathioprine**
 - (a) Purposes: (i) Probably beneficial in controlling active disease and reducing the rate of disease flares. (ii) Reduce steroid requirements.
 - (b) Lupus nephritis (esp. type IV): glucocorticoids plus cyclophosphamide (pulse monthly or oral daily) can significantly reduce the incidence of renal failure, but not survival rate. Azathioprine as the second drug is less beneficial but is also effective.
 - (c) Side effects of cytotoxic drugs: bone marrow suppression, increased infection with opportunistic organisms such as herpes zoster, irreversible ovarian failure (cyclophosphamide), hepatotoxicity (azathioprine), bladder toxicity (cyclophosphamide), alopecia, and increased risk for malignancy.
 - (d) Azathioprine (50 mg/tablet) is the least toxic; recommended doses are 2 to 3 mg/kg per day orally (usually 100 mg daily).
 - (e) **Cyclophosphamide** is the most effective, but most toxic for lupus nephritis. (i) **IV pulse therapy (10 to 15 mg/kg)** monthly for 6 months, then quarterly for at least 2 years. (ii) **Daily oral doses (2 mg/kg/day)**. (iii) Compared with oral therapy, pulse therapy has less urinary bladder toxicity than daily oral doses, but bone marrow suppression can be severe. (iv) Modify dose based on the renal function and the bone marrow suppression (WBC counts).

3. SOME MANIFESTATIONS OF SLE DO NOT RESPOND TO STEROID OR IMMUNOSUPPRESSIVE AGENTS

- (1) **Thrombosis or recurrent fetal loss due to antiphospholipid syndrome:** may be treated with aspirin and anti-coagulant agent (IV heparin, subcutaneous low-molecular-weight heparin, oral warfarin maintenance); successful pregnancy may require continuous treatment with subcutaneous low-molecular-weight heparin for the whole course of pregnancy (warfarin is teratogenic).
- (2) **Seizures without other serious SLE manifestations:** treated with anti-convulsants.
- (3) **Behavioral abnormalities or psychosis not caused by SLE:** anti-psychotic drugs; taper steroid if steroid-induced psychosis is suspected.
- (4) **Pure membranous glomerulonephritis:** treatment with steroid and immunosuppressives can be tried several weeks, but should be abandoned if improvement is not obvious. May try cyclosporine.
- (5) **Sclerotic renal damage.**

4. Side effects of steroid and the management: see the table on the next page.

** Other undesirable effects of chronic steroid therapy: cushingoid habitus, weight gain, capillary fragility, acne, hirsutism, cataracts, glaucoma, diabetes mellitus, myopathy, hypokalemia, irregular menses, irritability, insomnia, and psychosis.

** Alternate-day steroid therapy: reduce the side effect of steroid, but not osteoporosis.

5. Other managements

- (1) **Cyclosporin A:** May be beneficial in the management of lupus membranous nephropathy as well as in non-renal manifestations in lupus patients at the dose (2.5 to 5 mg/kg/day) lower than that used in transplantation. Monitor the renal function and blood pressure.
- (2) **Plasma exchange** by plasmapheresis: the only unequivocal indication in SLE is for the treatment of thrombotic thrombocytopenic purpura. Plasma exchange followed by pulse cyclophosphamide has been suggested in treating life-threatening acute pulmonary hemorrhage in SLE. In addition, thrombocytopenia may respond to plasma exchange after the failure of other modalities. Other inductions are equivocal.
- (3) Sex hormones: (1) **Dehydroepiandrosterone (DHEA)**, an adrenal steroid with limited androgenic activity has been shown to be effective in lupus patients with mild to moderate disease activity. (2) **Danazol**, an attenuated androgen, maybe effective in thrombocytopenia.
- (4) Immunizations with influenza and pneumococcal vaccines are safe and should be given to prevent from infection if disease is stable.
- (5) Antibiotic prophylaxis for all SLE patients undergoing dental and other forms of nonsterile surgery has been recommended, since infectious endocarditis may complicate lupus valve disease.

(G) Prognosis

1. Survival rates: 90~95% at 2 years, 82~90% at 5 years, 71~80% at 10 years, and 63~75% at 20 years.
2. Lupus mortality has a bimodal distribution: (1) Increased death rate in the first 5 years of disease (usually due to complications of the disease, infection or its treatment). (2) Increased death at 15-20 years, primarily due to early **coronary artery disease** (possibly due to hypertension, small vessel coronary arteritis, and hyperlipidemia due to nephrotic syndrome and/or corticosteroids).
3. **Infections and renal failure** are the leading causes of death in the first decade of disease. **Thromboembolic events** are frequent causes of death in the second decade.
4. Poor prognosis (50% mortality in 10 years): (1) At the time of diagnosis: high serum creatinine levels, nephrotic syndrome, anemia, hypoalbuminemia, and hypocomplementemia at the time of diagnosis. (2) socioeconomic status. Other factors associated with a poor prognosis in some but not all studies include thrombocytopenia, serious CNS involvement, and antibodies to phospholipids.
5. The clinical courses of different patients may vary a lot. Approximately 20 percent of patients experience disease remissions (with a mean duration of 5 years), regardless of the severity of disease at diagnosis. The likelihood of remission increases with each decade after diagnosis. Some patients remain in remission for decades.

(H) Some important issues related to SLE

1. Pregnancy and SLE

- (1) Pregnancy is associated with lupus exacerbation in less than one quarter of patients. However, more than one half of pregnancies are uneventfully. Patients should be encouraged to plan pregnancy during the period of complete remission.
- (2) Steroid (except, dexamethasone and betamethasone) can be used safely during pregnancy. Dexamethasone and betamethasone that can cross placenta easily should not be used in the pregnant lupus patients.
- (3) Hydroxychloroquine has been shown to be safe during pregnancy, but warning about the low possibility of fetal abnormality still should be delivered to patients.
- (4) Cyclophosphamide and methotrexate ideally should be stopped 3 to 6 months prior to pregnancy.
- (5) Fertility is normal in women with SLE, but the pregnancy wastage is increased: factors associated with fetal loss include increased lupus activity, antiphospholipid antibodies, active lupus nephritis, hypertension and a history of prior fetal loss. Subcutaneous low-molecular weight heparin is effective for successful the pregnancy
2. The potential effect of hormone replacement therapy (HRT) on SLE activation is unknown. Closely monitoring the lupus activity in patients on HRT is advised. In addition, oral contraceptive pill may be avoided. Progesterone alone is safe.
3. Neonatal lupus: Congenital heart block is associated with the presence of anti-Ro and anti-La autoantibodies in SLE or other connective tissue diseases. Treatments include plasma exchange and the use of dexamethasone that can cross the placenta, but may cause oligohydramnios, IUGR and adrenal insufficiency. Non-cardiac manifestations (skin lesions, cholestasis, cytopenia) may resolve 6 months after birth (due to the disappearance of maternal antibodies).

Scleroderma

(A) **Classification criteria:** one major criteria (scleroderma proximal to MCP or MTP joints) or two minor criteria.

Criteria for the Classification of Systemic Sclerosis (Scleroderma)*

A. Major criterion

Proximal scleroderma: Symmetric thickening, tightening, and induration of the skin of the fingers and the skin proximal to the

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abc

Subsets of systemic sclerosis

B. Diffuse Cutaneous Scleroderma

- Proximal skin thickening involving face/neck, trunk, and symmetrically the fingers, hands, arms and legs
 - Rapid onset of disease following appearance of Raynaud's phenomenon
 - Significant visceral disease: lung, heart, gastrointestinal, or kidney
 - Associated with antinuclear antibodies and absence of anticentromere antibody
 - Variable disease course but overall poor prognosis: survival 40%–60% at 10 years
- * F Limited Cutaneous Scleroderma
- Skin thickness limited to symmetrical change of fingers, distal arms, legs, and face/neck.
 - Progression of disease after onset of Raynaud's phenomenon
 - Late visceral disease with prominent hypertension and digital amputation
 - CREST syndrome
 - Association with anticentromere antibody
 - Relatively good prognosis: survival ≥70% at 10 years

Overlap Syndromes

- Diffuse or limited scleroderma with typical features of one or more of the other connective tissue diseases
- Mixed connective tissue disease: features of systemic lupus erythematosus, scleroderma, polymyositis, rheumatoid arthritis, and presence of anti-U₁ RNP

Undefined Connective Tissue Disease

- Patients with features of systemic sclerosis (scleroderma) who do not have definite clinical or laboratory findings to make a diagnosis

Localized Scleroderma

- Morphea: plaques of fibrotic skin and subcutaneous tissue without systemic disease
- Linear scleroderma: longitudinal fibrotic bands that occur predominantly on extremities and involve skin and deeper tissues

(B) **Clinical manifestations**

1. **Raynaud's phenomenon:** usual initial symptom with or without finger puffiness; Blanching, cyanosis and hyperemia with numbness and pain; triggered by cold exposure and emotion; abnormal capillary loops by nailfold capillaroscopy; DD from primary Raynaud's phenomenon by normal capillaroscopy and ESR and negative ANA.
 - (1) Limited scleroderma: Raynaud's phenomenon for 5 to 10 years before the development of scleroderma.
 - (2) Diffuse scleroderma: rapid evolution of systemic disease after appearance of Raynaud's phenomenon.
2. **Skin lesions:** scleroderma; "salt and pepper" appearance with patchy hypo- and hyper-pigmentation of skin over the trunk; **Sclerodactyly:** digital pitting scar; loss of subcutaneous tissue of fingertips.
3. **GI:** decreased intestinal motility of GI tract; dysphagia and reflux esophagitis with atypical chest pain, dysfunction of lower esophagus; delayed stomach emptying; intestinal dilatation and ileus with secondary bacterial overgrowth. Abdominal cramps, malabsorption and mainly constipation, sometimes alternating with diarrhea, are the clinical manifestations. Unique to scleroderma is the development of wide-mouthed, often square-shaped **pseudodiverticula** along the anti-mesenteric border of the transverse and descending colon.
4. **Pulmonary involvement:** (1) Diffuse scleroderma: interstitial lung disease (2) limited scleroderma: pulmonary hypertension. (3) Others: pulmonary hemorrhage, pneumothorax, increased risk of lung cancer.
5. **Renal involvement:** proteinuria, azotemia and hypertension in 20-30% of diffuse scleroderma; scleroderma renal crisis (severe hypertension, azotemia and microangiopathy with anemia).
6. **Cardiac involvement:** (1) **Coronary artery disease** of the intramural coronary arteries and arterioles (most patients have peripheral Raynaud's phenomenon) (2) **Conduction defects** are not uncommon (caused by fibrosis of the conduction system; no specific treatment). (3) Involvement of myocardium and pericardium is common, but clinical evidence is subtle or absent (pericarditis, pericardial effusion, myocarditis, myocardial fibrosis, and arrhythmia). (4) Heart failure is a late finding. (5) Large pericardial effusion is a poor prognostic sign. (6) Valvular heart disease is rare in patients with systemic sclerosis.
7. **Others:** arthralgia/arthritis; tendon friction rub; muscle weakness.
8. **CREST:** Calcinosis, Raynaud's phenomenon, Esophageal involvement, Sclerodactyly, Telangiectasia.

(C) **Lab tests and examinations**

1. CBC, ESR, ANA (positive in more than 95%), anti-centromere (associated with limited scleroderma); HLA DR3 and anti-scl70 (associated diffuse scleroderma and pulmonary fibrosis).
2. Chest X ray, pulmonary function tests (vital capacity and DLCO; restrictive lung disease indicating interstitial fibrosis, reduced diffusing capacity indicative of pulmonary fibrosis), HRCT and bronchoalveolar lavage for lung involvement.
3. Urinalysis and renal function for kidney involvement.
4. Barium swallow esophagogram or esophageal manometry for dysmotility, esophageal scintigraphy for the transit time early esophageal involvement
5. Capillaroscopy for avascularity in Raynaud's phenomenon.
6. X ray finding of hands: Soft tissue (tapered, conical fingertip; retraction of fingertip; loss of skin folds; calcinosis cutis); bone (acroosteolysis, distal tuft resorption).

(D) **Treatment**

1. D-penicillamine 750 mg daily for diffuse systemic sclerosis
2. Raynaud's phenomenon: protective warm clothing; avoid cold exposure; quit smoking; avoid non-selective β-blocker and vasoconstrictive agents; Nifedipine 30-120 mg/day; intravenous carboprostacycline (Iloprost); local treatment for ulcers.
3. No satisfactory treatment for calcinotic nodules: colchicines for inflammatory component.
4. GI: PPI and metoclopramide for reflux esophagitis; dilation for esophageal strictures; antibiotics for chronic diarrhea due to intestinal stasis and bacterial overgrowth.
5. Renal: scleroderma renal crisis requires prompt treatment, and an ACEI, captopril, is the drug of choice; associated with diffuse scleroderma.
6. Heart involvement: NSAID and steroid for pericarditis; steroid for myocarditis.
7. Poor prognosis: male, onset after the age of 45 years, involvement of lung, renal and heart.
8. Survival: Limited (90% at 5 years, 75% at 10 years); diffuse (70% at 5 years, 55% at 10 years); after using ACEI, lung disease is the major challenge.

Polymyositis and Dermatomyositis

(A) Diagnostic Criteria and classification

Criteria for the Diagnosis of Polymyositis and Dermatomyositis*

CRITERION	DEFINITION
Symmetrical weakness	Weakness of limb-girdle muscles and anterior neck flexors, progressing over weeks to months, with or without dysphagia or respiratory muscle involvement
Muscle biopsy evidence	Evidence of necrosis of Type I and II fibers, phagocytosis, regeneration with basophilia, large vesicular sarcolemmal nuclei and prominent nucleoli, atrophy in a perifascicular distribution, variation in fiber size, and an inflammatory exudate, often perivascular
Elevation of muscle enzymes	Elevation in serum of skeletal muscle enzymes, particularly creatine phosphokinase and often aldolase, serum glutamate oxaloacetate, and pyruvate transaminases, and lactate dehydrogenase
Electromyographic evidence	Electromyographic triad of short, small, polyphasic motor units, fibrillations, positive sharp waves, and insertional irritability, and bizarre, high-frequency repetitive discharges
Dermatologic features	A lilac discoloration of the eyelids (heliotrope) with periorbital edema, a scaly, erythematous dermatitis over the dorsum of the hands (especially the metacarpophalangeal and proximal interphalangeal joints, Gottron's sign), and involvement of the knees, elbows, and medial malleoli, as well as the face, neck, and upper torso

* Confidence limits can be defined as follows. For a definite diagnosis of dermatomyositis, three of four criteria plus the rash must be present; for a definite diagnosis of polymyositis, four criteria must be present without the rash. For a probable diagnosis of dermatomyositis, two criteria plus the rash must be present; for a probable diagnosis of polymyositis, three criteria must be present without the rash. For a possible diagnosis of dermatomyositis, one criterion plus the rash must be present; for a possible diagnosis of polymyositis, two criteria must be present without the rash.

(Abbreviation: PM, polymyositis ; DM, dermatomyositis)

(B) Clinical features

1. Classifications
 - (a) Based on the clinical manifestations

EPIDEMIOLOGIC CHARACTERISTICS OF POLYMYOSITIS-DERMATOMYOSITIS CLINICAL CLASSIFICATION SUBSETS						
	Adult poly- myositis	Adult dermato- myositis	Childhood	Connective tissue disease overlap	Malignancy overlap	All patients
Proportion of all patients	50%	20%	10%	10%	10%	
Age at diagnosis (mean)	45	40	10	35	60	45
Incidence sex ratio (F:M)	2:1	2:1	1:1	10:1	1:1	2.5:1
Incidence race ratio (B:W)	5:1	3:1	1:1	3:1	2:1	3:1

- (b) Based on the autoantibodies

Classification based on autoantibody

Autoantibody	Clinical features
Anti synthetase*	PM/DM with acute onset associated with interstitial lung disease, fever, "mechanic's" hand, arthritis, Raynaud's disease, moderate response to treatment
Anti-signal recognition particle (SRP)	PM with very acute onset, severe muscle weakness, poor response to treatment
Anti-Mi2	DM, "V" or shawl sign, cuticular overgrowth, good response to treatment

* Includes anti-Jo-1 (histidyl-tRNA synthetase); anti-PL-7 (theonyl-tRNA synthetase); antiPL-12 (alanyl-tRNA synthetase) and anti OJ (soleucyl-tRNA synthetase)

2. Adult PM/DM:

- (1) Affect individuals at the age of 45-60 years; Female:male = 2:1
- (2) Insidious proximal muscle weakness in weeks to months: difficulty in standing up, climbing stairs, and raising arms to comb hair.
- (3) Muscle pain and tenderness in about a half of patients.
- (4) Rarely, acute onset with rhabdomyolysis.
- (5) Cardiopulmonary involvement: (a) Myocarditis, arrhythmias and conduction disturbances are most common for heart involvement. (b) Pulmonary vasculopathy and primary interstitial lung disease. (c) Anti-inflammatory therapy rarely helps and a poor prognosis is indicated.
- (6) Others: Raynaud's phenomenon, interstitial lung disease, and symmetrical peripheral arthritis.
- (7) **Skin:** **Heliotrope rash** of dermatomyositis (erythematous and/or violaceous rash over the eyelid); **Gottron's papules** over the MCP joints of hands and elbow; '**Machinist's hands**' (cracking and fissuring of the distal digital skin of fingerpads); "**Shawl sign**" (V shaped rash over the necklace area)

3. Juvenile PM/DM:

- (1) Onset in the early childhood with vasculitis (palpable purpura, GI vasculitis with bleeding), myocarditis and muscle weakness.
- (2) Soft tissue calcinosis and other features of adult DM/PM

4. Myositis with connective tissue diseases: Usually milder symptoms with only elevation of CK and EMG abnormality.

5. Myositis with malignancy

- (1) The onset of myositis after 50 years old.
- (2) Malignancy usually occurs two years after the onset of PM/DM.
- (3) DM has stronger association than PM with ovary, breast and stomach cancers.

(C) Lab tests and examination

1. **Muscle enzymes:** increased levels of CK, LDH, GOT and GPT; useful for monitoring the muscle damage, but **no good correlation between the extent of muscle damage and the elevated muscle enzymes levels**
2. **EMG:** short, small polyphasic motor units with insertional irritability along with bizarre, high frequency repetitive discharge.
3. **Muscle biopsy:** inflammatory cell infiltrate with myofiber degeneration
4. Positive **ANA** in 20% patients; antibody to **histidyl-transfer RNA synthetase (anti-Jo-1)** in 1/3 of patients with myositis.
5. Search for malignancy: no consensus as to how rigorously to search for malignancy; but ultrasonography, X-ray and Pap smear should be requested.

(D) Treatment

1. Prednisolone

- (1) Start with 1-2 mg/kg/day for 12 weeks, and then taper it. Be aware of the side effects of large-dose steroid and any signs of infection.
- (2) Usually improvement is noticeable by 6-8 weeks.
- (3) If no improvement by 12 weeks, need to review the diagnosis (inclusion body myositis is not responsive to steroid). If diagnosis is confirmed, then add azathioprine 2-3mg/kg/day.
2. Methylprednisolone 1000 mg/day or 20 mg/kg/day for severe cases with rapid deterioration (respiratory failure, myocarditis).
3. Cytotoxic agents: It is widely accepted that early use of cytotoxic agent in combination with steroid, as the initial treatment, may be beneficial for severe manifestations in connective tissue diseases. However, some physicians may reserve it to patients who (1) is not responsive to steroid (2) have steroid side effects or (3) have disease flare while reducing the steroid dosage. Frequently used cytotoxic agents include azathioprine, cyclophosphamide, methotrexate and cyclosporin A.
4. Monitor the levels of CK, GOT, GPT and the muscle power during treatment. Stable CK level with deteriorated muscle strength may indicate steroid myopathy.

Sjögren's Syndrome

(A) Classification criteria (4 of 6 criteria)

Criteria for the Classification of Sjögren's Syndrome*

1. Ocular symptoms

- Definition.* A positive response to at least one of the following three questions:
- Have you had daily, persistent, troublesome dry eyes for more than 3 months?
 - Do you have a recurrent sensation of sand or gravel in the eyes?
 - Do you use tear substitutes more than three times a day?

2. Oral symptoms

- Definition.* A positive response to at least one of the following three questions:
- Have you had a daily feeling of dry mouth for more than 3 months?
 - Have you had recurrent or persistently swollen salivary glands as an adult?
 - Do you frequently drink liquids to aid in swallowing dry foods?

3. Ocular signs

Definition. Objective evidence of ocular involvement, determined on the basis of a positive result on at least one of the following two tests:

- Schirmer-I test (≤ 5 mm in 5 minutes)
- Rose bengal score (≥ 4 , according to the van Bijsterveld scoring system)

4. Histopathologic features

Definition. Focus score ≥ 1 on minor salivary gland biopsy (focus defined as an agglomeration of at least 50 mononuclear cells; focus score defined as the number of foci per 4 mm^2 of glandular tissue)

5. Salivary gland involvement

Definition. Objective evidence of salivary gland involvement, determined on the basis of a positive result on at least one of the following three tests:

- Salivary scintigraphy
- Parotid sialography
- Unstimulated salivary flow ($\leq 1.5 \text{ ml in 15 minutes}$)

6. Autoantibodies

Definition. Presence of at least one of the following serum autoantibodies:

- Antibodies to Ro/SS-A or La/SS-B antigens
- Antinuclear antibodies
- Rheumatoid factor

Exclusion criteria: preexisting lymphoma, acquired immunodeficiency syndrome, sarcoidosis, or graft-versus-host disease

* For primary Sjögren's syndrome, the presence of three of six items showed a very high sensitivity (99.1%), but insufficient specificity (57.8%). Thus, this combination could be accepted as the basis for a diagnosis of probable primary Sjögren's syndrome. However, the presence of four of six items (accepting as serologic parameters only positive anti-Ro/SS-A and anti-La/SS-B antibodies) had a good sensitivity (93.5%) and specificity (94.0%), and therefore may be used to establish a definitive diagnosis of primary Sjögren's syndrome.

(B) Introduction

- Can occur in patients of all ages, but it affects primarily females during the fourth and fifth decades of life with a female:male ratio of 9:1.
- Symptoms of dry eyes and dry mouth were correlated with elevated levels of anti-Ro(SS-A) and La(SS-B) antibodies.

(C) Clinical manifestations

1. Exocrinopathy

- Dry eyes with keratoconjunctivitis sicca (diminished tear production), xerostomia (dry mouth, decreased production of saliva by the salivary glands, causing increase in dental caries), xerotrachea and vaginal dryness.
- Parotid or salivary gland enlargement: in 60% of primary Sjögren's syndrome patients; episodic in many cases, but can be chronic and persistent; may begin unilaterally but often becomes bilateral later. Differential diagnosis for enlarged parotid gland: (a) Bilateral: viral infections (mumps, influenza, EBV, coxsackie A, CMV, HIV); sarcoidosis; recurrent parotitis. (b) Unilateral: neoplasm (esp. lymphoma, but may have pseudolymphoma); bacterial infection; chronic sialadenitis.
- Hoarseness, recurrent bronchitis and pneumonitis result from dryness of upper respiratory tract as well as the oropharynx. Loss of exocrine function may also lead to loss of pancreatic function and hypochlorhydria. Patients may also experience dermal dryness and loss of vaginal secretions.

2. Extraglandular disease: with frequency in primary Sjögren's syndrome.

- Constitutional symptoms: fatigability, low-grade fever, myalgia and arthralgia.
- Nonerosive polyarthritis** (50%, arthralgia, morning stiffness, intermittent synovitis and chronic polyarthritis, Jaccoud's arthropathy);
- Raynaud's phenomenon (35%) without telangiectasia or digital ulceration (in contrast to scleroderma).
- Skin lesions: (a) Vasculitis (5%): affects small and medium-sized vessels; manifest as purpura, recurrent urticaria, skin ulcerations and mononeuritis multiplex; infiltrating cells on pathology can be the neutrophils (associated with hypergammaglobulinemia, high titers of rheumatoid factor, antibodies to Ro and hypocomplementemia) or mononuclear cells. (b) Others: annular erythema and pernio-like lesions
- GI tract involvement: dysphagia (caused by pharynx dryness or abnormal esophageal motility); nausea and epigastric pain are common; chronic atrophic gastritis with lymphocytic infiltrates; hypopepsinogenemia,

- elevated serum gastrin, low levels of serum vitamin B12 and antibodies to parietal cells. Subclinical pancreatitis (hyperamylasemia in around 25% patients); associated with chronic liver disease (hepatomegaly in 25% and antimitochondrial antibodies (AMA) in 5%) with increased liver enzymes and alkaline phosphatase (mild intrahepatic bile duct inflammation); increased incidence of primary biliary cirrhosis.
- (6) Pulmonary Involvement: dry cough due to xerotrachea or dyspnea from interstitial lung disease (very mild in Sjögren's syndrome) or airway obstruction. **Pseudolymphoma** or frank lymphoma should always be suspected when lung nodules or hilar and/or mediastinal lymphadenopathy are present in chest radiographs. Pleural effusion is usually found in Sjögren's syndrome associated with other rheumatic disorders and not in primary Sjögren's syndrome
 - (7) Kidney: The rare renal tubular disease of Sjögren's syndrome is usually a form of renal tubular acidosis of minor clinical importance; Occasionally nephrocalcinosis; membranous glomerulopathy associated with Sjögren's syndrome is less common.
 - (8) Renal involvement: hyposthenuria and **hypokalemic, hyperchloremic distal renal tubular acidosis** with abnormal urine acidification test and interstitial infiltration and destruction by lymphocytes (35%, usually clinically silent but may lead to renal stones, nephrocalcinosis and compromised renal function), less commonly, proximal tubular acidosis with Fanconi's syndrome; Membranous or membranoproliferative glomerulonephritis in few patients with cryoglobulinemia and hypocomplementemia; interstitial cystitis.
 - (9) Nervous system: neuropathy as a consequence of small-vessel vasculitis.
3. 50% of patients are associated with other autoimmune diseases: RA (most often), SLE, systemic sclerosis, or polymyositis.
 4. Increased risk by 44 folds of lymphoma: primarily of B cell origin, highly undifferentiated or well differentiated (immunocytomas); can present as monoclonal gammopathy; it is difficult to distinguish true lymphoma from pseudolymphoma, even using immunophenotyping and genotyping.
 5. Pseudolymphoma: tumor-like lymphocyte clusters without meeting criteria for malignancy; should always be suspected in a patient with lymphadenopathy, organomegaly or major salivary gland enlargement.

(D) Laboratory tests and investigations (with frequencies):

1. CBC: mild anemia of chronic disease (25%), leukopenia (10%), thrombocytopenia is rather infrequent.
2. Elevated ESR (80-90%), whereas CRP levels are normal.
3. Hypergammaglobulinemia (80%) and high immune complexes
4. Positive autoantibodies: rheumatoid factor, ANA, and antibodies to gastric parietal cell, thyroglobulin thyroid microsome, mitochondria, smooth muscle and salivary duct; anti-Ro(SS-A) and anti-La(SS-B)
5. Ophthalmology examinations: (a) Schirmer's Tear Test: evaluation of tear secretion by the lacrimal glands. Wetting of less than 5mm per 5 minutes is a strong indication for diminished secretion. (b) Rose Bengal staining: diagnosis of KCS.
6. Gland examinations: (a) Sialometry: measures salivary flow rates, with or without stimulation, for the individual parotid or submandibular and sublingual glands, or for total saliva production. (b) Sialography: assess anatomic changes in the salivary gland duct system; is as sensitive and specific as the labial minor salivary gland biopsy; correlate with hypergammaglobulinemia, anti-Ro antibodies, extraglandular manifestations and parotid swelling. (c) Scintigraphy: highly sensitive, but not disease specific; functional evaluation of all the salivary glands by observing the rate and density of 99mTc pertechnetate uptake and time of appearance in the mouth during a 60-minute period after intravenous injection. In patients with Sjögren's syndrome the uptake and secretion are delayed or absent.
7. Biopsy of lip salivary gland: the best studied organ for its involvement in almost all patients and easy accessibility (actually lymphocytic infiltration occurs in all organs affected); predominantly CD4+ lymphocyte infiltration
8. Differential diagnosis from diseases that may have dry eyes, xerostomia and parotid gland enlargement: (a) Sarcoidosis: the minor salivary gland biopsy reveals noncaseating granulomas and absent anti-Ro and anti-La. (b) Lipoproteinemias (types II, IV and V). (c) Chronic graft-versus-host disease (d) Amyloidosis (e) HIV infections have presented with sicca manifestations, parotid gland enlargement, pulmonary involvement and lymphadenopathy; but the lymphocytes infiltrating the salivary glands are CD8+T-cells prominent and have no anti-Ro and anti-La. (f) Hepatitis C virus (HCV) may produce a chronic lymphocytic sialadenitis which mimics Sjögren's syndrome, in approximately 50% of the infected individuals.

(E) Treatment

1. Treatment for dry eyes: artificial tear drops; avoid windy or low humidity environments; Avoid drugs with anticholinergic effects (phenothiazines, tricyclic antidepressants, antispasmodics, and anti-Parkinsonian agents); avoid smoking
2. Treatment of xerostomia: no constantly effective method; stimulation of salivary flow by sugar-free lozenges; avoid smoking and anticholinergic drugs; adequate oral hygiene; pilocarpine hydrochloride (5 mg orally tid).
3. Hydroxychloroquine, 200 mg daily, for arthralgia and myalgia.
4. Systemic steroid for severe extraglandular diseases (diffuse interstitial pneumonitis, glomerulonephritis, vasculitis, peripheral neuropathy).

Overlap Syndromes

- Patients with overlap syndromes may present with a combination of major features of more than one rheumatic disease and cannot be classified into only one disease entity.
- **Overlap syndrome** is defined to have a group of distinctive features that constitute a recognizable rheumatic syndrome, such as myositis, scleroderma and Sjögren's syndrome. Otherwise, ***undifferentiated connective tissue diseases (UCTD)*** should be used for patients with incomplete features (for example a patient with Raynaud's phenomenon, arthralgia and a weak positive antinuclear antibody).
- Raynaud's phenomenon, arthritis and sclerodactyly are common in overlap syndrome; and polymyositis and fibrosing alveolitis are frequently the more serious manifestations.

<A> Classification of overlap syndrome

1. **Classification based on the clinical involvement:** disease-specific clinical features (such as thickening of the skin proximal to the fingers in scleroderma and the articular erosions in RA) can be used to define an overlap syndrome. Other common features of autoimmune diseases, such as Raynaud's phenomenon, sclerodactyly and alveolitis, cannot be used on their own to define a syndrome.
2. **Classification based on the autoantibody detection:** (1) Anti-U1 RNP for patients with mixed connective tissue disease (MCTD) (overlap syndrome of SLE, systemic sclerosis and polymyositis). (2) Autoantibodies to Jo-1 and the other tRNA synthetases for polymyositis/fibrosing alveolitis overlap syndrome (3) Anti-PM/Scl for polymyositis/scleroderma overlap syndrome. (4) Anti-Ro and Anti-La can be considered to be the marker of Sjögren's/SLE overlap syndrome.

 Mixed Connective Tissue Disease (MCTD)

1. Mixed connective tissue disease (MCTD) is an overlap syndrome combining features of SLE, scleroderma and polymyositis, together with the high titers of anti-U1 RNP antibodies. MCTD can potentially evolve into SLE.
2. Diagnostic criteria: one of several proposed criteria is provided below.
3. Epidemiology: (1) The prevalence of MCTD is about 10/100,000. (2) Female to male ratio is about 9:1. (3) No particular environmental agents have been associated with the disease. (4) Several studies have shown its association with DR4.
4. **Clinical features:** Being an overlap syndrome, MCTD lacks any distinctive clinical features.
 - (1) Raynaud's phenomenon is very common and is often associated with edema of the hands. (Swollen hands also occur in early scleroderma, eosinophilic fasciitis and the anti-transfer RNA (tRNA) synthetase antibody associated overlap syndromes).
 - (2) Arthritis and arthralgias: common, but no unique pattern; range from a mild SLE-like synovitis through to erosive disease typical of RA and even arthritis mutilans have been described.
 - (3) **Pulmonary hypertension** is the major cause of death. Myositis and fibrosing alveolitis are the two most important common features of the syndrome and are potentially fatal.
 - (4) Other clinical features: reflect those of the diseases that it overlaps. (a) Skin: sclerodactyly, scleroderma (usually restricted), calcinosis, telangiectasia, photosensitivity, malar rash and the heliotrope rash. (b) Lung: pleurisy, interstitial lung disease and pulmonary hypertension (due to intimal proliferation) (c) Heart: all three layers can be involved; pericarditis most common, RVH on EKG. (d) GI: dysmotility of GI tract as scleroderma. (e) Low frequency of the involvement of nervous system. As in scleroderma, the most common nervous involvement is **trigeminal neuropathy** (in about 25%). (f) Renal involvement: either membranous nephritis, or less commonly, the renal vasculopathy characteristic of scleroderma leading to malignant hypertension. (g) **Sjögren's syndrome** in about 50% of patients.
 - (5) Juvenile MCTD: associated with more morbidity.
5. The prognosis of MCTD is worse than lupus, most of the deaths being attributable to pulmonary hypertension.
6. **Laboratory tests and investigations**
 - (1) High titer of anti-U1 RNP antibodies: there is not a defined limit to define "high titer"; anti-U1 RNP antibodies give a speckled nuclear staining pattern on indirect immunofluorescence.

Diagnostic Criteria for MCTD

- | | |
|---|---|
| I. Common Symptoms | 1. Raynaud's phenomenon
2. Swollen fingers or hands |
| II. Anti-U1 Ribonucleoprotein Antibody | |
| III. Mixed Features | |
| A. Systemic lupus erythematosus-like findings | 1. Polyarthritis
2. Lymphadenopathy
3. Facial erythema
4. Pericarditis or pleuritis
5. Leukopenia or thrombocytopenia |
| B. Scleroderma-like findings | 1. Sclerodactyly
2. Pulmonary fibrosis, restrictive changes, or reduced diffusion capacity
3. Hypomotility or dilation of the esophagus |
| C. Polymyositis-like findings | 1. Muscle weakness
2. Elevated serum muscle enzymes
3. Myogenic pattern on electromyogram |

Diagnosis is made when the following three conditions are fulfilled:

1. Positive in either of two common symptoms
2. Positive anti-U1 ribonucleoprotein antibody
3. Positive in one or more findings in two or three of disease categories A, B, or C

Modified from Doria A, Ghirardello A, deZambiasi P, et al: Japanese diagnostic criteria for mixed connective tissue disease in Caucasian patients. J Rheumatol 19:259-264, 1992.

- (2) Cardiac echo may be important to detect early pulmonary hypertension.
- (3) It is advised to perform pulmonary function tests and DLCO at presentation and at subsequent intervals to assess progression of lung involvement.
- (4) Other common tests for connective tissue diseases: (a) CBC (anemia, leukopenia, lymphopenia, thrombocytopenia), positive Coombs' tests (not rarely overt hemolytic anemia), high ESR, high serum immunoglobulins (may be extremely high with IgG levels reaching over 4 g/dl in some patients). (b) Not like SLE, complement levels are usually normal. (c) Rheumatoid factors are elevated in approximately 70%. (d) Anti-Sm and anti-DNA antibodies should be negative.
- (5) There is no single laboratory test that can be used for monitoring disease activity. At intervals, a full survey of autoantibodies, including anti-Sm and anti-dsDNA, should be performed since MCTD can differentiate into SLE.

7. Treatment

- (1) The treatment depends entirely on the pattern of clinical involvement. On the other hand, MCTD can also differentiate into SLE with lethal complications.
- (2) Mild diseases, such as arthralgia, require symptomatic treatment only. Whereas, severe complications, such as myositis or fibrosing alveolitis, need high-dose corticosteroids, often in combination with immunosuppressive drugs.
- (3) MCTD patients are liable to hypersensitivity to DMARDs.
- (4) **High-dose corticosteroids** are indicated for the treatment of severe systemic disease such as **vasculitis**, **myositis** or **fibrosing alveolitis**. May combine with immunosuppressive drugs.
- (5) **Immunosuppressive drugs** (usually **cyclophosphamide**) are used for the induction of remission or for their steroid-sparing effects:
 - (a) The most common indication for induction of remission is **fibrosing alveolitis**, although any SLE-like manifestation such as **nephritis** or **systemic vasculitis** may also require immunosuppression.
 - (b) Cyclophosphamide in a daily oral dose of 1-2mg/kg/day in combination with high-dose corticosteroids.
 - (c) Cyclophosphamide may also be given as pulse therapy: (i) Single IV infusions of 500mg-1g spaced at intervals four weeks or (ii) Weekly oral pulses of 300mg.

Vasculitis

Abbreviation: PAN, polyarteritis nodosa WG, Wegener's granulomatosis MP, microscopic polyangiitis
 CSS, Churg-Strauss syndrome
 HSP, Henoch-Schönlein purpura

(A) Classification of vasculitis

1. Vasculitis may be classified by (a) **the size and type of vessel involvement** (In 1994, the Chapel Hill consensus conference), (b) **the histopathologic features** (leukocytoclastic, granulomatous vasculitis, etc.), (c) **the presence of antineutrophil cytoplasmic antibody (ANCA)**, (d) **the pattern of clinical feature**, or by (e) the **etiological basis** of vasculitis (primary and secondary vasculitis).
2. Classification of primary vasculitis based on the vessel size and the presence of ANCA or immune complex deposition.
3. Vasculitis with the presence of granuloma formation
 - (1) Large-vessel vasculitis: giant cell arteritis, takayasu's arteritis
 - (2) Small-vessel vasculitis: WG, CSS.
4. Major clinical groups of vasculitis:
 - (1) Primary systemic necrotizing vasculitis: PAN, WG, MP, CSS and cryoglobulinemia; patients may present with the following clinical features, which may be progressive and life-threatening.
 - (2) Large-vessel vasculitis: present with symptoms related to large vessel involvement; visual disturbance, headache and temporal tenderness, transient ischemic attacks; **Polymyalgia rheumatica** (Proximal muscle pain with morning stiffness; often occur in giant cell arteritis, but not in other vasculitis)
 - (3) Leukocytoclastic vasculitis (cutaneous vasculitic syndrome): present predominantly with skin vasculitis; HSP, hypersensitivity vasculitis, serum sickness
5. Primary vasculitis and secondary vasculitis (associated with infection, connective tissue diseases, rheumatoid arthritis, spondyloarthropathy, malignancy, or drugs)

(B) Epidemiology

Demographic Associations of the Vasculitides			
Age group	Male-to-female ratio	Ethnic origin	Type of vasculitis
Child	M = F	Any	Henoch-Schönlein purpura
	M > F	Asian > white > others	Kawasaki disease
Young adult	M = F	Middle Eastern > others	Behçet's disease
	F > M	Asian >> others	Takayasu's arteritis
Middle age	M > F	Any	Wegener's granulomatosis, polyarteritis nodosa, Microscopic polyangiitis, Churg-Strauss vasculitis
Elderly	F > M	Caucasian >> others	Giant cell arteritis

(C) Differential Diagnosis for primary systemic vasculitis

- * **Conditions That Can Mimic Primary Systemic Vasculitis:** other connective tissue disorders; systemic infection (esp. infective endocarditis); malignancy; antiphospholipid antibody syndrome; embolic disease; atrial myxoma; cholesterol embolization; vessel stenosis or "spasm"; atherosclerosis; fibromuscular dysplasia; drug-induced vasospasm (e.g., ergots, cocaine, phenylpropanolamine); intravascular lymphoma; vessel thrombosis; disseminated intravascular coagulopathy; thrombotic thrombocytopenic purpura; heparin- or warfarin-induced thrombosis.

Note: Pauci-immune necrotizing crescentic GN can occur alone (as is called primary) or together with other systemic manifestations in ANCA-associated vasculitis.

(D) Wegener's granulomatosis (WG)

1. Young and middle-aged, slight male dominant, past history of chronic sinusitis or upper airway obstruction.
2. Clinical features:
 - (1) Fever, malaise, weight loss
 - (2) **Necrotizing granulomatous lesions of the respiratory tract: chronic sinusitis** (purulent sinus drainage,

nasal ulceration with epistaxis; more seriously with nasal septal perforation or saddle-nose deformation), otitis media (may be with injury of facial nerve), and upper respiratory tract stenosis (often in the subglottic region); a minority of patients initially have indolent or aggressive upper respiratory tract disease alone, but most also have pulmonary disease.

- (3) Pulmonary involvement: (a) Pulmonary infiltration (may be transient and asymptomatic). (b) **Necrotizing granulomatous pulmonary nodules** (may mimic TB and malignancy; could have cavitation); rarely pleural effusion; symptoms of cough and hemoptysis. (c) Pulmonary hemorrhage caused by alveolar capillaritis. **Massive pulmonary hemorrhage caused by capillaritis is the most life-threatening manifestation of ANCA-associated small-vessel vasculitis and warrants rapid institution of aggressive immunosuppressive therapy.**
- (4) **Pauci-immune necrotizing and crescentic glomerulonephritis:** (a) Initial presentation in 20% of patients; but eventually occurs in 80%. (b) Characterized by focal necrosis, crescent formation, and the absence or paucity of immunoglobulin deposits (c) **Same glomerulonephritis in patients with microscopic polyangiitis, Churg-Strauss syndrome, or primary Pauci-immune necrotizing and crescentic glomerulonephritis** (a vasculitic disease limited to the kidney). (d) Causes proteinuria, hematuria and renal function impairment.
- (5) Other manifestations: (a) Ocular inflammation: uveitis, conjunctivitis, scleritis, episcleritis, suppurative otitis (b) Skin lesions: cutaneous purpura, ulceration and nodules. (c) Peripheral neuropathy: mononeuritis multiplex, cerebral vasculitis, cranial nerve deficits. (d) Polyarthritis. (e) Abdominal visceral involvement: abdominal pain, GI bleeding, intestinal infarction, bloody diarrhea. (f) Others: orbital pseudotumor, mastoiditis and hearing loss.

3. Laboratory tests and examinations

- (1) Check CBC and eosinophilia to rule out CSS.
- (2) Elevated CRP and ESR.
- (3) 90% patients will have positive **c-ANCA (proteinase 3-ANCA)**.
- (4) Chest X ray for pulmonary involvement.
- (5) Nasal biopsy for chronic sinusitis to reveal granulomatous change.
- (6) Check renal function test and blood in stool.

4. Treatment

- (1) **Treatment for aggressive WG as well as MP and CSS.**
- (2) Induction of remission: prednisolone (1 mg/kg/day) and/or cyclophosphamide (2 mg/kg/day)
- (3) Approximately 50% of patients with WG have at least one relapse within five years. Treatment similar to the induction regimen is usually reinstated.
- (4) Because relapses may be associated with respiratory tract infections (esp. *Staphylococcus aureus* colonization in nose), the antimicrobial agent trimethoprim-sulfamethoxazole has been evaluated for maintenance of remission, with mixed results.

(E) Polyarteritis nodosa (PAN) and microscopic polyangiitis (MP)

- ◆ Initially included in PAN, MP has been distinguished from PAN in the Chapel Hill consensus conference in 1994 with small vessel (arterioles, capillaries, and veinules) involvement, whereas PAN involves medium-sized arteries.

1. Classification

- ◆ The ACR criteria were developed before the distinction between classic PAN and MP was fully appreciated. **The ACR criteria for the classification of PAN are not particularly helpful for the clinician to use in the diagnosis.**
- ◆ **Distinguishing classic PAN from MP:** Both PAN and MP can involve kidney, peripheral nerves, muscle, and gut. **Only MP, but not PAN, can involve skin and lung and can have glomerulonephritis and positive ANCA. Whereas, PAN may have hepatitis infection and angiographic finding of aneurysms.**

2. Clinical features: may present in a variety of ways. There is a spectrum of severity from mild, limited disease to progressive disease, which may be fatal. Any organ may eventually be affected.

- (1) Constitutional symptoms - fever, anorexia, weight loss.
- (2) **Skin involvement in MP, but not in PAN:** palpable purpura (most common), infarctions, livedo reticularis, ulcerations, subcutaneous nodules and ischemic changes of the distal digits. Skin biopsy: necrotizing vasculitis, with or without leukocytoclasia, of small blood vessels and capillaries (should include dermis to detect medium-sized vessel involvement.)
- (3) Myalgia, arthralgia and **asymmetric, episodic, nondeforming polyarthritis.**
- (4) **Nerve system involvement:** (a) Neuropathy: affects the lower extremities somewhat more often than the upper extremities. The onset may be sudden, with pain and paresthesias radiating in the distribution of a peripheral nerve and it may progress asymmetrically to involve other peripheral nerves (**mononeuritis multiplex**). The final result may be a symmetric polyneuropathy involving all sensory modalities and motor functions. (b) CNS involvement: less common; includes headache, seizures, cranial nerve dysfunction, cerebral hemorrhage, and stroke, caused by cerebral vasculitis
- (5) Renal involvement
 - (a) **PAN: vascular nephropathy without glomerulonephritis;** hypertension; multiple renal infarctions resulting in renal failure; renal angiography of multiple aneurysms (may be complicated with perinephric

- hematoma) and infarcts.
- (b) **MP: necrotizing, and sometimes rapidly progressive, glomerulo- nephritis** is the major feature of MPA. Proteinuria is common and, rarely, a nephrotic syndrome may develop.
- (6) Gut involvement: (a) Abdominal pain, infarction, hemorrhage, mesenteric thrombosis, and liver function abnormalities. (b) Angiography in PAN shows microaneurysm. The location and extent of vascular involvement on angiography does not correlate with the severity or type of abdominal organ involvement. (c) **Hepatitis B infection is associated with PAN.**
- (7) **Pulmonary involvement:** (a) **Common in ANCA-positive small-vessel vasculitis, including MP;** (b) **PAN does not involve lung, except pleural effusion.** (2) Pulmonary infiltrates (can be diffuse), nodules, cavities or interstitial fibrosis; pulmonary hemorrhage (29% of MPA). (c) MP should be considered in the differential diagnosis of any acute pulmonary-renal syndrome.
- (8) Cardiac involvement: is common pathologically, but not clinically significant. Features include AMI, cardiomegaly, CHF (due to coronary artery disease and/or severe hypertension) and cardiomyopathy. Pericarditis is rare except as a complication of uremia.
- (9) Antineutrophil cytoplasmic antibodies found predominately in microscopic polyangiitis.
- (10) Secondary PAN: RA, Sjögren's syndrome, mixed cryoglobulinemia, hairy cell leukemia, myelodysplastic syndrome and other hematological malignancies.

3. Laboratory tests and examinations

- (1) Most tests are nonspecific and reflect the systemic inflammation; elevated ESR and CRP; normochromic, normocytic anemia, thrombocytosis; diminished levels of serum albumin. Low complements in secondary PAN.
- (2) Impaired renal function and nephritis (red cells, red cell casts) in MP.
- (3) PAN usually manifests within the first 6 months of hepatitis B infection. MP is not associated with hepatitis B infection. Hepatitis C infection is associated with polyarteritis, especially in the context of cryoglobulins and hypocomplementemia.
- (4) ANCA: Using the Chapel Hill definition, ANCA occurs rarely in classic PAN. In contrast, ANCA are sensitive markers for MP (50% c-ANCA) and other types of arteritis associated with pauci-immune glomerulonephritis.
- (5) Angiography: long segments of smooth arterial stenosis alternating with areas of normal or dilated artery, smooth tapered occlusions, thrombosis and the lack of significant atherosclerosis. The dilated segments include saccular and fusiform aneurysms which strongly suggest classic PAN

4. Treatment and prognosis

- (2) The management should be based on the extent and rate of involvement: (a) for patients with limited and nonprogressive disease, **daily or divided daily doses of prednisolone** will usually suffice. (b) For patients with extensive visceral involvement (especially cardiac, CNS or renal disease): initial treatment with high dose of **prednisolone (1 mg/kg/day)**. **Cytotoxic agent** (cyclophosphamide or azathioprine) may be added as steroid-sparing agents or for patients who do not respond well to steroid. As the clinical status improves and as the **ESR** returns to normal, tapering of the prednisolone can begin (initially, 5-10mg every 1-2 weeks less decrements for low dose steroid). Frequently the patient must be maintained on a low dose of prednisolone for an indefinite period of time. (c) It is unclear whether antiviral therapy should supersede conventional regimens in patients with hepatitis B associated vasculitis.
- (3) Minimize vascular comorbidity: stop smoking; control hypertension, hyperlipidemia and diabetes mellitus.
- (4) Cases poorly responding to adequate steroid: glucocorticoid-resistant vasculitis, superimposed infection, or progression of occlusive vasculopathy.

(F) Churg-Strauss syndrome (CSS)

1. CSS has three phases:
 - (1) Past history of **asthma** or **allergic rhinitis**.
 - (2) Eosinophilic infiltration phase: (a) Virtually all patients have eosinophilia (more than 10% eosinophils in the blood). (b) Cause eosinophilic pneumonia or gastroenteritis.
 - (3) The vasculitic phase: (a) Characterized by systemic small-vessel vasculitis with granulomatous inflammation. (b) Occurs within three years of the onset of asthma, although it may be delayed for several decades.
2. Approximately 70% of patients with this disease have ANCA, usually p-ANCA (MPO-ANCA).
3. Compared with MG and microscopic polyangiitis, CSS has much less frequent and less severe renal disease, but more frequent neuropathy and cardiac disease.
4. **Coronary arteritis** and **myocarditis** are the principal causes of morbidity and mortality, accounting for approximately 50% of deaths, and can be reduced by early treatment. **High-dose steroid** treatment alone is often adequate, although refractory or relapsing disease may require the addition of a cytotoxic drug (e.g. cyclophosphamide) in a regimen similar to that used for WG or microscopic polyangiitis.

(G) Henoch-Schönlein purpura (HSP)

1. It is the most common systemic vasculitis in children with a peak incidence at five years old.
2. HSP is clinically defined as a form of small-vessel vasculitis with the triad of nonthrombocytopenic purpura, arthritis and abdominal pain. However, pathological demonstration of vascular deposition of **IgA-dominant immune complexes** (preferentially in veinules, capillaries, and arterioles) is required for the diagnosis. So it may be associated with IgA nephropathy.

3. Clinical features

- (1) Often begins after an upper respiratory tract infection.
- (2) The common manifestations: (a) **Purpura**, (b) **Polyarthrits**: predominantly involving the lower limbs and is transient; may precede the rash and usually precedes the renal manifestations. (c) **GI symptoms**: severe cramping and colicky abdominal pain; sometimes with GI bleeding; rarely, protein-losing enteropathy and even GI perforation. There is no direct temporal relationship between articular and intestinal symptoms.
- (3) Around half the patients have hematuria and proteinuria, but only 10% to 20% have renal insufficiency. Rapidly progressive renal failure is rare.
- (4) Pulmonary disease and peripheral neuropathy are uncommon.

4. Laboratory tests

- (6) Similar to other small-vessel vasculitis and ANCA for organ involvement and for differential diagnosis.
- (7) Skin biopsy to reveal IgA deposition.

5. Treatment

- (1) Usually remits spontaneously within a week, but recurrences are frequent before complete remission is achieved. Supportive care may be the only treatment needed. The overall prognosis is excellent.
- (2) The main long-term morbidity is from progressive renal disease. End-stage renal disease develops in approximately 5 percent of patients.
- (3) Treatment for aggressive HSP purpura glomerulonephritis is controversial. It is shown that combined therapy with steroid and azathioprine may be beneficial.

(H) Cutaneous leukocytoclastic vasculitis (hypersensitivity vasculitis)

1. Cutaneous vasculitis refers to **vasculitis within the small to medium-sized vessels in the skin**. It is called as "leukocytoclastic vasculitis" because of the classical pathological finding in the vessel wall (fibrinoid necrosis of the vessel walls with infiltration of polymorphonuclear leukocytes, some of which are disrupted, resulting in the presence of nuclear debris with the tissue).
2. **Circulating immune complexes**, together with cytokines and endothelial cell dysfunction, have been postulated to be involved in the pathogenesis.
3. Cutaneous leukocytoclastic vasculitis can be found in several systemic diseases. It therefore can be part of systemic manifestations.
 - (1) Other vasculitic syndromes: WG, PAN, MP.
 - (2) Other rheumatic diseases: SLE, RA, dermatomyositis, Sjögren's syndrome.
 - (3) Infection: HBV, infective endocarditis, HIV, streptococcus.
 - (4) Paraproteins: cryoglobulinemia, hyperglobulinemia, macroglobulinemia, cryofibrinogenemia, serumsickness.
 - (5) Others: inflammatory bowel diseases, neoplasm (**paraneoplastic vasculitis**).

4. Clinical features

- (1) Skin: (a) Vary from transient urticaria-like lesions to necrosis, depending on the size of the vessel involved. (b) Most common are **palpable purpura** and **urticaria-like lesions (urticular vasculitis)**; in contrast to urticaria, the lesions are often long-lived, lasting between 6 and 72 hours, may resolve with some residual pigmentation or ecchymosis, and are felt painful or burning rather than pruritic. (c) Less common are livedo reticularis, ulcerations or necrosis. (d) Most forms of cutaneous vasculitis are systemic disorders that may or may not have recognizable abnormalities in other organ systems.
- (2) Systemic involvement: depending on the underlying systemic disease. Arthritis, glomerulonephritis, gastrointestinal hemorrhage and colic are the most common manifestations since the vascular supply is rich in the gut, the kidneys, the lungs and the musculoskeletal system.
- (3) **Urticular vasculitis**: DD from chronic urticaria (see the table).
- (4) Vasculitis associated with paraproteinemia: (a) Occur in patients with an abnormal circulating protein. (b) **Cryoglobulinemia**: a chronic or recurrent cutaneous vasculitis associated with hepatitis C infection; a predilection for acral disease; treated with interferon has led to disease control. (c) **hyperglobulinemic purpura**: some early lesions may be nonpalpable; the late lesions may not reveal leukocytoclastic vasculitis on biopsy; associated with Sjögren's syndrome and SLE with anti-Ro antibody.

5. Laboratory investigations

- (1) Find an etiologic association.
- (2) For acute disease with an obvious etiology such as a drug or infection, the evaluation need not assess all possible causes.
- (3) For chronic disease, or in whom there is not an obvious etiology, the workup is more extensive. An assessment for **paraproteins** is necessary in this group of patients.
- (4) Elevated ESR and hypocomplementemia.
- (5) Assess the presence, and severity, of systemic involvement.
- (6) Skin biopsy is required for diagnosis

6. Treatment

- (2) The acute variant is often self-limited.
- (3) Prognosis is dependent upon the organ systems involved and the severity of involvement.
- (4) Treat the underlying disease.
- (5) Patients without an identifiable cause or associated phenomenon who require therapy can be treated with a variety of agents, including steroid, colchicine, NSAID. Steroid in a high enough dosage is almost always effective.
- (6) Severe systemic necrotizing vasculitis should be treated rapidly and aggressively with systemic corticosteroids and an immunosuppressive agent.

(I) Other vasculitis

<1> Giant cell arteritis (Temporal arteritis)

1. Giant cell arteritis commonly accompanies polymyalgia rheumatica.
2. **Very rare in Asians.**
3. Seldom occurs below 50 years of age, mean age is 70; female:male = 2:1.
4. Clinical features:
 - (1) The onset can be acute or insidious.
 - (2) Constitutional features: fever, fatigue, anorexia, weight loss.
 - (3) Symptoms related to involved arteries: usually **headache** around the temporal and occipital arteries. The vessels may become thickened, tender and nodular with absent or reduced pulsation.
 - (4) Ophthalmologic features: caused by ocular vessel occlusion; visual disturbance in 25-50% of cases; blindness in 6-10%.
 - (5) Others: pain on chewing (claudication of jaw muscles); loss of taste.
5. Laboratory tests:
 - (1) Elevated ESR; anemia; normal WBC and thrombocyte levels.
 - (2) Temporal artery biopsy.
6. Treatment:
 - (1) Steroid with prednisolone in the dose of 40 – 60 mg daily is mandatory for rapid symptom improvement and reduce the incidence of complication, such as blindness. Steroid should be started immediately when giant cell arteritis is suspected.

<2> Takayasu's arteritis

1. A chronic inflammatory disorder primarily affecting **the aorta and its major branches**.
2. **More common in Asians.**
3. Most commonly in women under 40 years old (mainly 15-25 years old;
4. Female : male = 9 : 1.
5. Clinical features:
 - (7) The early systemic phase: malaise, fever, night sweats, weight loss, fatigue, myalgias, arthralgias and pain over the artery.
 - (8) Late occlusive phase: claudication (particularly in the upper limbs), headaches, postural dizziness, syncope, and paresthesia. The visual disturbances (reduced visual acuity, diplopia and amaurosis fugax) may be dependent on posture (partial neck flexion may be needed to prevent from vascular insufficiency in sever cases). Hypertension (with renal artery stenosis) is common. Pleuritis, pericarditis, angina, Raynaud's phenomenon, and hemiplegia (as a consequence of cerebral infarction) are uncommon. Skin lesions are rare.
 - (9) Physical examination: **arterial bruits** (in most cases, particularly in the subclavian, carotid and abdominal regions); **Reduced or absent upper limb pulses** (depends upon the stage of disease); different limb blood pressures; funduscopic abnormalities.
3. Lab tests and examination: (1) Mild anemia of chronic disease and mild leukocytosis; elevated ESR in ~ 85% of patients; possibly elevated immunoglobulin levels. (2) Chest radiography: widened aortic shadow, irregularity of the descending aorta, pulmonary arterial changes and cardiac enlargement with hilar fullness. (3) **Arteriography** is the critical diagnostic procedure: the most commonly involved sites are subclavian, carotid and renal arteries

- as well as the aorta. (4) Others: Ultrasonography for carotid artery stenosis.
- Treatment: (1) Most will respond to high dose steroid (prednisolone in a dose of 1mg/kg) (2) Patients who fail to respond to steroid (as shown by persistent systemic symptoms or progressive vascular insufficiency), may be treated with a cytotoxic agent (either methotrexate, azathioprine or cyclophosphamide). (3) Percutaneous transluminal angioplasty for arterial stenosis (particularly helpful for renovascular hypertension). (4) Surgical intervention with artery reconstruction and aortic bypass. Suppression of inflammation prior to surgery may be needed to decrease the complication of anastomotic false aneurysms and graft occlusion.

<3> Cryoglobulinemic Vasculitis

- Cryoglobulinemic vasculitis involves inflammation of veinules, capillaries, and arterioles caused by the localization of ***mixed cryoglobulins*** in vessel walls.
- The average age of onset is approximately 50 years old. Most patients have an associated with ***hepatitis C viral infection***.
- The most frequent manifestations are purpura, arthralgias, and nephritis. The main cause of morbidity is progressive glomerulonephritis, which most often has a type I membranoproliferative phenotype.
- Lab tests: cryoglobulins and rheumatoid factor, anti-HCV antibody, very low levels of early components (especially C4) with normal or slightly low C3 levels.
- Treatment: (1) Mild disease, such as slight purpura and arthralgias, usually is adequately treated with NSAIDs alone. (2) Treatment for glomerulonephritis: usually requires steroid and a cytotoxic drug (e.g. cyclophosphamide), which improves the outcome of glomerulonephritis and also ameliorates purpura, arthralgias, and other vasculitic symptoms. Plasmapheresis has been used, but its value is unproved. (3) Treatment of HCV infection with interferon.

Clinical Features and Primary Treatment of the Major Systemic Vasculitis Syndromes		
Vasculitis	Common presenting features	Primary treatment
Hypersensitivity vasculitis	Palpable purpura	Often self-limited if offending agent is removed. If isolated to skin, may not require therapy. In more severe cases, moderate- to high-dose corticosteroid therapy may be needed.
Henoch-Schönlein purpura	Palpable purpura, arthritis, glomerulonephritis, intestinal ischemia	Often self-limited and requires no treatment. Steroid therapy for some cases of gastrointestinal or renal involvement.
Cryoglobulinemia	Arthritis, Raynaud's phenomenon, glomerulonephritis, palpable purpura	Corticosteroids; plasmapheresis for severe involvement. Antiviral therapy required if associated with hepatitis C.
Polyarteritis nodosa	Peripheral neuropathy, mononeuritis multiplex, intestinal ischemia, renal ischemia, testicular pain, livedo reticularis	High-dose corticosteroids, often with cytotoxic agents (e.g., cyclophosphamide)
Microscopic polyangiitis	Pulmonary hemorrhage, glomerulonephritis	High-dose corticosteroids, often with cytotoxic agents (e.g., cyclophosphamide)
Churg-Strauss vasculitis	Allergic rhinitis, asthma, eosinophilia, pulmonary infiltrates, coronary arteritis, intestinal ischemia	High-dose corticosteroids, often with cytotoxic agents (e.g., cyclophosphamide)
Wegener's granulomatosis	Recurrent epistaxis or sinusitis, pulmonary infiltrates and/or nodules, glomerulonephritis, ocular involvement	High-dose corticosteroids and cyclophosphamide. Corticosteroids and methotrexate may be used for less severe involvement.
Kawasaki disease	Fever, conjunctivitis, lymphadenopathy, desquamating rash, mucositis, arthritis, coronary artery aneurysms	High-dose aspirin and intravenous immune globulin
Giant cell, or temporal, arteritis	Headache, polymyalgia rheumatica, jaw or tongue claudication, scalp tenderness, fever, vision disturbances	High-dose corticosteroids
Takayasu's arteritis	Extremity claudication, arthralgias, constitutional symptoms, renal ischemia	High-dose corticosteroids

Behçet's Disease

- ◆ A subset of vasculitis with the inflammatory condition of multiple organ systems, in which **recurrent oral and genital ulcers** are the most typical signs. It used to be classified as a member of spondyloarthropathy because of arthritic presentation.
- ◆ Less common: cerebral vasculitis, arterial aneurysms, deep vein phlebitis, aseptic meningitis, and bowel ulcers.
- ◆ It has been related to the spondyloarthropathies (since sacroiliitis and spondylitis may be present) and to inflammatory bowel disease. Virtually all features of Behçet's disease can be seen in Crohn's disease.
- ◆ Association with HLA-B51.
- ◆ Pathogenesis: (1) Oral ulcers: emigration of T cells and plasma cells from dermal vessels to epidermis. (2) **Immune complex-mediated vasculitis**: IgM and C3 deposits in dermal vessels; leukocytoclastic vasculitis in palpable purpura; dermal round cells and neutrophilic infiltrates in lesions (3) Venous occlusion could be caused by vasculitis with thrombus formation.

(A) Classification criteria

International criteria for classification of Behçet's disease <i>(The major criteria plus two of other criteria)</i>	
MAJOR CRITERIA : Recurrent oral ulceration	
Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient, which recurred at least 3 times in one 12-month period.	
OTHER CRITERIA :	
1. Recurrent genital ulceration	Aphthous ulceration or scarring, observed by physician or patient.
2. Eye lesions	Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination or retinal vasculitis observed by ophthalmologist
3. Skin lesions	Erythema nodosum observed by physician or patient, or pseudofolliculitis, or papulopustular lesions or acneiform nodules observed by physician in postadolescent patients not on corticosteroid treatment
4. Positive pathergy test	Read by physician at 24-48 h Sterile pustule development at the site of needle prick to the skin
OTHER MINOR CRITERIA EVOCATIVE OF BEHÇET DISEASE :	
<ul style="list-style-type: none"> • Subcutaneous thrombophlebitis – Deep vein thrombosis • Epididymitis • Arterial occlusion or/and aneurysms • Central nervous system involvement • Arthralgia – Arthritis • Familial history of Behçet disease • Gastrointestinal features 	

(B) Clinical Manifestations: all events are episodic

1. **Mucosal ulcers:** (a) **Multiple painful oral aphthous ulcers** precede other signs in nearly all patients. Residual scarring is uncommon. (b) **Painful genital ulcers** are less prevalent.
2. **Eye lesions:** (a) **Uveitis**: can involve anterior and posterior uvea as well as retina; may develop within months or years after oral ulcers. (b) **Hypopyon**, an extreme form of anterior uveitis. (c) May have combination of uveitis and **retinal vasculitis**. (d) Symptoms: painless blurring of vision; spots in the vision. Could cause blindness within years.
3. **Cutaneous lesions:** (a) **Recurring papules and pustules**: several millimeter in diameter on upper trunk and thighs. (b) **Erythema nodosum** (c) **Pathergy response**: is an erythematous papule or pustule (more than 2-5 mm) arising 24-48 hours after a skin injection or needle prick (**Pathergy test**).
4. **Arthritis:** (a) 1/2 of patients have non-erosive arthritis in large joints, usually during exacerbation. (b) Synovial fluid: inflammatory (5000-25000/mm³) with PMN dominant. (c) Sacroiliitis with low back pain can occur.
5. **CNS involvement:** (a) Aseptic meningitis with headache, fever and neck stiffness. (b) May be associated with stroke. (c) Neurological deficits from ischemic vasculitis: hemiparesis, cerebellar ataxia. The deficits may remain after treatment. (d) Cerebral venous thrombosis: headache with increased CSF pressure.
6. **Involvement of vessels:** (a) **Phlebitis**: 20% of patients have deep vein phlebitis. Could result in IVC and SVC syndromes and Budd-Chiari syndrome. (b) Nodules caused by superficial phlebitis on extremities are more common. (c) **Arterial pseudoaneurysm** is more common than ischemic occlusion, and may result in rupture. (d) Pulmonary embolism is rare. (e) Phlebitis or aneurysms at the sites of trauma, such as venous or arterial puncture sites.
7. **Pulmonary involvement:** (a) Pulmonary arterio-bronchial fistula: sudden and severe hemoptysis. (b) Pulmonary embolism.
8. **GI lesions:** Mucosal ulcerations of the GI tract result in abdominal pain, bleeding and perforation.
9. Others: **Nephritis, secondary amyloidosis, epididymitis**.
10. **DIFFERENTIAL DIAGNOSIS:** (1) Crohn's disease may also have aphthous ulceration, uveitis and skin lesions, but reveals granulomatous enteritis on pathology. (2) Cicatricial or mucous membrane pemphigoid and lichen planus. (3) Oral-genital ulceration in hypereosinophilic syndrome, myelodysplastic syndrome and AIDS. (4) **A patient should not be diagnosed with Behçet's disease when the oral and genital ulcers are the only findings.**

(C) **Laboratory tests**

1. No specific pathologic or serologic tests for diagnosis or for evaluating the disease activity. However, laboratory tests should be aimed at the exclusion of other rheumatic diseases. Acute phase reactants are sometimes elevated in active disease, but uveitis could be active when ESR is normal.
2. May arrange skin biopsy for erythema nodosum.
3. Arrange angiography and/or venous scan for detecting vessel thrombosis.
4. Checking HLA-ABC to detect the presence of HLA-B51 may be helpful for diagnosis.
5. Detection of CNS involvement: (1) Brain SPECT scan may be useful to detect and evaluate the CNS involvement. (2) Cerebral angiography is seldom indicated because the vessels involved usually small. (3) CSF examination is not diagnostic. The finding includes: (i) Increased cell count (usually less than 100/mm³) when Behçet's vasculitis present. PMN dominance in acute stage, lymphocytes dominance a few days later. (ii) Protein could be normal or slightly elevated.
6. Positive pathergy test is less prevalent in Taiwan.

(D) **Treatment**

1. Topical corticosteroid for oral ulcers.
2. **Prednisolone** at low dose may be effective for mild systemic manifestations. High dose of steroid, even IV pulse methylprednisolone may be needed for acute cerebral and pulmonary vasculitis.
3. **Colchicine** (0.6-1.2 mg/day) can reduce the severity and frequency of oral and eye lesions because of the increase in neutrophil potentiating activity in Behçet's disease.
4. Cytotoxic agents may be added for intractable manifestations: **Azathioprine** or **Cyclosporin A**.
5. Anti-coagulant as well as low-dose aspirin is indicated in cases with the evidence of vessel occlusion.
6. Other agents: (1) **Plasma exchange** sometimes is used to treat resistant CNS involvement. (2) **Thalidomide** (50-200 mg/day) suppresses the resistant ulceration, but be aware of the side effect of axonal neuropathy. (3) Chlorambucil is recommended in the textbook, but its toxic side effects, especially bone marrow suppression limit its use.

Immunodeficiency diseases

<1> Introduction

- Definition: diseases due to the disruption of the immune integrity
- Classifications:
 - T cell (cellular) immunodeficiency; B cell (humoral or antibody) immunodeficiency; macrophages defect, neutrophil defect, and complement deficiency
 - Primary or secondary immunodeficiency
 - Transient or permanent defects
- Primary immunodeficiency: usually inherited
 - T cell defect with combined immunodeficiencies
 - Severe combined immunodeficiency (SCID)
 - Adenosine deaminase (ADA) deficiency
 - Reticular dysgenesis
 - Antibody immunodeficiencies
 - X-linked agammaglobulinemia (XLA)
 - IgA deficiency
 - Hyper-IgM syndrome
 - Common variable immunodeficiency (CVID)
 - Transient hypogammaglobulinemia of infancy
 - Other well-defined syndromes
 - Wiskott-Aldrich syndrome with eczema, thrombocytopenia and repeated infections)
 - Ataxia telangiectasia (cerebellar ataxia, oculocutaneous telangiectasia and immunodeficiency
 - DiGeorge's syndrome (isolated T cell deficiency)
 - Syndromes associated with immunodeficiency
 - Down syndrome, chronic mucocutaneous candidiasis, hyper-IgE syndrome, chronic granulomatous disease, partial albinism and WHIM syndrome (warts, hypogammaglobulinemia, infection, myelokathexis [retention of leukocytes in a hypercellular marrow]), phagocytic defects with early onset of periodontal disease.
 - Complement deficiencies
- Secondary immunodeficiency
 - Infections (HIV-1 and HIV-2)
 - Immunodeficiency due to malignancies, malnutrition, protein-losing enteropathy, drugs (treatment with immunosuppressive agents), X-ray treatment, chronic stress, IgA deficiency associated with phenytoin or penicillamine, thymoma associated with hypogammaglobulinemia

<2> Eiology

- Inheritance Patterns of primary immunodeficiency:
 - X-linked inheritance pattern,
 - Autosomal recessive inheritance such as in some forms of SCID, CGD, and hyper-IgM syndrome.
- Other primary immunodeficiencies do not have a defined pattern of inheritance but clearly are found in families.
- Secondary immunodeficiency due to causes mentioned above.

<3> Suspect a immunodeficiency disease based on the medical history

- Medical history: a thorough history of illness is necessary for a directed, concise evaluation for suspected immunodeficiency.
- The time of onset of symptoms: infants who present with frequent infections developing from birth to 3 months of age are likely to have maternal immunoglobulin present. Deficiencies in the immune system at this age are likely due to severe deficiencies in other immune components such as neutrophil defects, complement defects, or T cell and combined immunodeficiencies.
- Congenital immunodeficiency usually (but not always) has a characteristic appearance in infants, children, and adults according to the sex of the child, age of the patient, immunization history with live vaccines, and exposure to infections.

- Due to the presence of protective maternal immunoglobulin, infants with primary immunoglobulin defects such as Bruton agammaglobulinemia usually do not present with serious infection until 3 months to 6 months of age when these antibodies are lost, or later if they have been treated with antibiotics for upper respiratory infections.
- Infection with encapsulated organisms is the hallmark of humoral immunodeficiency.
- Recurrent serious infections, especially with opportunistic organisms, is the hallmark of cellular immunodeficiency.
- Recurrent infection, especially with staphylococcal or gram negative bacterial organisms and aspergillus or other fungal organisms is the hallmark of phagocytic immunodeficiency.
- Diseases produced by various forms of neutropenia are relatively common, but inherited forms of neutrophil dysfunction are quite rare.
- Physical examination of the patient is essential with attention to cutaneous or other deep-seated abscesses and organomegaly.
- Infants with Wiskott-Aldrich syndrome, or immunodeficiency with thrombocytopenia and eczema, also usually present prior to 18 months of age.
- In contrast, patients with selective IgA deficiency generally do not present until after 18 months of age.
- Common variable immunodeficiency typically presents in the second decade of life, but may present earlier or much later.
- Immunization history: a history of infection to a live viral vaccine is suspicious for immune deficiency since infants with T cell defects, T and B cell defects, and B cell defects may contract severe or fatal infections from live vaccines.
- The history of the type and severity of illness and infection:
 - Prolonged course or unexpected complications of infection in children.
 - **Recurrent infections:** that involve more than one site are more suspicious for immunodeficiency than those involving a single site.
 - **History of unusual severe infections:** pneumonia, meningitis, sepsis, septic arthritis, osteomyelitis, or abscess
 - Infection with microorganisms with low pathogenicity (opportunistic organisms): *Candida albicans* or *Pneumocystis carinii*.
 - Antibody deficiency tend to have the infection with extracellular pyogenic organisms such as with *Haemophilus*, *Pneumococcus*, and *Streptococcus*. In contrast, patients with defects in cell-mediated immunity have recurrent infections with viruses, fungi, protozoa and mycobacteria. Furthermore, infections with unusual bacteria such as with *Serratia marcescens*, *Staphylococcus epidermidis*, and *Pseudomonas* may indicate a possible neutrophil defect. Disseminated neisserial infections may be found in individuals deficient in the terminal complement components.
- Family history is vital in evaluation of suspected immunodeficiency. A history of early infant deaths should be sought. A clear pattern of inheritance may be found; information regarding possible consanguinity should be obtained. Family members of immunodeficient patients will often have histories of autoimmune disease or of connective tissue disease.

Laboratory tests for the investigation of the integrity of immunity

- (1) Complete blood count and differential to evaluate the total numbers of neutrophils, lymphocytes, eosinophils, and platelets.
 - If the absolute lymphocyte count is normal, it is unlikely that the patient has a severe T lymphocyte defect.
 - It is important to remember, however, that infant lymphocyte counts are normally very high. For example, at 9 months of age when infants affected with severe cellular immunodeficiency are likely to present, the lower limit of normal is 4,500 lymphocytes/mm³.
- (2) **Tests to evaluate the cellular (T cell) immunodeficiency**
 - A chest radiograph, especially a lateral view, may delineate a small thymus gland and interstitial lung disease, hallmarks of congenital T cell deficiency.
 - Delayed hypersensitivity skin tests
 - T cell functional assays, such as lymphocyte proliferation assays to mitogens, antigens, and allogeneic cells.
 - Consideration should be given to performing tests for HIV infection.
- (3) **Tests for evaluating the humoral immunity**
 - Serum immunoglobulin measurements.
 - Serum isohemagglutinin titer.

- Humoral immune responses to vaccination.
- Measurement of IgG subclasses.

(4) Tests for evaluating phagocytic cell disorder

- Neutrophil count
- Phagocyte chemotaxis.
- Phagocyte oxidative burst assay for chronic granulomatous disease
- Patients with elevated neutrophil counts at all times need to have a test of neutrophil surface glycoproteins (leukocyte adhesion deficiency).

(5) Tests for evaluating complement deficiency

- Total hemolytic complement (CH_{50})
- Alternative pathway hemolytic assay (APH_{50})
- Normal C3 and C4 levels in the face of undetectable CH_{50} is strong evidence of congenital complement component deficiency, whereas a decrease in C4 and/or C3 with undetectable CH_{50} suggest complement consumption.
- The evaluation of specific component deficiency requires tests not available in the majority of clinical laboratories.

Selective IgA Deficiency

- Frequency: approximately one out of every 600 people
- Lack of immunoglobulin A (IgA), a type of antibody that protects against infections of the mucous membranes lining the mouth, airways, and digestive tract.
- *Causes of IgA deficiency:* failure of B cells to switch to IgA-producing B cells
- *The symptoms of IgA deficiency:* Many people with IgA-deficiency are healthy, with no more than the usual number of infections. Those who do have symptoms typically have recurring ear, sinus, or lung infections.
- *The diagnosis of IgA deficiency:* People with IgA deficiency have low levels of IgA antibodies in their blood. In contrast, their levels of IgM and IgG usually are normal. IgA-deficient people also have normal levels of immune system cells, including T cells and phagocytes, and complement proteins.

Common Variable Immunodeficiency (CVI)

- In most cases, however, symptoms do not show up until the teen years or early adulthood.
- CVI is also called as hypogammaglobulinemia, adult-onset agammaglobulinemia, late-onset hypogammaglobulinemia, acquired agammaglobulinemia
- *The signs and symptoms of CVI:* frequent bacterial infections of the ears, sinuses, bronchi, and lungs, painful swollen joints in the knee, ankle, elbow, or wrist, problems involving the digestive tract, an enlarged spleen and swollen glands or lymph nodes
- Along with other autoimmune problems, some develop autoantibodies that attack their own blood cells. People with CVI also have an increased risk of developing some cancers.
- *The diagnosis of CVI:* decreased levels of IgG and IgA with low-to-normal IgM levels
- *How is CVI treated:* CVI patients receive intravenous immunoglobulin (IVIG) every 3 to 4 weeks to restore normal antibody levels. Bacterial infections are treated with antibiotics..

X-Linked Agammaglobulinemia (XLA)

- Prevalence: one out of 100,000 people have XLA.
- Gene mutation in XLA: Mutations in a gene, BTK, on the X chromosome cause XLA. This gene normally produces a protein that B cells need to mature.
- *The symptoms of XLA:* Infants with XLA develop frequent pus-producing infections of the inner ear, lungs, and sinuses. Serious infections can develop in the bloodstream and internal organs. They tend to cope well with most short-term viral infections, but are very susceptible to chronic viral infections such as hepatitis, polio, and ECHO viruses. They may fail to grow to normal height or to gain weight. Their tonsils and adenoids are often missing.
- *The diagnose of XLA:* low levels of mature B cells and serum immunoglobulin levels. No antibody response to specific vaccines.

Hyper-IgM Syndrome

- Hyper-IgM is a rare immunodeficiency disease in which the immune system fails to produce IgA and IgG antibodies.
- The cause of hyper-IgM syndrome: Most cases of hyper-IgM syndrome are linked to the X chromosome. X-linked

Hyper-IgM syndrome is caused by mutation in CD40L gene.

- The symptoms of hyper-IgM syndrome: Infants usually develop recurring upper and lower respiratory infections within the first year of life. Other signs of the disease include enlarged tonsils, liver, and spleen, chronic diarrhea, and an increased risk of unusual or opportunistic infections.
- The diagnosis of hyper-IgM syndrome: The doctor will order laboratory tests that show normal numbers of T and B cells, but high levels of IgM and very low IgG and IgA. Patients also may have neutropenia, a low number of white blood cells.

Chronic Granulomatous Disease (CGD)

- Frequency: about four or five of every million people
- Males are four times more likely to get this disease than are females.
- The causes of CGD: mutations in one of four different genes. The abnormal genes cannot make proteins necessary to produce oxygen radicals, such as hydrogen peroxide and superoxide, which kill bacteria and fungi.
- The symptoms of CGD: children between three months and two years of age who have had fever, skin rash, persistent cough, gum disease, swollen glands or lymph nodes, enlarged liver and spleen. Children with CGD, however, may not develop symptoms until as late as adolescence. Repeated infections can result in granuloma formation in the skin, lungs, lymph nodes, liver, or bones.
- The diagnosis of CGD: Testing the respiratory burst in phagocytes.

Leukocyte Adhesion Deficiency (LAD)

- Frequency: one out of every million people.
- LAD is autosomal recessive disease
- The causes of LAD: a lack of CD18, which is normally found on the cell surface of phagocytes.
- The symptoms of LAD: children with LAD cannot clear pathogens due to the failure of the migration of phagocytes into the inflammatory site
- The diagnosis of LAD: detecting the expression of CD18.

Severe combined immunodeficiency (SCID)

● **Background**

- SCID is a heterogeneous group of genetic disorders that lead to severe dysfunction of T and B cells. Without intervention, the severe immune dysfunction results in severe infection and death in children by age 2 years.
- Approximately 1 in 100,000 births.

● **Various SCID disorders and their the genetic alteration:**

(1) **X-linked SCID:**

- The most common genetic condition responsible for SCID: these patients account for approximately 50% of all patients with SCIDs.
- Mutation of the common γ chain for the receptors of IL-2, IL-4, IL-7, IL-9, and IL-15.
- Loss of IL-4R function leads to the inability of B cells to class switch. Loss of IL-7R function leads to the loss of an anti-apoptotic signal, resulting in a loss of T-cell selection in the thymus. Loss of IL-7R function is also associated with the loss of a T-cell receptor (TCR) rearrangement. Loss of IL-15R function leads to the ablation of NK cell development.
- Lymphopenia occurs primarily from the absence or near absence of T cells ($CD3^+$) and natural killer (NK) cells. Variable levels of B cells occur, which do not make functional antibodies.

(2) **JAK3 deficiency:** JAK3 is a protein tyrosine kinase that associates with the common γ chain of the IL receptors. Deficiency of this protein results in the same clinical manifestations as those of X-linked SCID.

(3) **Adenosine deaminase (ADA) deficiency and purine nucleoside phosphorylase (PNP) deficiency:**

- These are associated with enzyme deficiencies in the purine salvage pathway; toxic metabolites are responsible for the destruction of lymphocytes that cause the immune deficiency.
- Lymphopenia occurs from the death of T and B cells secondary to the accumulation of toxic metabolites in the purine salvage pathway. Functional antibodies are decreased or absent.

(4) **Bare lymphocyte syndrome:**

- Deficiency of major histocompatibility complex (MHC). MHC type II is decreased on mononuclear cells. MHC type I levels may be decreased, or MHC type I may be absent. The defect occurs in a gene regulating expression of MHC type II.
- The lymphocyte count is normal or mildly reduced, the $CD4^+$ T cells are decreased, and the $CD8^+$ T

cell numbers are normal or mildly increased. The B-cell numbers are normal or mildly decreased, but the ability to make antibodies is decreased.

(5) IL-2 deficiency:

- a. These occur secondary to poorly defined defects in IL-2 production.
- b. Normal, or near normal, numbers of T cells exist (both CD4⁺ and CD8⁺). The T cells fail to proliferate in vitro when stimulated with mitogens, unless IL-2 is added to the culture medium. The production of functional antibody is decreased.

(6) ZAP-70 deficiency:

- a. ZAP-70 is a tyrosine kinase, which is important in T-cell signaling and in positive and negative selection of T cells in the thymus.
- b. Lymphopenia occurs because of the absence of CD8⁺ T cells. As in all types of SCID, no antibody formation is present.

(7) Omenn syndrome:

- a. A mutation that impairs the function of immunoglobulin and TCR recombinase genes (ie, *Rag1*, *Rag2* genes) is now believed to be responsible for this syndrome.
- b. Normal or elevated T-cell numbers are present, but these are of maternal not fetal origin. The B cells are usually undetectable, NK cells are present, and the total immunoglobulin level is markedly low with poor antibody production. Eosinophils are elevated, and the total serum immunoglobulin E (IgE) level is elevated.

● **Clinical Manifestations**

- Failure to thrive, manifesting as decreased weight, height, and head circumference
- Fever from sepsis, systemic fungal infections, or generalized herpes
- No lymphadenopathy or increased tonsillar tissue despite serious infections
- Lymphadenopathy and hepatosplenomegaly in Omenn syndrome or bare lymphocyte syndrome
- Usual pathogens
 - *Pneumocystis carinii* pneumonia
 - Atypical mycobacterium
 - Herpes viruses
 - Candidiasis and other systemic fungal infections
 - *Cryptosporidium*
 - *Pneumococcus* and other common bacteria

● **Treatment for immunodeficiency**

- Management of cellular immunodeficiencies
 - All blood products given to patients with suspected cellular immunodeficiency must be irradiated, leukocyte-poor, and virus-free.
 - Potentially curative treatments of cellular immune deficiencies by bone marrow transplantation, enzyme replacement therapy; stem cell (placental cord blood) replacement therapy; and gene replacement therapy.
 - Avoidance of live viral vaccines
 - Patient education and genetic counseling.
 - The carrier state of females with some X-linked forms of cellular immunodeficiency can be determined.
 - Molecular genetic testing.
 - Control and avoid infection.
- Management of humoral (antibody) deficiencies
 - Intravenous immunoglobulin (IVIG) replacement therapy
 - IVIG therapy for patients with normal humoral immunity but recurrent infections has no scientific rationale.
 - IVIG replacement therapy in humoral immunodeficient patients is usually life-long.
 - Concomitant therapy with systemic antibiotics
 - Avoidance of live viral vaccines
 - Patient/parent education and genetic counseling
- Management of phagocyte defects
 - Patient/parent education and counseling
 - Some cases of CGD will respond to interferon gamma treatment.
 - Most patients with phagocytic immune defects can only be treated with supportive care and appropriate antibiotics. Occasionally granulocyte transfusions can be used.

- Phagocytic disorders may be due to causes other than primary dysfunctions.
- Gene therapy may be available in the future.
- Management of complement deficiency
 - No specific treatment for the congenital deficiency of complement components.
 - In C1 inhibitor deficiency, the administration of semi-synthetic androgens such as danazol and stanozolol is associated with a decrease in angioedema attacks and increased levels of C1 inhibitor.
 - A purified C1 inhibitor preparation for treatment of hereditary angioedema attacks
 - Prevent severe infections
 - Patients with deficiency of early complement components may develop autoimmune diseases particularly SLE or glomerulonephritis.
 - Patients may be immunized with vaccines for pneumococci, H. influenzae, and Neisseria meningitidis.
 - Gene therapy

Rheumatoid Arthritis

** Introduction

- ◆ A disease of multifactorial origin, characterized by immune-driven chronic inflammation joint inflammation, resulting to symmetric polyarthritis and bony erosions.
- ◆ Marked by a variable course, involving exacerbations and remissions of disease activity. Many cases are chronic and progressive, resulting in severe disability and sometimes death.
- ◆ Main target organ is the synovial lining of joints, bursae and tendon sheaths.
- ◆ Synovitis results in erosion of articular cartilage and marginal bone, with subsequent joint destruction.
- ◆ Extra-articular features are common, numerous and sometimes serious. Most are due to serositis, nodule (granuloma) formation or vasculitis.

(A) Classification criteria

Criteria for the Classification of Rheumatoid Arthritis*

CRITERION	DEFINITION
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2. Arthritis of three or more joint areas	At least three joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3. Arthritis of hand joints	At least one area swollen (as defined above) in a wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

* For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least four of these seven criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with two clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is *not* to be made.

(B) Epidemiology and pathogenesis

1. A prevalence of 0.5~1% reported in diverse populations worldwide. Annual incidence is approximately 0.1-0.2/1000 in males and 0.2-0.4/1000 in females.
2. Female:male = 2~4:1 at the age between 35 and 50 years (especially female before menopause); Female:male = 1:1 in the elderly.
3. Risk factors:
 - (1) Genetics: (a) 4-fold increase in concordance in monozygotic compared with dizygotic twins. (b) Association with HLA-DR4 and DR1. (c) But no increased frequency of rheumatoid factor positivity in the relatives of RA.
 - (2) Immune response in host factors: A number of autoimmune diseases are recognized to occur more commonly in individuals with RA, including thyroid disease and insulin dependent diabetes.
 - (3) Hormone: female excess.
 - (4) Environmental factors: Infectious agents (EBV, Parvovirus B19), smoking.
4. Negative association between RA activity and Gout (hyperuricemia).
5. Onset and exacerbation are more frequent in the winter.
6. Precipitation factors: not clear; possibly trauma, infection, emotion, vaccination; Symptoms more severe in wet weather with temperature change.
7. Synovial pathology:
 - (1) Early: swelling of synovial membrane and the underlying connective tissues with infiltration of lymphocytes and macrophages, which secrete cytokines and chemokines.
 - (2) Followed by synovial proliferation and hypertrophy with pannus formation then takes place, which destroy periarticular bone and cartilage at the margin between synovium and bone.
 - (3) Later, fibrous adhesion and bony ankylosis can occur.
8. Cytokines and chemokines:
 - (1) Includes IL-1, IL-2, IFN- γ , IL-6, IL-8, IL-10, IL-13, IL16, IL-17, IL-18, TNF- α , GM-CSF, TGF- β , macrophage

- CSF, PDGF, and IGF.
- (2) Secreted by lymphocytes, macrophages, and fibroblasts and endothelial cells.
 - (3) Play a major role in the pathogenesis of synovitis and synovial membrane hypertrophy.

(C) Clinical manifestations

1. After diagnosis of RA, the disease may be categorized as (a) **early disease** (no clinical evidence of joint damage or radiographic signs of cartilage loss or bone erosion), (b) **progressive disease** (continuous disease activity despite treatment). In addition to persistent polyarthritis, these individuals usually have an elevated erythrocyte sedimentation rate (ESR), positive rheumatoid factor test and early radiographic evidence of joint erosions. They may also have one or more of the systemic features of RA.) (c) **late disease** (definite joint damage with all its attendant complications).

2. Patterns of initial presentation of early disease

- (1) Onset may be **acute** (8-15%, with a few days), **gradual** (15-20%, over days and weeks), or **insidious** (55-70%, over weeks and months).
- (2) **Gradual or insidious onset:** affecting small peripheral joints such as the wrists, MCP, PIP, ankles or MTPs; usually symmetric with considerable morning stiffness and the patient complaining of difficulty making a fist and poor grip strength. The morning stiffness may last minutes to hours.
- (3) **Acute Polyarthritis:** shoulders, elbows, wrists, fingers, hips, knees, ankles and feet, with intense joint pain, diffuse swelling and limitation leading to incapacitation; may affect patients at any age, but has particular significance in the elder-onset RA (see below).
- (4) Joint involvement at onset: (a) Most commonly involved first: MCP, PIP and wrists. (b) Asymmetric joint involvement is common with more symmetric involvement later in the course.
- (5) Unusual pattern of early disease
 - (a) Acute monoarthritis, chronic monoarthritis
 - (b) **Palindromic Rheumatism:** *abrupt onset and variable episodes of polyarthritis* that suddenly affect one or more large and/or peripheral joints, *last a few hours or a few days*, and *then spontaneously subside* with complete clearing of all rheumatic signs between attacks. These short-lived episodes may recur over weeks or months, with increasing frequency and severity, and may herald the onset of persistent polyarthritis. *At least one-third of these palindromic cases evolve into typical RA (esp. with HLA-DR4)*. 15% of patients will have complete remission. Around 50% have persistent palindromic rheumatism.
- (c) **Adult-onset Still's disease:** (i) Pink to salmon colored macules or slightly elevated papules several millimeters in size on the trunk and extremities, but rarely on the palms and soles; (ii) Maximal during episodes of fever and are prominent in areas of minor skin trauma (Koebner's phenomenon); (iii) Irregular in shape and have no associated purpura or vesicles and asymptomatic or only mildly pruritic; (iv) The lesions do not spread, and last only minutes to hours. When the rash recurs, lesions are in new locations. (v) No oral lesions accompany the rash; (vi) Quotidian fever, diffuse palpable lymphadenopathy and polyarthritis.

Adult Still's disease		Criteria for diagnosis of adult Still's disease
Characteristic[†]	Percentage	
Clinical Manifestations		A diagnosis of adult Still's disease requires the presence of all of the following:
Female	51	Fever $\geq 39^{\circ}\text{C}$ (102.2°F)
Childhood episode (≤ 15 years)	16	Arthralgia or arthritis
Onset 16–35 years	76	Rheumatoid factor $<1:80$
Arthralgia	100	Antinuclear antibody $<1:100$
Arthritis	94	In addition, any two of the following are required:
Fever $\geq 39^{\circ}\text{C}$	97	White blood cell count $\geq 15,000 \text{ cells/mm}^3$
$\leq 39.5^{\circ}\text{C}$	87	Still's rash
Sore throat	92	Pleuritis or pericarditis
JRA rash	88	Hepatomegaly or splenomegaly or generalized lymphadenopathy
Myalgia	84	
Weight loss $\geq 10\%$	76	
Lymphadenopathy	63	
Splenomegaly	52	
Abdominal pain	48	
Hepatomegaly	42	
Pleuritis	31	
Pericarditis	30	
Pneumonitis	27	
Alopecia	24	
Laboratory Tests		
Elevated ESR	99	Differential diagnosis of adult Still's disease
WBC $\geq 10,000/\text{mm}^3$	92	
$\geq 15,000/\text{mm}^3$	81	Granulomatous disorders
Neutrophils $\geq 80\%$	88	Sarcoidosis Crohn's disease
Serum albumin $<3.5 \text{ gm/dl}$	81	Idiopathic granulomatous hepatitis
Elevated hepatic enzymes [‡]	73	Vasculitis
Anemia (hemoglobin $\geq 10 \text{ gm/dl}$	68	Serum sickness Polyarteritis nodosa
Platelets $\geq 400,000/\text{mm}^3$	62	Wegener's granulomatosis Takayasu's arteritis
Negative antinuclear antibody test	92	Thrombotic thrombocytopenic purpura
Negative rheumatoid factor	93	

SUBSETS OF SERONEGATIVE ELDERLY-ONSET INFLAMMATORY DISORDERS			
	EORA	PMR	RS ₃ PE
Proximal joints	+	+++	-
Peripheral joints	+++	+	+++
Tenosynovitis	++	+ / -	++ +
Edema	+	+	++ +
RF +	+ / -	-	-
High ESR	+	+++	+
HLA	CW3, DR4	DR4	B7

EORA: Elderly-onset RA; PMR: polymyalgia rheumatica; RS₃PE: remitting seronegative symmetrical synovitis with pitting edema.

(6) **Elderly-onset RA:** more than 60 years old

- (a) Polyarthralgias and polymyalgias affecting the neck and shoulders or hips and knees, with associated profound fatigue; fever for weeks.
- (b) More rheumatoid factor negativity, more strong association with HLA-DR4, high ESR.
- (c) Most people have benign course, some even more severe (may follow more progressive course or good prognosis with resolution within a year - benign RA of the aged with stormy onset)
- (d) NSAIDs are rarely effective; in patients with stroke, joint progression is spared on the paralyzed site.
- (e) Differential diagnosis: (i) May mimic seronegative spondyloarthritis (ii) Polymyalgia rheumatica with ESR and fever (iii) Syndrome of 'remitting, seronegative, symmetric, synovitis with pitting edema (**RS₃PE syndrome**) in aged males.

3. **Subsequent course of RA: the patterns of progression**

- (1) No matter what the onset or initial presentation is, the patient's subsequent progress may follow several different patterns: brief or episodic, prolonged and progressive, or something intermediate.
- (2) **Monocyclic pattern** with long clinical remission: a single cycle with remission seen in 10-20% of patients; usually have acute onset with marked fever and severe joint pain.
- (3) **Polycyclic pattern:** seen in 70% of patients with either intermittent subtype or continuing (or progressive) subtype (smoldering activity with incomplete remission or progression); follow rapid or slow course with the same endpoint of bone destruction and disability.
- (4) **Progressive pattern:** with increasing joint involvement seen in about 10% of patients. Malignant RA would fall under this last category. Most authorities would agree with these general observations, but many current ideas on the natural history of RA must remain speculative until the results of modern, long-term clinical population studies become available.
- (5) **Intermittent course:** 15-20%; remission is longer than exacerbation; a few joint initially, but more joints in subsequent exacerbations.

4. Health status self-report questions may be helpful for assessing the ongoing progress or prognosis of disease.

5. **Constitutional features:** morning stiffness, fatigue, anorexia, generalized weakness, weight loss, feverishness and fever (but temperature elevation in excess of 38°C is unusual), and vague musculoskeletal symptoms

6. **Articular features:**

- (1) Chronic **polyarthritis** in a **symmetric** distribution predominantly involving upper limbs (mainly PIP, MCP, wrist joints).
- (2) **Inflammatory synovitis:** cause cartilage destruction and bone erosions of (usually) peripheral joints on radiography; joint swelling and tenderness, limitation of motion, and morning stiffness for more than one-hour.
- (3) In approximately one-third of patients, symptoms may initially be confined to one or a few joints.
- (4) **Cervical spine involvement:** involvement of other spine area is rare.
 - (a) Cervical instability due to apophyseal joint destruction.
 - (b) **Atlantoaxial (C1-C2) subluxation** (most commonly anteriorly to cause spinal cord compression; less common are vertical and posterior), occurring in 50% of individuals with RA.
 - (c) Symptoms: pain radiation to the occiput; slowly progressive quadriplegia with painless sensory loss in hands (need to rule neuropathy and nerve compression); paresthesia in shoulders and arms during head movement; can severely cause spinal shock and death.
 - (d) The neurologic symptoms may not correlate with the degree of subluxation.
 - (e) Examinations: Radiographs for (C1-C2) subluxation by open-mouth PA view and the lateral view with neck in flexion (atlantodental interspace more than 3 mm); CT and/or MRI.
- (5) **Popliteal (Baker's) cyst** and knee extension lag: the cyst can extend from its location in the gastrocnemius bursa down into the medial aspect of the calf; can lead to rupture of the synovial cyst, with extravasation of inflammatory synovial fluid into the calf presenting a picture that mimics acute thrombophlebitis. A hemorrhagic 'crescent' sign in the skin about the ankle below the malleoli is characteristic of synovial rupture and is not a feature of thrombophlebitis.

7. **Extraarticular Manifestations**

- (2) The most important extra-articular complications of RA are due to an inflammatory vascular disease, giving rise to digital arteritis, peripheral neuropathy and arteritis of viscera.

- (3) Occur in individuals with high titers of autoantibodies to the Fc component of immunoglobulin G (rheumatoid factors).
- (4) **Rheumatoid nodules** (20 to 30 % of RA): firm, nontender, flesh colored subcutaneous lesions about 0.5-4cm in diameter which may be movable or fixed to periosteum or deep fascia. Common locations include the olecranon bursa (areas of pressure), the proximal ulna, the Achilles tendon, and the occiput. Nearly all of these patients are observed to be serologically positive for rheumatoid factor. The initial event may be a focal vasculitis.
- (5) Weakness and atrophy of skeletal muscle are common.
- (6) Hematologic abnormalities: (a) **Anemia**: usually normochromic and normocytic; Caused by decrease in iron utilization and erythropoietin level, ineffective erythropoiesis, or drug-induced hemolytic anemia, bone marrow suppression, or folic acid deficiency; anemia correlates with disease activity; may be complicated by other conditions (blood loss with IDA, poor nutrition, intercurrent infections, or drugs). (b) **Thrombocytosis**: a frequent finding in active RA; correlates with the number of joints with active synovitis and may be associated with extra-articular features. (c) Eosinophilia: sometimes associated with extra-articular manifestations (esp. pulmonary complication), high rheumatoid factor titers, elevated serum gammaglobulins, diminished serum complement levels, and treatment with gold. (d) Felty's syndrome with thrombocytopenia and leukopenia: see below. (e) Lymphadenopathy: frequent with active RA; usually detected in the axillary, inguinal, and epitrochlear areas; mobile and nontender; subsides after disease is controlled, DD from lymphoma (esp. in patients with combined Sjögren's syndrome).
- (7) **Rheumatoid vasculitis**: Inflammation of the small- and medium-sized arteries in the extremities (rheumatoid nodules, cutaneous ulceration and dermal necrosis, digital gangrene) and peripheral nerves (polyneuropathy and mononeuritis multiplex), and occasionally other organs (infarction, e.g. AMI; but **renal vasculitis is rare**); associated with HLA-DRB1 alleles and particularly B1 0401; pathology similar to polyarteritis (PAN and MP) with immune deposits.
- (8) **Pleuropulmonary manifestations**: (a) Pleurisy and pleural effusions (50%): may improve spontaneously or may require treatment. Persistent effusions can lead to fibrosis. (b) **Diffuse interstitial pulmonary fibrosis** (more common in men and in long-standing, nodular, seropositive patients). (c) **Pulmonary nodules**: generally asymptomatic; in seropositive RA patients who have widespread synovitis and usually nodules elsewhere; tend to be peripheral in location; can be cavitated and large up to 6-8cm in diameter and cause pleural effusion or fistula; DD from tumor, tuberculosis and fungal infection; usually improved after treatment of the underlying rheumatoid disease; **Caplan's syndrome**: with pulmonary nodulosis and pneumoconiosis in patients with RA. (d) **Broncholitis obliterans organizing pneumonia (BOOP)** can be associated with RA (responds to steroid) and has a generally good prognosis. In contrast, **obliterative or constrictive bronchiolitis**, responds poorly to treatment and has a poor prognosis -- pulmonary biopsy should be performed to aid in therapeutic decisions. (e) Pneumonitis, and arteritis and rarely pulmonary hypertension. (f) Pulmonary complications of methotrexate or D-penicillamine.
- (9) Cardiac involvement: (a) Caused by mechanisms of vasculitis, nodule formation, amyloidosis, serositis, valvulitis and fibrosis. (b) **Pericarditis**: is common, but asymptomatic; similar analysis of pericardial fluid to those of rheumatoid pleural effusion; commonly the pericarditis resolves as the rheumatoid disease is controlled; generally respond to NSAIDs and, occasionally needed, steroid; chronic, constrictive pericarditis is an infrequent sequela. (b) **Myocardial disease** resulting from nodular granulomatous lesions or more diffuse fibrosing lesions: usually asymptomatic nonspecific myocarditis; rarely affects cardiac size or function (c) Endocardial involvement is rarely clinically significant.
- (10) Active RA may be associated with an elevation of liver enzymes (especially GOT and alkaline phosphatase), which may parallel the anemia, thrombocytosis and increased ESR. With control of the RA, the liver function abnormalities return to normal.
- (11) Ocular lesions: (a) Keratoconjunctivitis sicca (KCS) most common (10 to 35%; the severity of the symptoms may not be correlated with that of the arthritis). (b) Episcleritis (usually correlates with the activity of RA). (c) Scleritis is less common (correlated with vasculitis, long-standing arthritis and active joint inflammation; may progress to scleromalacia). Control of the RA may not improve the episcleritis or scleritis. (d) Other rare ocular findings: uveitis, episcleral nodulosis, corneal melt and peripheral ulcerative keratitis (PUK)
- (12) Neuropathy: (a) Spinal cord compression due to atlantoaxial subluxation. Subaxial cervical spine involvement, including subluxation, spondylodiskitis and apophyseal joint changes, may occur at multiple levels, leading to pain and neurologic compromise. (b) **Entrapment neuropathy**: most frequently carpal (pain and paresthesia in the wrist and hand, waking the patient at night and extending to the forearm) and tarsal tunnel syndromes secondary to proliferative synovitis or joint deformities. (c) **Peripheral neuropathy** due to vasculitis: (i) A mild distal sensory symmetric **polyneuropathy** may occur in RA, especially in patients who have long-standing erosive disease, nodules and high titer IgM rheumatoid factor; feeling numbness and burning paresthesia; upper limb symptoms are less frequent. (ii) **Mononeuritis multiplex**: less common but potentially more severe form of neuropathy; usually occurs in patients with more severe disease manifestations. Symptoms of motor impairment usually accompany sensory symptoms. (d) **Amyloid neuropathy** and **neuropathy due to drugs or coincidental diseases**. Neurologic manifestations also may result from atlantoaxial or midcervical spine subluxations.
8. **Felty's syndrome**: **chronic RA, splenomegaly** (PMN counts of less than 1500 cells/ μ l), **neutropenia, anemia**

and **thrombocytopenia**; frequently with high titers of rheumatoid factor, subcutaneous nodules, and other manifestations of systemic rheumatoid disease; more likely to have vasculitis; one-third have no active synovitis at the time Felty's syndrome develops; circulating immune complexes are often present; complement consumption.

(D) Laboratory tests and investigations

1. RA factor: autoantibodies to the Fc component of immunoglobulin G (rheumatoid factors); 5% of healthy persons, 10 to 20% over 65 years old have a positive test. High RA factor titers tend to have more severe and progressive disease.
2. Disease activity: ESR, ceruloplasmin, CRP, anemia, leukocytosis, thrombocytosis, and eosinophilia (usually reflects severe systemic disease).
3. Normochromic, normocytic **anemia** (ineffective erythropoiesis; large stores of iron are found in the bone marrow); **thrombocytosis** and **mild leukocytosis** (esp. when active arthritis exists).
4. No tests are specific for diagnosing RA. However, rheumatoid factors, which are autoantibodies reactive with the Fc portion of IgG, are found in more than two-thirds of adults with the disease. Widely utilized tests largely detect IgM rheumatoid factors. The presence of rheumatoid factor is not specific for RA. Rheumatoid factor is found in 5 percent of healthy persons. The frequency of rheumatoid factor in the general population increases with age, and 10 to 20 percent of individuals over 65 years old have a positive test. In addition, a number of conditions besides RA are associated with the presence of rheumatoid factor. These include systemic lupus erythematosus, Sjögren's syndrome, chronic liver disease, sarcoidosis, interstitial pulmonary fibrosis, infectious mononucleosis, hepatitis B, tuberculosis, leprosy, syphilis, subacute bacterial endocarditis, visceral leishmaniasis, schistosomiasis, and malaria. In addition, rheumatoid factor may appear transiently in normal individuals after vaccination or transfusion and also may be found in relatives of individuals with RA.
5. Rheumatoid vasculitis: high titers of rheumatoid factor, low serum complements, and presence of cryoglobulins and circulatory immune complexes; elevated ESR, anemia, thrombocytosis, and a diminished serum albumin.
6. Rheumatoid interstitial pulmonary disease: High resolution CT; histologic findings and results of bronchoalveolar lavage can be variable, ranging from lymphocytic alveolitis to neutrophilic inflammation to pulmonary fibrosis.
7. Synovial fluid analysis: usually is not necessary for making diagnosis; Synovial fluid in RA will show reduced viscosity, increased protein content, and a slightly decreased or normal glucose concentration; WBC varies between 5 and 50,000 (PMN predominate); decreased in C3 and C4
8. Pleural or pericardial effusion: transudate; a variable white blood cell count (predominately lymphocytes), high protein levels, decreased complement levels, decreased glucose level (often less than 25mg/dl), and the presence of rheumatoid factor and immune complexes. Sometimes it is difficult to be distinguished from infection.

** Note: pleural effusion from SLE usually has increased protein, but normal sugar level.

(E) Radiographic features

◆ Key radiographic features of RA

- | | |
|--|--|
| (1) Symmetrical soft tissue swelling
(3) Marginal bone erosions
(5) Subchondral cysts
(7) Uniform loss of joint space | (2) Juxta-articular osteoporosis
(4) Absence of bone repair
(6) Subluxation and dislocation |
|--|--|

2. Radiographic features are most commonly seen in hands and feet.
3. Radiographic findings of hand/feet and wrists:
 - (1) Early radiographic changes: (a) Hands and feet: soft-tissue swelling bilaterally and symmetrically around the joints; juxta-articular osteoporosis; pseudocysts; marginal erosion (erosions of areas lacking articular cartilage) with loss of continuity of the white cortical line, which may be subtle. Soft-tissue swelling and juxta-articular osteoporosis are nonspecific changes but help to confirm the presence of an inflammatory problem. (b) The wrist: soft-tissue swelling; juxta-articular osteoporosis; erosions in the ulnar styloid, the radial styloid, the midportion of the scaphoid, the lateral portion of the hamate as it articulates with the fifth metacarpal, the distal radial aspect of the trapezium and the waist of the capitate.
 - (2) Late radiographic changes: (a) Hands: symmetric loss of joint space with a decrease in soft-tissue swelling; juxta-articular osteoporosis progresses to diffuse osteoporosis; the subtle marginal erosions progress to become large subchondral erosions; boutonniere or swan-neck deformities of the phalanges; ulnar drift of the proximal phalanges at MCP; uniform involvement of the MCP and PIPs with relatively spared DIP; possible digital fibrous ankylosis, but no bone ankylosis. (b) Wrist: ulnar deviation; ankylosis (most common in wrists); pancompartmental loss of the joint spaces. Eventually, the radiographic image may be one of 'arthritis mutilans'.
4. Radiographic findings of other joints
 - (1) Knee: bilateral, symmetric, uniform loss of the cartilage in all three compartments without repair response;



Marginal erosion

- tend to have intraosseous synovial cysts and large synovial cysts are described as geodes (should not be mistaken for a neoplasm).
- (2) Hip: erosive change is first seen at the chondroosseous margin of the femoral head where it joins the neck; axial (superomedial) migration toward the acetabulum due to uniform loss of cartilage; no reparative response in the form of osteophytes or subchondral bone formation; acetabular protrusion (the acetabular line is medial to the ilioischial line by 3mm in males and by 6mm in females); osteoporosis.
 - (3) Shoulder: RA usually involved all three compartments of shoulders: the glenohumeral and acromioclavicular joints and the acromiohumeral space with space narrowing; upward migration of the humeral head; rotator-cuff tear; erosion over the distal end of the clavicle, superior lateral aspect of the humeral head adjacent to the greater tuberosity and at the attachment of the coracoclavicular ligament to the clavicle.
 - (4) C-spine: see above; two most important views for examining the C-spine are a **flexed lateral view** (evaluation of ligamentous laxity and apophyseal joint disease) and an **open-mouth frontal view** (demonstrating the odontoid).
 5. Chest X ray: small pleural effusion; rheumatoid nodules that can cavitate (necrobiotic nodules); diffuse or interstitial fibrosis.
 6. CT scan plays a minor role in evaluation of RA. But it may be useful for evaluating the pelvis and the cervical spine.

(F) Evaluating and monitoring RA activity

1. **Subjective evaluation:** degree of joint pain; duration of morning stiffness; presence of fatigue; limitation of function; the parameter: patient global assessment of disease activity.
2. **Objective evaluation by physical examination:** presence and number of actively inflamed joints; document mechanical joint problems (loss of motion, crepitus, instability, malalignment or deformity); document extra-articular manifestations; the parameters: physician global assessment of disease activity and functional status assessment.
3. **Radiography:** perform X-ray of involved joints to document any bone erosion and deformity.
4. **First visit:** evaluate the subjective and objective evidence of active disease and laboratory tests (CBC, ESR, CRP, rheumatoid factor, baseline liver and renal function tests, urinalysis).
5. **Periodical evaluation:** Evidence of disease progression on physical examination; progression of radiographic damage of involved joints; CRP or ESR.
6. **Poor prognostic factors:** high rheumatoid factor titer; shared epitope of HLA-DR; the early presence of bony erosions; the number of affected joints; the presence of extra-articular features; a considerable degree of physical disability at onset; older age at onset; a lower level of formal education.
7. **Joint count: 28 joint score** has been recommended for assessing both tenderness and swelling of the joints: 10 PIP joints, 10 metacarpophalangeal (MCP) joints, 2 wrists, 2 elbows, 2 shoulders and 2 knees. However, joints not included may still be of clinical importance in the management of individual patients. And, tenderness and swelling may provide different information.

(G) Treatment

- ◆ **Internationally accepted core set variables are used for disease assessment.**
 - ◆ **Treatment goals have shifted from the control of symptoms to the control of the disease process.**
 - ◆ **NSAIDs and DMARDs are used to treat active inflammatory synovitis. And, DMARDs should be started early in the disease. Combination therapy is superior to monotherapy.**
 - ◆ **New anti-rheumatic therapy, anti-TNF and anti-IL-1 therapies, could be a cornerstone of treatment for active inflammatory synovitis.**
 - ◆ **A multidisciplinary approach is mandatory for those patients with inadequately controlled disease.**
- (Abbreviation: DMARDs, disease modifying anti-rheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs)

1. The goals of treatment: (1) Pain relief (2) Maintenance of joint function (3) prevention and correction of joint deformities (4) Disease modification (induction of remission).
2. Drugs used to control pain: NSAIDs, analgesics and steroid (systemic administration or intra-articular injection).
3. Drugs used to induce remission and control disease progression: **disease modifying anti-rheumatic drugs (DMARDs)**, including **methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, cyclosporine**. D-penicillamine is rarely used now.
4. Initial treatment for RA patients should include
 - (1) An **NSAID**: NSAIDs (non-steroidal anti-inflammatory drugs)(e.g. Voltaren, Naproxen) are widely used to provide effective anti-inflammatory and analgesic therapy for patients with rheumatoid arthritis, but gastrointestinal side effects are common. The problem of GI complications was found to be due to the competitive inhibition of COX-1 through non-selective COX (cyclooxygenase) enzyme inhibition. Celecoxib (Celebrex®) and etoricoxib (Arcoxia®) are new NSAIDs that selectively inhibit COX-2 and will reduce the risk of GI toxicity.

- (2) A **DMARD**: the traditional DMARDs, including hydroxychloroquine, D-penicillamine, sulfasalazine, cyclosporine, leflunomide; usually become effective 3-6 months after initiation of therapy. In contrast, the 'new' drugs, **sulfasalazine and methotrexate**, **may show clinical efficacy after 3-6 weeks**, and therefore are preferred in the initial therapy. **The dose of methotrexate is 7.5 to 15 mg per week (three to 6 tablets per week)**. However, **discontinuation of fast-acting DMARDs may rapidly provoke a flare**.
- (3) **Low-dose steroid (prednisolone 5 to 10 mg/day)**: result in prompt relief of the inflammatory symptoms, such as pain, swelling and morning stiffness and other systemic complaints (fatigue and loss of appetite). It is considered as a '**bridge therapy**', which aims to relieve symptoms of RA during the period between initiation of DMARDs and onset of effects. But it is shown to have the protective effect against progression of bone damage.
5. Some biological agents have been recently developed to treat arthritis in RA patients.
- (1) **Anti-TNF therapy**: Three biologic agents that block the TNF- α action (TNF- α blocker) have been shown to effectively improve the clinical symptoms and joint inflammation in conjunction of using methotrexate. Possible side effects of anti-TNF therapy: injection reactions, infections. Tuberculosis infection and reactivation is the major concern in Taiwan
 - (a) Infliximab (Remicade[®]), a chimeric mouse/human monoclonal antibody to TNF- α .
 - (b) Etanercept (Enbrel[®]): A fusion protein that contains extracellular domain of p75 TNF- α type II receptor fused to the Fc region of IgG1.
 - (c) Adalimumab (Humira[®]): a fully human antibody to TNF- α .
 - (d) Golimumab(Simponi[®]):A human monoclonal antibody; used SC once a month
 - (e) Certolizumab pegol (Cimzia[®]): a pegylated antibody without Fc region of antibody; cannot go through placenta and therefore can be used in pregnant patients; used SC twice a month
 - (2) **Anakinra (Kineret[®])**(will not be available in Taiwan):Anakinra is a recombinant interleukin-1 antagonist (IL-1RA) protein that has been shown to control arthritis in combination with methotrexate in RA patients. It is used by daily subcutaneous administration.
 - (3) **Tocilizumab (Actemra[®])**: a humanized anti-interleukin-6 (IL-6) receptor monoclonal antibody. Tocilizumab Monotherapy or in combination with DMARDs (such as methotrexate) can significantly reduce the signs and symptoms of RA. Patients who had previously failed anti-TNF-a therapy had significant improvement in signs and symptoms of RA after treatment with Actemra.
 - (4) **Abatacept (Orencia[®])**: A soluble CTLA4-Ig fusion protein that contains the external domain of human CTLA4 fused to the heavy-chain constant region of human IgG1. The dose and mode of administration for abatacept are 10 mg/kg by 30-minute intravenous infusion on days 1, 15, and 29 and then once every 28 days.
 - (5) **Rituximab (MabThera[®])**: a chimeric murine/ human monoclonal antibody against CD20 that is expressed on B cells. Rituximab can deplete B cells (but not immature B cells and plasma cells) and, in combination with methotrexate, has been shown to effectively control joint inflammation for RA refractory to anti-TNF- α therapy. The dose and mode of administration for rituximab are 1000 mg intravenous infusion slowly on Day 1 and Day15, and the treatment can be repeated 6 months later, since B cells are markedly depleted for a prolonged time (more than 6 months).
- (6) **Small molecules: tofacitinib and baricitinib are JAK inhibitors that block cytokine signal transduction**
6. A combination of DMARDs may be initiated early for severe, progressive RA: the rationale include (1) Influence different pathophysiologic mechanisms operative in RA. (2) Combining DMARDs of different toxicities to minimize risks. (3) Combining lower doses to reduce toxicity. (4) Combining higher doses of toxic drugs in combination to eradicate RA. (5) biological agents can be used alone or together with DMARDs.
7. Pulse methylprednisolone therapy (1000mg/days for 3 days) is sometimes used to obtain prompt control of the inflammatory process.
8. Calcium supply may be needed for preventing osteoporosis. Folic acid supply may be needed for patients treated with methotrexate.
9. Evaluate the effect of treatment: suppression of the acute phase response (ESR or CRP), improvement in hemoglobin and a (slow) decrease of RF titer. An exception seems to be azathioprine (and probably cyclosporin A), which can influence clinical disease activity without affecting variables such as ESR.
10. Treatment for rheumatoid vasculitis: (a) **High doses of steroid** may be needed initially to control the inflammation. (b) Cytotoxic drugs (**cyclophosphamide**), given possibly in pulses, may be necessary to allow long-term control and reduction of the corticosteroid dose. (c) Low dose aspirin as an anti-platelet agent and pentoxifylline as an inhibitor of tumor necrosis factor may also be considered. (d) Local wound care and reducing trauma to involved areas. (e) Stop smoking.
11. Surgical indications in RA: (1) Restore function (2) Carpal tunnel syndrome (3) Rupture of tendons (4) Arthrodesis of painful joints (5) Atlantoaxial dislocation

Note:

- (4) **In this handout, the term "DMARDs" will be used in other chapters to indicate the same group of drugs used to treatment RA, although some of these drugs may not be proven to be able to modify the courses of other rheumatic diseases, such as ankylosing spondylitis.**

(5) The recommended strategies for monitoring the side effects are provided on the next page.

Monitoring Drug Therapy in Rheumatoid Arthritis

*Recommended monitoring strategies for drug treatment of rheumatoid arthritis**

DRUGS	TOXICITIES REQUIRING MONITORING†	BASELINE EVALUATION	MONITORING	
			SYSTEM REVIEW/EXAMINATION	LABORATORY
Salicylates, nonsteroidal anti-inflammatory drugs	Gastrointestinal ulceration and bleeding	CBC, creatinine, AST, ALT	Dark/black stool, dyspepsia, nausea or vomiting, abdominal pain, edema, shortness of breath	CBC yearly, LFTs, creatinine testing may be required‡
Hydroxychloroquine	Macular damage	None unless patient is over age 40 or has previous eye disease	Visual changes, funduscopic and visual fields every 6–12 months	–
Sulfasalazine	Myelosuppression	CBC, and AST or ALT in patients at risk, G6PD	Symptoms of myelosuppression§, photosensitivity, rash	CBC every 2–4 weeks for first 3 months, then every 3 months
Methotrexate	Myelosuppression, hepatic fibrosis, cirrhosis, pulmonary infiltrates or fibrosis	CBC, chest radiography within past year, hepatitis B and C serology in high-risk patients, AST or ALT, albumin, alkaline phosphatase, and creatinine	Symptoms of myelosuppression§, shortness of breath, nausea/vomiting, lymph node swelling	CBC, platelet count, AST, albumin, creatinine every 4–8 weeks
Gold, intramuscular	Myelosuppression, proteinuria	CBC, platelet count, creatinine, urine dipstick for protein	Symptoms of myelosuppression§, edema, rash, oral ulcers, diarrhea	CBC, platelet count, urine dipstick every 1–2 weeks for first 20 weeks, then at the time of each (or every other) injection
Gold, oral	Myelosuppression, proteinuria	CBC, platelet count, urine dipstick for protein	Symptoms of myelosuppression§, edema, rash, diarrhea	CBC platelet count, urine dipstick for protein every 4–12 weeks
D-penicillamine	Myelosuppression, proteinuria	CBC, platelet count, creatinine, urine dipstick for protein	Symptoms of myelosuppression§, edema, rash	CBC, urine dipstick for protein every 2 weeks until dosage stable, then every 1–3 months
Azathioprine	Myelosuppression, hepatotoxicity, lymphoproliferative disorders	CBC, platelet count, creatinine, AST or ALT	Symptoms of myelosuppression§	CBC and platelet count every 1–2 weeks with changes in dosage, and every 1–3 months thereafter
Corticosteroids (oral ≤ 10 mg of prednisone or equivalent)	Hypertension, hyperglycemia	BP, chemistry panel, bone densitometry in high-risk patients	BP at each visit, polyuria, polydipsia, edema, shortness of breath, visual changes, weight gain	Urinalysis for glucose yearly
Agents for refractory RA or severe extraarticular complications				
Cyclophosphamide	Myelosuppression, myeloproliferative disorders, malignancy, hemorrhagic cystitis	CBC, platelet count, urinalysis, creatinine, AST or ALT	Symptoms of myelosuppression§, hematuria	CBC and platelet count every 1–2 weeks with changes in dosage, and every 1–3 months thereafter, urinalysis and urine cytology every 6–12 months after cessation
Chlorambucil	Myelosuppression, myeloproliferative disorders, malignancy	CBC, urinalysis, creatinine, AST or ALT	Symptoms of myelosuppression§	CBC and platelet count every 1–2 weeks with changes in dosage, and every 1–3 months thereafter
Cyclosporin A	Renal insufficiency, anemia, hypertension	CBC, creatinine, uric acid, LFTs, BP	Edema, BP every 2 weeks until dosage stable, then monthly	Creatinine every 2 weeks until dose is stable, then monthly; periodic CBC, potassium, and LFTs

* CBC = complete blood cell count (hematocrit, hemoglobin, white blood cell count) including differential cell and platelet counts; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LFTs = liver function tests; BP = blood pressure.

† Potential serious toxicities that may be detected by monitoring before they have become clinically apparent or harmful to the patient. This list mentions toxicities that occur frequently enough to justify monitoring. Patients with comorbidity, concurrent medications, and other specific risk factors may need further studies to monitor for specific toxicity.

‡ Package insert for diclofenac (Voltaren) recommends that AST and ALT be monitored within the first 8 weeks of treatment and periodically thereafter. Monitoring of serum creatinine should be performed weekly for at least 3 weeks in patients receiving concomitant angiotensin-converting enzyme inhibitors or diuretics.

§ Symptoms of myelosuppression include fever, symptoms of infection, easily bruising, and bleeding.

(6)

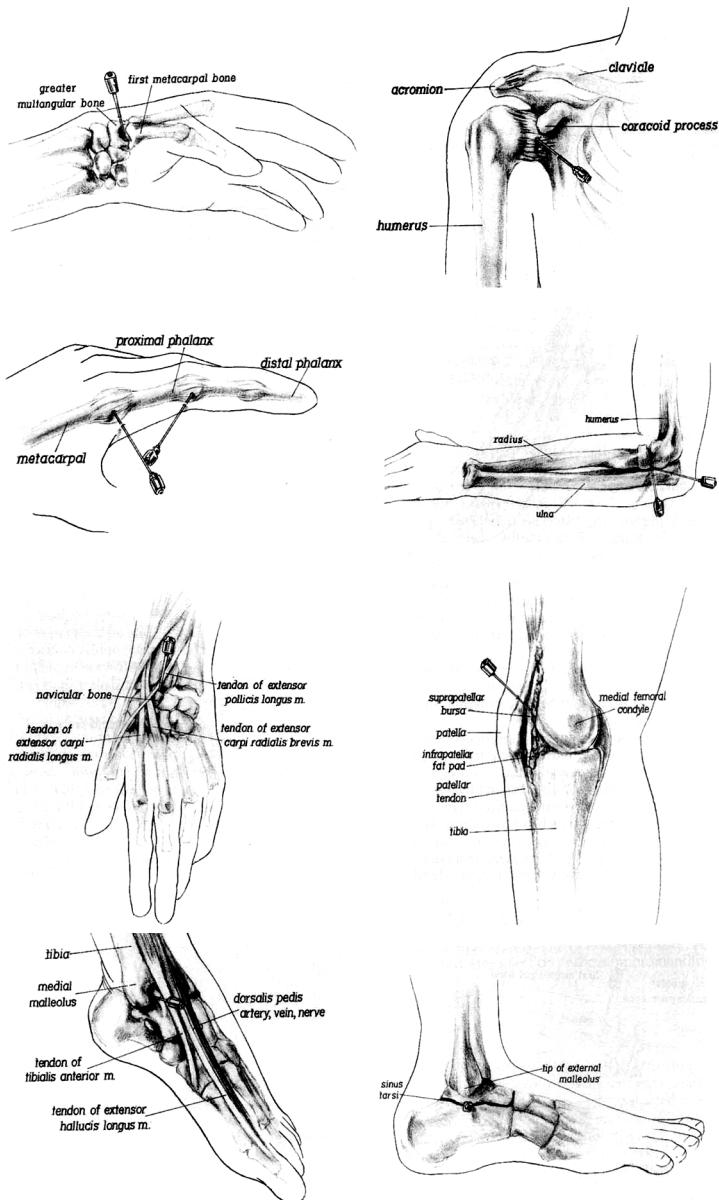


Table 40-6. CONTRAINDICATIONS TO INTRA-ARTICULAR GLUCOCORTICOID INJECTIONS

- Periarticular sepsis
- Bacteremia
- Unstable joints
- Most spinal joints
- Intra-articular fracture
- Septic joint: Do not forget the possibility of tuberculosis.
- Difficult access to nondiarthrodial joints (e.g., symphysis pubis); sternomanubrial injections may prove helpful
- Marked juxta-articular osteoporosis
- Failure to respond to prior injections
- Blood-clotting disorders

Table 40-5. INDICATIONS FOR NONARTICULAR GLUCOCORTICOID INJECTIONS

- Shoulder**
 - Bicipital tendinitis
 - Subacromial bursitis
 - Supraspinatus tendinitis
 - Periarthritis (adhesive capsulitis, frozen shoulder)
- Elbow**
 - Lateral epicondylitis—"tennis elbow"
 - Medial epicondylitis—"golfer's elbow"
 - Olecranon bursitis
 - Cubital tunnel syndrome
- Wrist and Hand**
 - Ganglion
 - DeQuervain's disease—stenosing tenosynovitis of extensor pollicis brevis and abductor pollicis longus
 - Trigger (snapping) fingers
 - Carpal tunnel syndrome
- Hip**
 - Trochanteric bursitis
- Knee**
 - Anserine bursitis
 - Prepatellar bursitis and neuritis
- Pelvis**
 - Ischial bursitis
 - Iliopectineal bursitis
- Back**
 - Fibromyalgia trigger points
 - Herniated presacral fat pads (Stockman's nodules)
- Foot**
 - Achilles tendinitis
 - Achilles bursitis
 - Calcanal bursitis
 - Morton's neuroma
 - Tarsal tunnel syndrome

Spondyloarthropathy

(A) Classification criteria for spondyloarthropathy Criteria for the Classification of Spondyloarthropathy*

- Inflammatory spinal pain
or
Synovitis
Asymmetric or
Predominantly in the lower limbs
and one or more of the following
Positive family history
Psoriasis
Inflammatory bowel disease
Urethritis, cervicitis, or acute diarrhea within 1 month before arthritis
Buttock pain alternating between right and left gluteal areas
Enthesopathy
Sacroiliitis

* This classification method yields a sensitivity of 78.4% and a specificity of 89.6%. When radiographic evidence of sacroiliitis was included, the sensitivity improved to 87.0% with a minor decrease in specificity to 86.7%. Definition of the variables used in classification criteria follow.

VARIABLE	DEFINITION
Inflammatory spinal pain	History or present symptoms of spinal pain in back, dorsal, or cervical region, with at least four of the following: (a) onset before age 45, (b) insidious onset, (c) improved by exercise, (d) associated with morning stiffness, (e) at least 3 months' duration
Synovitis	Past or present asymmetric arthritis or arthritis predominantly in the lower limbs
Family history	Presence in first-degree or second-degree relatives of any of the following: (a) ankylosing spondylitis, (b) psoriasis, (c) acute uveitis, (d) reactive arthritis, (e) inflammatory bowel disease
Psoriasis	Past or present psoriasis diagnosed by a physician
Inflammatory bowel disease	Past or present Crohn's disease or ulcerative colitis diagnosed by a physician and confirmed by radiographic examination or endoscopy
Alternating buttock pain	Past or present pain alternating between the right left gluteal regions
Enthesopathy	Past or present spontaneous pain or tenderness at examination of the site of the insertion of the Achilles tendon or plantar fascia
Acute diarrhea	Episode of diarrhea occurring within one month before arthritis
Urethritis	Nongonococcal urethritis or cervicitis occurring within one month before arthritis
Sacroiliitis	Bilateral grade 2-4 or unilateral grade 3-4, according to the following radiographic grading system: 0 = normal, 1 = possible, 2 = minimal, 3 = moderate, and 4 = ankylosis

Reprinted from Dougados M, Van Der Linden S, Juhlin R, et al: The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum 34:1218-1227, 1991, with permission of the American College of Rheumatology.

** Seronegative spondyloarthropathy includes the following arthropathies

- (1) Ankylosing spondylitis (AS)
- (2) Reactive arthritis, Reiter's syndrome
- (3) Psoriatic arthropathy
- (4) Arthropathy of inflammatory arthritis (Enteropathic arthropathy)
- (5) Undifferentiated spondyloarthropathy
- (6) Juvenile onset ankylosing spondylitis (a subset of juvenile chronic arthritis)

** Some common features for the members of spondyloarthropathy

- (1) Significant family aggregation: association with HLA-B27.
- (2) Inflammatory arthritis: axial skeletal involvement (spinal syndesmophytes, sacroiliitis, and atlantoaxial (C1-C2) subluxation) and peripheral joint involvement (predominantly lower limb and asymmetric).
- (3) Extra-articular features: acute anterior uveitis, symptomatic or asymptomatic inflammatory colitis, aortitis and aortic valvular disease, conducting abnormality, IgA nephropathy.
- (4) Absence of rheumatoid factor.

(B) Ankylosing spondylitis

- A chronic systemic inflammatory rheumatic disorder with predilection for axial skeletal involvement and sacroiliitis that cause low back pain and eventually limitation of spinal mobility.

- Strong genetic predisposition associated with HLA-B27 and therefore with psoriasis, chronic inflammatory bowel disease and reactive arthritis in some patients.
- The clinical diagnosis of AS depends primarily on history and physical examination, and is confirmed by radiographic examination.

<1> Classification criteria

Modified New York criteria for AS, 1984

- Low back pain at least three month's duration improved by exercise and not relieved by rest
- Limitation of lumbar spine in sagittal and frontal planes
- Chest expansion decreased relative to normal values for age and sex
- Bilateral sacroiliitis grade 2-4
- Unilateral sacroiliitis grade 3-4

Definite ankylosing spondylitis if unilateral grade 3 or 4, or bilateral grade 2-4 sacroiliitis and any clinical criterion

<2> Epidemiology

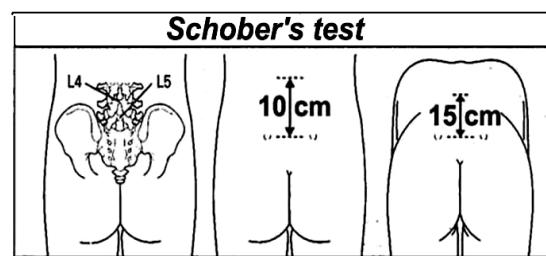
- Affect young individuals **below 40 years of age**.
- The link between AS and HLA-B27 holds in all populations. Those with a low frequency of HLA-B27 have low frequencies of AS.
- Two epidemiological surveys in China and Taiwan have estimated prevalence rates of AS to be 0.26% and 0.2-0.5%, respectively. Approximately 6% of B27-positive Chinese have had AS.
- The male to female ratio is 5:1.

<3> Clinical manifestations

- Inflammatory of axial skeleton:** causing low back pain (inflammation of ligaments, discitis or spondylodiscitis); chest pain; neck pain; morning stiffness and rest stiffness; relieved by exercise; restricted spine movement (fixed neck, limited chest expansion and limited lumbar spine movement) at the late stage of disease.
- Symmetric, bilateral sacroiliitis.**
- Other joints that may be involved include anterior central joints (manubrio- sternal and sternoclavicular joints, symphysis pubis) and large peripheral joints (hips, shoulder, knees). It rarely involves small peripheral joints.
- Presentation with peripheral joint involvement may be dominant without evidence of sacroiliitis in adolescent and young adult patients (pauciarticular juvenile chronic arthritis).**
- Extra-articular manifestations:
 - Anterior uveitis** (20-30% of AS patients, **usually unilateral**).
 - Heart involvement: (a) **Aortitis**, which frequently results in mild **aortic regurgitation** because of aortic root dilatation; **endocarditis prophylaxis is indicated**. (b) **Conduction disturbances**, caused by a subaortic fibrotic process extending into the base of the septum and resulting in high degree atrioventricular block. (c) Myocardial and pericardial disease are rare in AS
 - Pulmonary fibrosis; anterior atlantoaxial subluxation; asymptomatic colitis; IgA nephropathy.
- There is no close temporal relationship between severity of uveitis and spondylitis**, therefore the eye disease is treated as a separate entity.

<4> Examinations and laboratory tests

- Physical examination for **sacroiliitis** includes (a) Direct compression over the SI joint to elicit pain. (b) Lateral compression of the pelvis to elicit pain. (c) **Ganslen's sign**: lies supine with buttock over the edge of bed and right knee flexed, then drop and stretch the unsupported left leg off the bed to elicit pain over right SI joint, and vice versa for the other SI joint. (d) **Patrick test**: In supine position, flex one knee and place patient's heel on the opposite knee, and then push downward on the flexed knee to elicit pain on the contralateral SI joint.



2. **Schober's test** for lumbar spine mobility: make marks at the level of post. sup. Iliac spine and at 10 cm above the level. When flexing forward maximally, the distance between two marks should exceed 15 cm in normal individuals.
3. Occiput-to-wall distance for neck movement limitation
4. Limited chest expansion: less than 5 cm expansion during deep inspiration.
5. Laboratory tests: CBC, ESR and CRP, IgA level, and HLA-B27.
6. Radiography:
 - (1) KUB for sacroiliitis: Grade I (suspicious, mild blurring SI joint), Grade II (minimal, pseudowidening due to erosions, subchondral sclerosis); Grade III (moderate, narrowing of SI joint); Grade IV (complete loss of joint space); CT scan is more sensitive for sacroiliitis.
 - (2) Spine x-ray may show "shiny corner" sign, bridging marginal syndesmophyte, bamboo spine and osteoporosis in long-standing cases, and ossification of interspinous ligaments.
 - (3) Enthesitis: bony erosions at the side of tendon insertion; proliferative bony margins and whiskering spicules; can occur over pelvis at sacrotuberous and sacrospinal ligament insertions, femoral greater trochanter, plantar fascia and Achilles tendon.
7. Differential diagnosis:
 - (1) Diffuse idiopathic skeletal hyperostosis (DISH): in elderly; hyperostosis of anterior longitudinal ligament without sacroiliitis.
 - (2) Osteitis condensans ilii: in multiparous women; dense sclerotic region over the iliac bones adjacent to the lower half of SI joint without affecting SI joints themselves.

<5> Treatment for AS

1. In contrast to RA, **no drugs have yet been claimed to have a disease-modifying effect on AS**.
2. **NSAIDs** are used extensively to provide symptom relief to patients with AS. Overall the objective of NSAIDs is to relieve pain sufficiently to allow free movement. All NSAIDs can be used in AS, although NSAIDs with long half-life is preferred to cover morning stiffness. Selection is always a balance of effectiveness and tolerance.
3. DMARDs used in the management of RA have been tried at some time in AS. No drugs have yet been claimed to have a disease-modifying effect on AS. Gold, penicillamine and antimalarials have been proven ineffective. However, some drugs have symptomatic benefit and possibly can modify the course of AS.
 - (1) **Sulfasalazine**: proven effective and safe in short-term treatment of AS. But it may reduce the sperm count.
 - (2) **Methotrexate**: This has been used to treat psoriatic arthritis and reactive arthritis. It has been given to patients with AS in similar low dosages, **7.5-15mg oral weekly** pulsed doses, to those used in RA and appears to have a beneficial effect on both peripheral joints and spinal disease.
 - (3) **Immunosuppressives**: Cyclophosphamide or azathioprine may be beneficial to peripheral joint synovitis and spinal pain.
 - (4) Anti-TNF therapy may be more promising in the future.
7. **Steroid: Long-term systemic corticosteroids have little part to play in the management of AS**. But, intravenous pulsed methylprednisolone is undoubtedly effective in reducing severe symptoms, although the indications for its use are poorly defined.
8. Biologics : anti-TNF drugs (such as, etanercept, adalimumab and golimumab) and anti-IL-17 agents
9. **Physiotherapy**: is widely recognized as the single most important aspect of management of AS. Exercise alone can produce adequate symptom relief in many patients with AS. Self-management with exercises must be continued on a lifelong basis.
10. Treatment for uveitis: ensure that the patients seek immediate medical advice on developing a painful red eye. The consequences of delayed or inadequate treatment are the formation of synechiae, which are adhesions from the back of the iris. Secondary glaucoma may then supervene. **Topical therapy with corticosteroid eye drops and mydriatics** is all that is required. Administration of corticosteroids orally or by intraocular injection is required when local treatment fails to relieve the inflammation.

(C) Psoriatic Arthropathy

- ◆ An inflammatory arthritis that may be axial or peripheral and occurs in 7-42% of patients with psoriasis.
- ◆ Psoriatic skin lesion may precede (75%), coincide (15%) or follow (10%) arthritis.
- ◆ Equal the sex ratio in psoriatic arthritis.
- ◆ Although the peak age of onset of psoriasis occurs between 5 and 15 years, the **peak age of onset of psoriatic arthritis** is much later and **similar to that of RA**.

<1> Clinical features

1. Articular manifestations:

- (1) Arthritis: frequent involvement of distal interphalangeal (DIP) joints with erosion and absorption of the terminal phalanges, accompanying . Involvement of the DIP joint is almost always associated with psoriatic changes in the associated nail.
 - (2) Usually asymmetric oligoarthritis as reactive arthritis, but sometimes RA-like symmetrical polyarthritis can occur – require DD with RA.
 - (3) Destructive arthritis (mutilans) with joint deformities
 - (4) Asymptomatic sacroiliitis (2/3 patients).
 - (5) Spondylitis: in 20-40% of patients; cervical spine involvement may occur more frequently; atlantoaxial subluxation.
2. Extra-articular manifestations:
- (1) Similar to reactive arthritis: ocular and cardiac lesions; “sausage digit”; enthesopathy; tenosynovitis; chronic psoriatic arthritis may be difficult to be distinguished from chronic reactive arthritis.
 - (2) Nail: hyperkeratosis; onycholysis, pitting and ridging of nail.
 - (3) Skin lesion: previously unrecognized psoriasis may be found in a flexural region, the scalp or nails.

<2> Laboratory tests and radiography

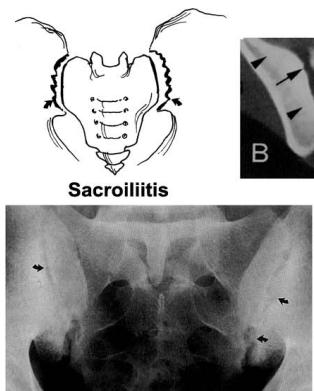
1. Elevated ESR and CRP can be found. If spondylitis alone is present in association with psoriasis, as in classic AS, there is little relationship between ESR and other acute phase reactants and clinical activity of disease.
2. Diagnosing psoriatic arthritis in the presence of a positive rheumatoid factor should be careful, especially in patients with symmetric polyarthritis.
3. Presence of HLA-B27 may be helpful. Uric acid may be elevated.
4. Ultrasonography may be helpful to identify tenosynovitis and Achilles tendonitis.
5. Radiography:
 - (1) **Peripheral arthritis:** (a) **DIP involvement:** DD with **erosive osteoarthritis**. (b) Asymmetric small joint involvement of the interphalangeal joints of the hands and feet (c) Marginal erosion with **fluffy periosteal new bone formation** resulting in 'whiskering' (d) A tendency to joint ankylosis (e) Osteolysis of phalangeal and metacarpal bones resulting in telescoping digits (f) “**pencil-in-cup” appearance**. (g) Proliferative new bone formation at entheses, particularly around the pelvis and the calcaneum (h) periorbititis
 - (2) **Spondylitis** associated with psoriasis and reactive arthritis is different from that in AS or enteropathic arthropathy:
 - (a) Sacroiliitis is asymmetric. Severe cervical spine involvement may cause atlantoaxial subluxation. The thoracolumbar spine is relatively spared.
 - (b) Syndesmophyte: fewer, skipped types of syndesmophytes; and asymmetric syndesmophytes.
 - (c) Difference in the shape of syndesmophytes: non-marginal.
 - (d) Fluffy hyperosteosis on the anterior surface of the vertebral bodies, particularly in the cervical spine.
 - (e) Paravertebral ossification

<3> Treatment

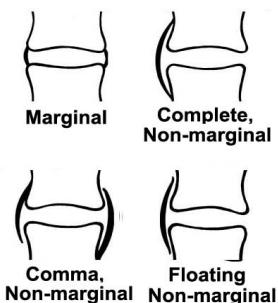
1. Treatment of psoriatic arthritis includes pharmacological, rehabilitative and surgical reconstructive therapies with concomitant skin management.
2. NSAIDs are effective for arthritis. There is no conclusive evidence suggestive of exacerbation or improvement of the underlying skin involvement with the use of NSAIDs. NSAIDs should be given at full dosage, and for a minimum of 4 weeks, to evaluate their efficacy fully.
3. DMARDs: most patients with psoriatic arthritis will require DMARDs.
 - (1) Combination therapy may be ideal therapy for psoriatic arthritis, although no evidence exists.
 - (2) DMARDs that has been used include sulfasalazine, methotrexate, antimalarials, gold compounds and penicillamine.
 - (3) **Methotrexate** and **sulfasalazine**, used alone or in combination, may be tried first due to the known effect of the agents on both the skin and joint involvement.
 - (4) Other therapeutic modalities such as vitamin D3 derivatives, retinoids, somatostatin, azathioprine, cyclosporin A and PUVA (psoralen plus ultraviolet A) have also been used, but most studies are hampered by the lack of appropriate controls.
4. **Cyclosporine** is one of the most effective therapeutic agents for the treatment of severe, recalcitrant psoriasis and its related arthritis. The clinical response of both skin and joint involvement is dose related. Lower dose (1.5-5mg/kg /day) than that used in transplantation is effective and less toxic.
5. Photochemotherapy with methoxysoralen (Psoralen Plus Ultraviolet A, PUVA) may induce clinical improvement of skin, but only a slight to moderate improvement of peripheral articular involvement.
6. Biologics : anti-TNF drugs (such as, etanercept, adalimumab and golimumab) and anti-IL-23 (or p19) agents; and anti-IL-17 agents

Radiography of Spondyloarthropathy

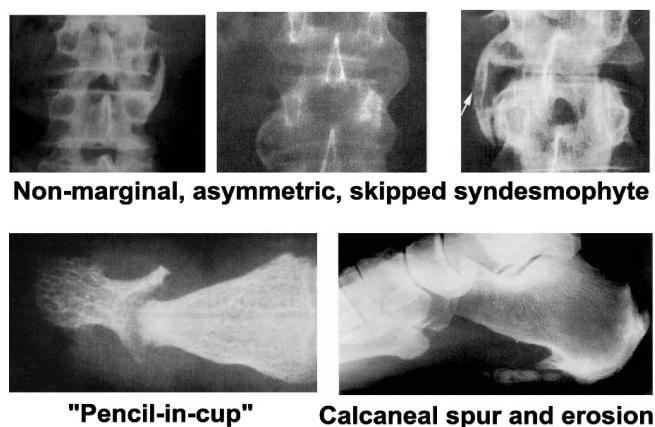
(A) Ankylosing spondylitis



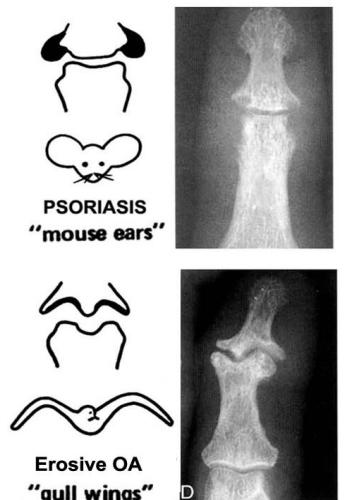
(B) Syndesmophyte



(C) Psoriatic arthritis and reactive arthritis



(D) DD psoriatic arthritis and erosive OA



(D) Reactive Arthritis / Reiter's Syndrome

1. Definition

- (1) **Reactive arthritis:** aseptic inflammatory arthritis after GU tract infection or dysentery caused by the following pathogens: ***Chlamydia, Salmonella, Shigella, Campylobacter, Yersinia, or Clostridia difficile.***
- (2) **Reiter's syndrome:** cases with typical triad of arthritis, urethritis and conjunctivitis; considered as one kind of reactive arthritis.
- (3) **Infection-associated arthritis:** arthritis related to all kinds of microbial infection, e.g. post-viral infection arthritis.

2. Clinical Manifestations of Reactive Arthritis:

* Patients may have one, more than one or all of the following manifestations.

- (1) **Peripheral arthritis syndrome:** **A**symmetric, **A**cute onset, **A**dditive, **O**ligoarticular arthritis in the **L**ower extremity that occurs **One** month after infection. Large synovial fluid accumulation can occur at knees and could cause popliteal cyst rupture. Other symptoms: joint tenderness, stiffness and restricted range of motion. Chronic cases may have marginal bone erosion of joints with periostitis and fluffy periosteal new bone formation (changes similar to psoriatic arthropathy).
- (2) **Enthesopathy syndrome (enthesis):** inflammation of ligaments and tendons at the sites of their insertion into the bone; Achilles tendonitis (heel pain, calcaneal erosion and spur formation); dactylitis ("sausage digit"), Fasciitis (e.g. plantar fasciitis); tenosynovitis (can be examined by ultrasonography).
- (3) **Pelvic and axial syndrome:** Asymmetric, **non-marginal**, skipped **syndesmophytes** (more often

in lower thoracic and upper lumbar spine); asymmetric **sacroiliitis**; causing low back pain).

(4) Extra-musculoskeletal syndrome

- (a) Genitourinary tract infections: urethritis (sexually transmitted, asymptomatic or symptomatic, non-purulent); prostatitis, cystitis, non-specific cervicitis in female patients.
- (b) Skin lesion: Keratoderma blennorrhagica, Balanitis circinata (painless shallow genital ulcer), painless oral ulcer.
- (c) Ocular: Conjunctivitis (frequently mild, transient and easily missed), acute anterior uveitis (more persistent and chronic disease)
- (d) Cardiac complications: aortitis, Aortic insufficiency, Heart block

3. Lab tests and examinations

- (1) ESR and CRP to evaluate the severity of inflammation; check HLA-B27.
- (2) Anti-chlamydial antibody for GU tract infection; stool culture for previous diarrhea is usually negative and is therefore not necessary.
- (3) Arthrocentesis may be needed for differential diagnosis.
- (4) Ultrasonography may be helpful to identify tenosynovitis and Achilles tendonitis.
- (5) Radiographic findings are similar to those found in psoriatic arthropathy (see above), commonly including calcaneal erosion and spur formation and spinal syndesmophytes.

4. Treatments

- (1) NSAIDs and sulfasalazine can be useful to control arthritis.
- (2) Methotrexate: 7.5 to 15 mg/weekly pulse therapy (1 tablet q12h) can be used for refractory cases.
- (3) Short-term low dose steroid or intra-articular steroid injection can be given to improve arthritis, but long-term steroid is not beneficial. Topical steroid can be given for skin or mucosal lesions (weak topical steroid for genital ulcer).
- (4) Doxycycline to control chlamydial infection.

(E) Enteropathic Arthropathy

- ◆ Sacroiliitis and spondylitis, but not peripheral arthritis, are associated with HLA-B27. HLA-B27 positivity is found in 66% of ulcerative colitis patients and in 53% of Crohn's disease patients with spondylitis.
- ◆ AS patients not carrying the HLA-B27 antigen are at a higher risk of developing IBD than are HLA-B27-positive AS patients.

1. Epidemiology:

- (1) Arthritis is the most common extraintestinal manifestation of IBD and appears in 2-20% of the patients with either UC or Crohn's disease.
- (2) The occurrence of peripheral arthritis is increased in patients with colonic involvement and with more extensive bowel disease.
- (3) Sacroiliitis and ankylosing spondylitis (AS) are also related to IBD. The frequency of AS in UC varies between studies, from 1 to 25%, and the frequency of AS in Crohn's disease from 2 to 7%.
- (4) Subclinical axial involvement in patients with IBD is more common than reported in many studies. Conversely, subclinical bowel inflammation is common in spondyloarthritis.

2. Clinical Features

- (1) Peripheral arthritis and tendinitis: (a) Pauciarticular, asymmetric, migratory, transient, but recurrent (b) Monoarthritis is not uncommon. (c) Men and women are equally represented. (e) Large and small joints are involved, predominantly those of the lower limbs (knees, ankles and MTP joints) (f) Arthritis of hips and shoulders is less frequent and tends to be associated with sacroiliitis and spondylitis. (g) Enthesopathy: heel (insertion of the Achilles tendon or the plantar fascia) or knee (insertion of the patellar tendon). (h) The joints can be affected before the onset of the intestinal symptoms
- (2) Axial involvement with sacroiliitis and spondylitis: (a) The prevalence in patients with IBD is 5%~12%, but many patients may have silent axial involvement (esp. sacroiliitis). (b) The male:female ratio is 3:1, which is comparable to uncomplicated AS. (c) The clinical features and the radiographic signs are similar to those in AS. Inflammatory low back pain, buttock pain and chest pain are most common. May have ankylosis of spine. (d) Axial involvement can precede the bowel disease by many years. (a) The peripheral arthritis, but not the axial involvement is associated with gut inflammation and can be improved after surgical treatment of the gut.
- (3) Other extraintestinal features: (a) **Acute anterior uveitis**: 3-11% of IBD patients; associated with HLA-B27 and axial involvement; acute at onset, unilateral and transient but frequently recurrent. (b)

Conjunctivitis and episcleritis are rare. (c) Skin lesions: occur in 10-25% of the patients. **Erythema nodosum** is most common and coincides with exacerbations of the gut inflammation and thus tends to occur in patients with active peripheral synovitis. **Pyoderma gangrenosum** is less frequent, is not related to the gut inflammation. (d) Secondary amyloidosis is encountered occasionally and is usually fatal.

3. Clinical investigations

- (1) Laboratory tests: iron deficiency anemia, leukocytosis, a marked thrombocytosis with platelet counts higher than 700,000/mm³ are not uncommon. ESR and other acute-phase reactants are elevated. Rheumatoid factor is absent.
- (2) Synovial fluid analysis is not characteristic, but may be useful for differential diagnosis. The WBC count ranges from 1500 to 50,000/mm³. Glucose level is not reduced. Microbiologic cultures are negative.
- (3) Genetic Markers: Familial aggregation both for Crohn's disease and UC has been documented. The association of IBD with HLA antigens is not obvious, but the axial involvement, but not peripheral arthritis, in IBD is associated with HLA-B27. Therefore, in HLA-B27-negative AS patients, occult IBD should be considered.
- (4) Radiographic Findings: The findings of sacroiliac and axial involvement in IBD are similar to those AS: typically bilateral sacroiliitis and bilateral marginal syndesmophytes. Radiography of peripheral joints usually shows negative finding, but erosion with adjacent new bone formation can occur. Rarely, a destructive granulomatous synovitis may be seen in Crohn's disease.

4. Treatment

- (1) NSAIDs are effective on the peripheral arthritis and the spondylitis, but they rarely can induce complete remission. However, these drugs may cause an exacerbation of the gut symptoms of ulcerative colitis.
- (2) Sulfasalazine that appears to be an effective treatment for the colonic involvement in UC and Crohn's disease, has been used with some success in the spondyloarthropathies.
- (3) Steroid, which has no effect on axial involvement, should only be used systemically to control the bowel disease. Intra-articular steroid injection can be useful, especially if only a small number of joints is involved.
- (4) Methotrexate has been reported to be effective in treating Crohn's disease but its efficacy in the associated arthritis is still unknown.
- (5) Biological agents: anti-TNF α therapy with etanercept or adalimumab has been shown to be effective for AS

Crystal-Induced Arthritis

(A) Gout

- ◆ Gout is a disease resulting from the deposition of **monosodium urate crystals** in synovial fluid and other tissues or the formation of **uric acid stones** in the kidney, which cause **acute and chronic arthritis, tophi, interstitial renal disease and uric acid nephrolithiasis**.
- ◆ **Hyperuricemia** is defined as a serum uric acid concentration above 7 mg/dL (420 µmol/L).
- ◆ Hyperuricemia is a risk factor for gout, but **acute gouty arthritis is often, but not always, associated with hyperuricemia**.
- ◆ Treatment goals include termination of the acute attack, prevention of recurrent attacks and prevention of complications associated with the deposition of urate crystals in tissues. Pharmacological management remains the mainstay of treatment. Acute attacks may be terminated with the use of nonsteroidal anti-inflammatory agents, colchicine or intra-articular injections of corticosteroids. Probenecid, sulfinpyrazone and allopurinol can be used to prevent recurrent attacks. Obesity, alcohol intake and certain foods and medications can contribute to hyperuricemia. These potentially exacerbating factors should be identified and modified.

<1> Epidemiology and pathogenesis

1. The prevalence of gout is equal in men and women, but men are six times more likely to have hyperuricemia.
2. Typically occurs during middle age. **Women rarely have attacks of gouty arthritis before menopause**.
3. Hyperuricemia has been associated with **hyper-triglyceridemia** and **DM**, and it may be a risk factor for the development of **coronary artery disease**.
4. Uric acid is the end product of purine metabolism. The 7 mg/dL of serum uric acid concentration is the limit of solubility for **monosodium urate** in plasma. At levels of 8 mg/dL or greater, monosodium urate is more likely to precipitate in tissues.
5. The causes of hyperuricemia: either **over-production** (e.g. genetic defect or lymphoproliferative disorders) or **under-excretion** (e.g. idiopathic or renal insufficiency) of uric acid. **In 90% of patients, gout is caused by the under-excretion of uric acid**.
6. In transplant recipients gout is common and is usually precipitated by therapy with diuretics, cyclosporine or both, and may present even in young women.

<2> Clinical Presentation

- ◆ Initial gout attacks: usually **monoarthritis**.
- ◆ **Asymmetric polyarthritis** attacks can also occur, especially in the patients with recurrent attacks of gout and in the elderly patients.
- ◆ More than 75 % of acute gout attacks affect a joint in the **lower extremity**.
- ◆ **Podagra**, an acute attack of gout in the metatarsophalangeal joint of great toe, accounts for over 50 percent of all acute attacks. Around 90% of patients with gout experience podagra at some point in the disease.
- ◆ Other areas affected include the insteps, heels, ankles, knees, fingers, wrists and elbows, but **not spine**.

Classification of Hyperuricemia		
URATE OVERPRODUCTION		
Primary idiopathic	Myeloproliferative diseases	Rhabdomyolysis
HPRT deficiency	Polycythemia vera	Exercise
PRPP synthetase overactivity	Psoriasis	Alcohol
Hemolytic processes	Paget's disease	Obesity
Lymphoproliferative diseases	Glycogenosis III, V, and VII	Purine-rich diet
DECREASED URIC ACID EXCRETION		
Primary idiopathic	Starvation ketosis	Drug ingestion
Renal insufficiency	Berylliosis	Salicylates (>2 g/d)
Polycystic kidney disease	Sarcoidosis	Diuretics
Diabetes insipidus	Lead intoxication	Alcohol
Hypertension	Hyperparathyroidism	Levodopa
Acidosis	Hypothyroidism	Ethambutol
Lactic acidosis	Toxemia of pregnancy	Pyrazinamide
Diabetic ketoacidosis	Bartter's syndrome	Nicotinic acid
	Down syndrome	Cyclosporine
COMBINED MECHANISM		
Glucose-6-phosphatase deficiency	Fructose-1-phosphate aldolase deficiency	Alcohol
		Shock

NOTE: HPRT, hypoxanthine phosphoribosyltransferase; PRPP, phosphoribosylpyrophosphate

1. Acute Gouty Arthritis

- (1) May occur without provocation or be provoked by **any abrupt change in the serum uric acid concentration** (conditions that raise or decrease uric acid levels), e.g. consuming binge amounts of alcohol or ingesting large amounts of protein and purine-rich foods (e.g., bacon, salmon, sweetbreads, scallops, turkey). Some patients are not hyperuricemic at the time of attack.
- (2) **Modifiable risk factors:** alcohol consumption, obesity, hypertension and occupational exposure to lead.
- (3) **Clinical features:** (a) Acute, sudden attack of swelling, erythema, warmth and tenderness in a joint (**may be misdiagnosed as septic arthritis or cellulitis**) with the **peak within one to two days** of symptom onset. (b) Usually **start during the night**. (c) Moderate pain in a joint is first noticed. The pain becomes persistently worse and has a continuous, gnawing quality. (d) Low-grade fever. (e) **Untreated attacks may last seven to 10 days**. (f) The joints in the great toe and other parts of the lower extremity are generally the first articulations to be affected.

2. Intercritical Gout

- (1) Interval or intercritical gout is the condition that occurs after the acute attack has resolved and the patient has become asymptomatic.
- (2) Prophylactic antihyperuricemic therapy: (a) Indicated in patients with hyperuricemia and recurrent attacks, chronic gout, tophi, gouty arthritis or nephrolithiasis. (b) Equivocal for the first attack of acute gouty arthritis (some physicians may initiate hyperuricemic treatment immediately after first attack has subsided, but others recommend withholding prophylactic therapy until additional attacks occur).

3. Tophaceous Gout

- (1) Tophi are nodular masses of monosodium urate crystals deposited in the soft tissues of the body as a late complication of hyperuricemia (approximately 12 years after the initial gout attack).
- (2) The most common sites: the base of the great toe, and the fingers, wrist, hand, olecranon bursae and Achilles tendon.
- (3) Complications of tophi include pain, soft tissue damage and deformity, joint destruction and nerve compression syndromes such as carpal tunnel syndrome.

4. Renal Manifestations

- (1) **Nephrolithiasis:** 10% to 25% of patients with primary gout. The solubility of uric acid crystals increases as the urine pH becomes more alkaline. Uric acid can also act as a nidus for calcium oxalate or phosphate stones.
- (2) **Acute gouty nephropathy:** usually results from the massive malignant cell turnover that occurs with the treatment of myeloproliferative or lymphoproliferative disorders.
- (3) Long-term deposition of crystals in the renal parenchyma can cause **chronic urate nephropathy**. The formation of microtophi causes a giant cell inflammatory reaction. This results in proteinuria and inability of the kidney to concentrate urine.
- (4) Gout attack is rare in patients with chronic renal failure, despite hyperuricemia. **If gout and renal failure are present together**, consider:
 - (a) **Familial juvenile hyperuricemia:** dominantly inherited disorder characterized by severe underexcretion of filtered urate (FEurate 3-4%); cause interstitial nephritis; affects males and females equally; frequently associated with renal failure.
 - (b) **Chronic lead intoxication:** associated with gout, renal failure and hypertension.
 - (c) Gout from **complete or partial deficiency of HPRT**: gross overproduction of urate that even treatment with allopurinol and fluid loading may be insufficient to prevent crystal nephropathy. Alkalizing the urine may not be effective in preventing crystal nephropathy and acute renal insufficiency; increasing the urine flow rate is the most useful measure. Less severe forms of HPRT deficiency may present as early-onset severe gout, sometimes with a family history.

<3> Diagnostic Evaluation

1. Examination of aspirated synovial fluid from inflamed joint
 - (1) Definitive diagnosis requires synovial fluid aspiration to reveal **needle-shaped and negatively birefringent monosodium urate crystals inside PMN cells** by polarizing microscopy.
 - (2) Can rule out other disorders that mimic gout, such as septic arthritis, pseudogout (CPPD deposition disease), and calcified tendinitis (basic calcium phosphate or calcium hydroxyapatite),

which may occur in patients who happen to have hyperuricemia. These diseases can also respond to colchicine.

- (3) Gout can co-exist with other rheumatic diseases (So, do not always blame gout every time on causing joint pain in patients with the past history of gouty arthritis).
2. Examine renal function and cardiovascular system (patients with gout typically have hypertension and impaired renal function).
3. Lab tests: serum uric acid level, CRP (could be very high).
4. Radiography is generally nonspecific and not very useful in diagnosing acute gouty arthritis, but may be helpful for differential diagnosis, especially when no crystal is found in the synovial fluid. Chronic arthritis with tophus may cause bony erosions seen on radiographs with classic radiologic features of **an overhanging edge of cortex and a "punched-out" erosion of bone with sclerotic borders** (see the radiography on the right side). Mineralization is normal, and joint spaces are preserved. Distribution includes the feet, ankles, knees, hands and elbows.



<4> Treatment

- **The therapeutic aims in gout:**

1. **Terminate acute attack immediately.**
2. **Prevent recurrence of acute gouty arthritis.**
3. **Prevent and reverse the complication caused by the deposition of crystals in kidney, joints or other sites.**
4. **Prevent and reverse the condition associated with gout, such as obesity, hyperlipidemia and hypertension.**

1. Non-pharmacological therapy

- Dietary and lifestyle changes: include weight reduction, decreased alcohol ingestion, decreased consumption of foods with a high purine content, and control of hyperlipidemia and hypertension.
- These methods probably cannot reduce serum uric acid levels to normal, which is the treatment goal for the prevention of acute gout attacks. **Symptomatic hyperuricemia usually requires medication.**

2. Treatment for acute gouty arthritis

- (1) Three treatments currently available: nonsteroidal anti-inflammatory drugs (**NSAIDs**), **colchicine** and **corticosteroids**. **Do not administer any anti-hyperuricemic drug until an acute attack of gouty arthritis has completely subsided, if that patient has not taken any anti-hyperuricemic drug before**, because of the risk of increased mobilization of uric acid stores that may prolong the attack.
- (2) **NSAIDs**: **These rapid-acting drugs are currently the most favored treatment** for acute gout attacks. Any NSAIDs, except aspirin, can be used. Usually, short-acting NSAIDs with rapid onset will be used, such as diclofenac (Voltaren) 150 mg/day, for several days to achieve rapid relief of pain and anti-inflammation. These drugs should be used with caution in patients with a history of allergy to NSAIDs, peptic ulcer disease, congestive heart failure or chronic renal failure.
- (3) **Colchicine**: Colchicine (0.5mg bid) will be given together with NSAID. After acute attack has subsided and NSAID has been discontinued, still continue colchicine to prevent recurrent, especially when anti-hyperuricemic agent is started. Colchicine has anti-inflammatory activity but no analgesic activity. **Maximal 1 mg/day (one tablet twice daily) of colchicine is enough to treat acute gouty arthritis and to prevent recurrence**, and the dose even needs to be reduced in the elderly patients, in patients with renal insufficiency or liver disease, or in patients intolerant to colchicine (e.g. 1/2 tablet bid). Side effects include diarrhea, neuropathy, bone marrow suppression, and renal or hepatic cell damage.
- (4) **Corticosteroids**: Monoarthritic gout responds well to corticosteroids given by intra-articular injection. Systemic corticosteroids (e.g. in a dosage of 20 to 30 mg/day of prednisolone) can be used only when NSAIDs and colchicine are not effective or are contraindicated (esp. in the elderly).

3. Prevention of recurrent attacks

- Reduction of serum uric acid levels to normal is the goal of treatment designed to prevent acute attacks of gout.
- Hyperuricemic therapy should be initiated in patients with **frequent gout attacks, tophi or urate nephropathy**.
- **Colchicine** is effective in preventing acute gouty attacks.

- ◆ A reasonable goal is to reduce the serum uric acid concentration to less than **6 mg/dL (360 µmol per L)**.

4. Anti-hyperuricemic drugs: two classes of drugs (a) **Uricosurics**, which increases renal excretion of uric acid. (b) **Xanthine oxidase inhibitors**, such as allopurinol, which inhibit uric acid production.

(1) **Uricosuric drugs:** Probenecid and sulfinpyrazone, **benzbromazone (Narcaricine)**; used in patients with under-excretion of uric acid; should **not be given to patients with tophus, a urine output of less than 1 mL/min, a creatinine clearance of less than 50 mL/min or a history of renal calculi**. The physiologic decline in renal function that occurs with aging frequently limits the use of uricosuric agents in the elderly patients.

(2) **Xanthine oxidase inhibitors**

(a) **Allopurinol:** The effect depends on the dosage (dosage of 300 mg/day has been reported to reduce serum urate concentrations to < 7 mg/dL in 70% of patients. (b) Drug of choice in patients with **severe tophaceous deposits, a history of impaired renal function, uric acid nephropathy or nephrolithiasis**. The pretreatment agent to protect against uric acid nephropathy in patients with **lymphoproliferative or myeloproliferative disorders**. (d) Side effects: skin rash (e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis), leukopenia and gastrointestinal disturbances. The dosage of allopurinol should be adjusted in patients with renal impairment. **Allopurinol and azathioprine together usually produce severe marrow depression.**

(b) **Febuxostat:** a new oral xanthine oxidase inhibitor. Unlike allopurinol, it does not frequently cause severe skin allergy.

<5> **Elderly-onset gouty arthritis**

- ◆ The clinical presentations the elderly patients may be different from those in younger patients (see the table below).
- ◆ Often occur in the elderly patients with renal function impairment and diuretic use (e.g. to treat heart failure).
- ◆ Could be polyarthritis over the upper extremities (especially fingers), which may require differential diagnosis from RA and spondyloarthropathy.
- ◆ Early onset of tophus formation is common.
- ◆ Treatments are similar to those used to treat younger patients mentioned above. Using NSAID and colchicine should more cautious in the elderly because of increased incidences of side effects of these drugs in this population. In this case, steroid (systemic administration for a short term or intra-articular injection for one or two joint involvement) may be considered in the elderly patients with acute attack of gouty arthritis.
- ◆ Allopurinol, rather than uricosuric agent, is favored for elderly patients, because patients usually have impaired renal function.

CLINICAL FEATURES OF GOUT—TYPICAL VERSUS ELDERLY ONSET GOUT

Feature	Typical Gout	Elderly Onset Gout
Age of onset	Peak in mid 40s	Over 65
Sex distribution	Men > Women	Men = Women Women > Men over 80
Presentation	Acute monoarthritis Lower extremity (Podagra 60%)	Polyarticular onset more often Upper extremity more often Finger involvement more often
Tophi	After years of attacks	May occur early or without history of prior attacks
Associated features	Elbows > Fingers Obesity Hyperlipidemia Hypertension Alcohol use, heavy	Possibly more often over fingers Renal insufficiency Diuretic use, especially in women Alcohol use less common

(B) **Pseudogout (CPPD deposition disease)**

- ◆ A degenerative joint disease characterized by the accumulation of calcium pyrophosphate dihydrate (CPPD) crystals in articular cartilage, synovium and periarticular tissues.
- ◆ CPPD crystals can accumulate normally within joints with advancing age. In elderly patients, they can therefore be regarded as a normal finding in association with chondrocalcinosis and osteoarthritis.
- ◆ Diseases associated with CPPD: **hyperparathyroidism, hypophosphatemia, hypomagnesemia, hemochromatosis, ochronosis**.

1. Clinical features:

- (1) Can be **asymptomatic** or present with the following clinical manifestations.
- (2) **Pseudogout**. (a) Acute or subacute arthritis that can last for several days. (b) May involve one or

more joints, mainly at knees. (c) Attacks very similar to gout, though usually not so severe. (d) Crystal deposition can occur in tendons, ligaments, and synovia, as well as in cartilage. (e) Surgery or illness can predispose to attacks.

- (3) **Pseudo-osteoarthritis.** Chronic CPPD disease may appear similar to osteoarthritis with progressive degeneration of multiple joints. Knees are most commonly affected, followed by wrists, MCP joints, hips, shoulders, and elbows. May have symmetric involvement.
- (4) **Pseudo-rheumatoid arthritis.** In 5%, calcium pyrophosphate disease causes symptoms similar to rheumatoid arthritis, including morning stiffness, fatigue, synovial membrane thickening, and elevated ESR. About 10% of patients with CPPD deposition have a positive rheumatoid factor.
- (5) Compared with gout: (a) Acute CPPD arthritis occurs almost exclusively in the elderly. (b) More common than gout in patients with chronic or end-stage renal failure (associated with secondary hyperparathyroidism; chondrocalcification is often present; chronic management is to control the phosphate concentration to alleviate the hyperparathyroidism, or receive para-thyroidectomy if necessary).

2. Investigations and diagnosis

- (1) Examination of aspirated synovial fluid: rod- or rhomboid-shaped CPPD crystals with positive birefringence.
- (2) CPPD crystals can be found in acute inflamed joint (**pseudogout**), in a destructive arthropathy with or without osteoarthritis, asymptomatic chondrocalcification and hypertrophic osteoarthritis.
- (3) Check the levels of calcium, phosphate and magnesium.
- (4) Radiography: osteoarthritis with joint space narrowing; chondrocalcification (most commonly seen in knee menisci, triangular cartilage of the wrist, and symphysis pubis fibrocartilage).



Typical articular chondrocalcification in the areas of the medial and lateral meniscus.



Radiograph of a wrist, showing typical articular chondrocalcification in the triangular cartilage distal to the ulna, and in the radiocarpal and intercarpal joints.

3. Treatment:

- (1) Joint aspiration to relieve intra-articular pressure.
- (2) NSAID or intra-articular steroid to reduce joint inflammation.
- (3) Daily prophylactic treatment with colchicine (like treatment for gout).
- (4) Intravenous steroid for polyarticular attacks.

(C) Hydroxyapatite

- ◆ Hydroxyapatite usually derived from calcified cartilage or subchondral bone. Hydroxyapatite within SF indicates **damage to calcified cartilage or underlying subarticular bone**.
- ◆ Loss of cartilage, sufficient to expose these structures, is seen most commonly in OA and RA.
- ◆ Periarticular inflammatory deposits of hydroxyapatite (due to ectopic deposition of calcium) in **uremic patients** may mimic arthritis, affect tendon sheaths, or occur in the eye (uremic red eye), in the skin or as subcutaneous inflammatory masses.
- ◆ Clinical features of patients with peri-articular hydroxyapatite deposits
 - (1) Asymptomatic radiographic abnormalities
 - (2) Acute synovitis and tendinitis: may cause synovitis in chronic stable OA (hot Heberden's nodes).
 - (3) Chronic destructive arthropathy: a specific arthropathy, "Milwaukee shoulder", is associated with larger apatite microspherules
- ◆ Diagnosis: identification of crystals in the synovial fluid or tissues.
 - (1) The small non-birefringent crystals can only be seen by electron microscopy, not by light microscope.
 - (2) Extracellular and intracellular crystals can be visualized by staining with **alizarin red S** to produce red-colored globules.
- ◆ Treatment for acute synovitis or tendonitis: (1) Symptoms usually resolve spontaneously for about a week. (b) Can be treated with NSAIDs, colchicine, or steroid, as treating other crystal-induced arthritis.