Musculoskeletal, Skin, and Connective Tissue

"Rigid, the skeleton of habit alone upholds the human frame."
—Virginia Woolf, *Mrs. Dalloway*

"Beauty may be skin deep, but ugly goes clear to the bone."
—Redd Foxx

"The finest clothing made is a person's own skin, but, of course, society demands something more than this."
—Mark Twain

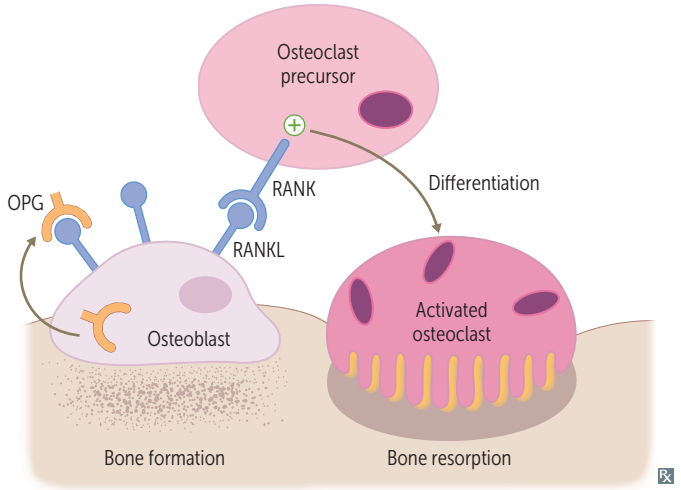
"To thrive in life you need three bones. A wishbone. A backbone. And a funny bone."
—Reba McEntire

This chapter provides information you will need to understand certain anatomical dysfunctions, rheumatic diseases, and dermatologic conditions. Be able to interpret 3D anatomy in the context of radiologic imaging. For the rheumatic diseases, create instructional cases or personas that include the most likely presentation and symptoms: risk factors, gender, important markers (eg, autoantibodies), and other epidemiologic factors. Doing so will allow you to answer the higher order questions that are likely to be asked on the exam.

Red squares contain the required MED exam material

Cell biology of bone

Osteoblast	Builds bone by secreting collagen and catalyzing mineralization in alkaline environment via ALP. Differentiates from mesenchymal stem cells in periosteum. Osteoblastic activity measured by bone ALP, osteocalcin, propeptides of type I procollagen.
Osteoclast	Dissolves ("crushes") bone by secreting H^+ and collagenases. Differentiates from a fusion of monocyte/macrophage lineage precursors. RANK receptors on osteoclasts are stimulated by RANKL (RANK ligand, expressed on osteoblasts). OPG (osteoprotegerin, a RANKL decoy receptor) binds RANKL to prevent RANK-RANKL interaction → ↓ osteoclast activity.
Parathyroid hormone	At low, intermittent levels, exerts anabolic effects (building bone) on osteoblasts and osteoclasts (indirect). Chronically ↑ PTH levels (1° hyperparathyroidism) cause catabolic effects (osteitis fibrosa cystica).
Estrogen	Inhibits apoptosis in bone-forming osteoblasts and induces apoptosis in bone-resorbing osteoclasts. Causes closure of epiphyseal plate during puberty. Estrogen deficiency (surgical or postmenopausal) → ↑ cycles of remodeling and bone resorption → ↑ risk of osteoporosis.



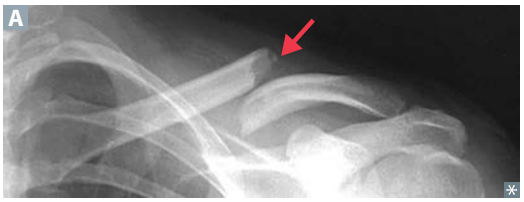
▸ MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—PATHOLOGY

Overuse injuries of the elbow

Medial epicondylitis (golfer's elbow)	Repetitive flexion or idiopathic → pain near medial epicondyle.
Lateral epicondylitis (tennis elbow)	Repetitive extension (backhand shots) or idiopathic → pain near lateral epicondyle.

Clavicle fractures

Common in children and as birth trauma. Usually caused by a fall on outstretched hand or by direct trauma to shoulder. Weakest point at the junction of middle and lateral thirds; fractures at the middle third segment are most common **A**. Presents as shoulder drop, shortened clavicle (lateral fragment is depressed due to arm weight and medially rotated by arm adductors [eg, pectoralis major]).

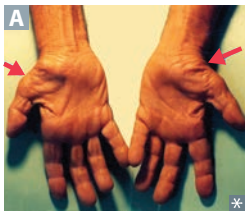


Wrist and hand injuries

Guyon canal syndrome

Compression of ulnar nerve at wrist. Classically seen in cyclists due to pressure from handlebars.

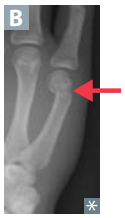
Carpal tunnel syndrome



Entrapment of median nerve in carpal tunnel (between transverse carpal ligament and carpal bones) → nerve compression → paresthesia, pain, and numbness in distribution of median nerve. Thenar eminence atrophies **A** but sensation spared, because palmar cutaneous branch enters hand external to carpal tunnel.

Suggested by ⊕ Tinel sign (percussion of wrist causes tingling) and Phalen maneuver (90° flexion of wrist causes tingling).
Associated with pregnancy (due to edema), rheumatoid arthritis, hypothyroidism, diabetes, acromegaly, dialysis-related amyloidosis; may be associated with repetitive use.

Metacarpal neck fracture

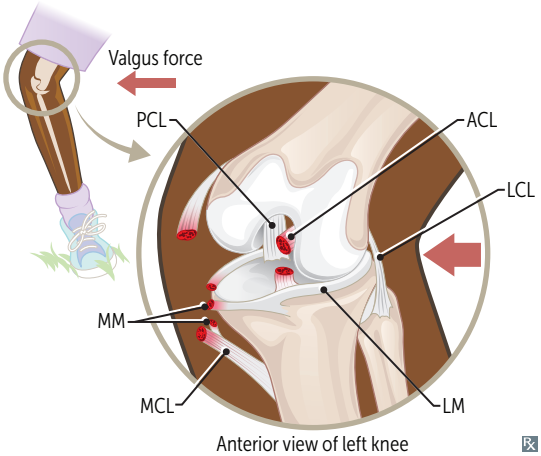


Also called boxer's fracture. Common fracture caused by direct blow with a closed fist (eg, from punching a wall). Most commonly seen in the 5th metacarpal **B**.

Common knee conditions

"Unhappy triad"

Common injury in contact sports due to laterally directed force to a planted foot. Consists of damage to the ACL A, MCL, and medial meniscus (attached to MCL). However, lateral meniscus involvement is more common than medial meniscus involvement in conjunction with ACL and MCL injury. Presents with acute pain and signs of joint instability.



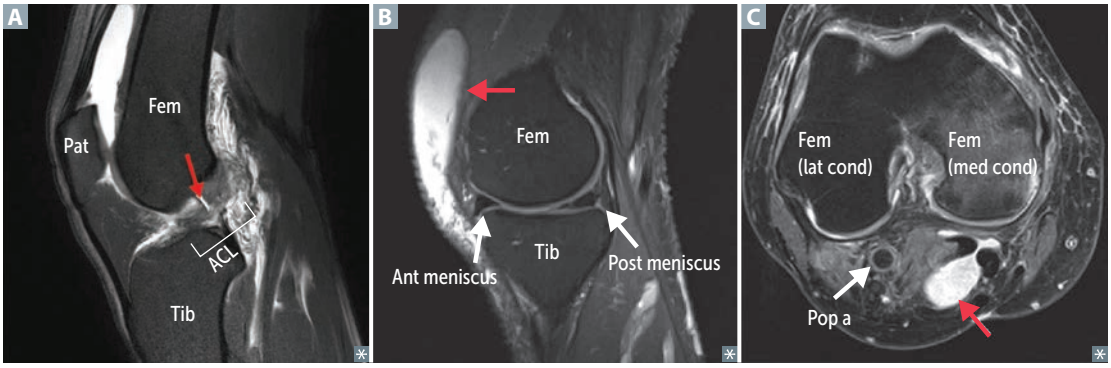
Anterior view of left knee

Prepatellar bursitis

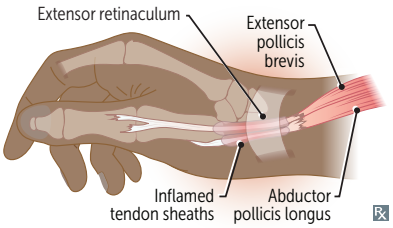
Inflammation of the prepatellar bursa in front of the kneecap (red arrow in B). Can be caused by repeated trauma or pressure from excessive kneeling (also called "housemaid's knee").

Popliteal cyst

Also called Baker cyst. Popliteal fluid collection (red arrow in C) in gastrocnemius-semimembranosus bursa commonly communicating with synovial space and related to chronic joint disease (eg, osteoarthritis, rheumatoid arthritis).

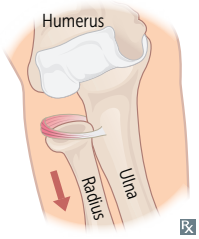


Common musculoskeletal conditions

De Quervain tenosynovitis	Noninflammatory thickening of abductor pollicis longus and extensor pollicis brevis tendons → pain or tenderness at radial styloid. ⊕ Finkelstein test (pain at radial styloid with active or passive stretch of thumb tendons). ↑ risk in new parent (lifting baby), golfers, racquet sport players, "thumb" texters. 
Ganglion cyst	Fluid-filled swelling overlying joint or tendon sheath, most commonly at dorsal side of wrist. Arises from herniation of dense connective tissue. Usually resolves spontaneously.
Iliotibial band syndrome	Overuse injury of lateral knee that occurs primarily in runners. Pain develops 2° to friction of iliotibial band against lateral femoral epicondyle.
Limb compartment syndrome	↑ pressure within fascial compartment of a limb → venous outflow obstruction and arteriolar collapse → anoxia and necrosis. Causes include significant long bone fractures, reperfusion injury, animal venoms. Presents with severe pain and tense, swollen compartments with passive stretch of muscles in the affected compartment. Increased serum creatine kinase and motor deficits are late signs of irreversible muscle and nerve damage. 5 Ps: pain, palor, paresthesia, pulselessness, paralysis.
Medial tibial stress syndrome	Also called shin splints. Common cause of shin pain and diffuse tenderness in runners and military recruits. Caused by bone resorption that outpaces bone formation in tibial cortex.
Plantar fasciitis	Inflammation of plantar aponeurosis characterized by heel pain (worse with first steps in the morning or after period of inactivity) and tenderness.
Temporomandibular disorders	Group of disorders that involve the temporomandibular joint (TMJ) and muscles of mastication. Multifactorial etiology; associated with TMJ trauma, poor head and neck posture, abnormal trigeminal nerve pain processing, psychological factors. Present with dull, constant unilateral facial pain that worsens with jaw movement, otalgia, headache, TMJ dysfunction (eg, limited range of motion).

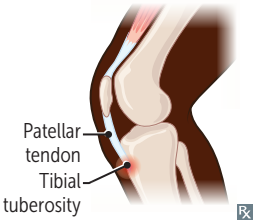
Childhood musculoskeletal conditions

Radial head subluxation



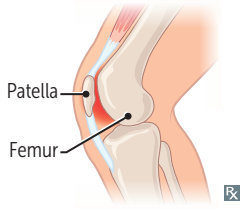
Also called nursemaid's elbow. Common elbow injury in children < 5 years. Caused by a sudden pull on the arm → immature annular ligament slips over head of radius. Injured arm held in slightly flexed and pronated position.

Osgood-Schlatter disease



Also called traction apophysitis. Overuse injury caused by repetitive strain and chronic avulsion of the secondary ossification center of proximal tibial tubercle. Occurs in adolescents after growth spurt. Common in running and jumping athletes. Presents with progressive anterior knee pain.

Patellofemoral syndrome



Overuse injury that commonly presents in young, female athletes as anterior knee pain. Exacerbated by prolonged sitting or weight-bearing on a flexed knee.

Developmental dysplasia of the hip

Abnormal acetabulum development in newborns. Risk factor is breech presentation. Results in hip instability/dislocation. Commonly tested with Ortolani and Barlow maneuvers (manipulation of newborn hip reveals a "clunk"). Confirmed via ultrasound (x-ray not used until ~4–6 months because cartilage is not ossified).

Legg-Calvé-Perthes disease

Idiopathic avascular necrosis of femoral head. Commonly presents between 5–7 years with insidious onset of hip pain that may cause child to limp. More common in males (4:1 ratio). Initial x-ray often normal.

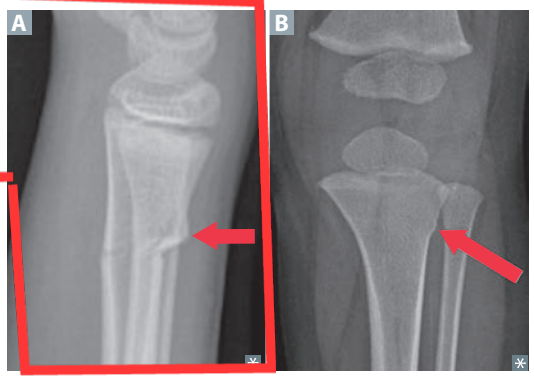
Slipped capital femoral epiphysis

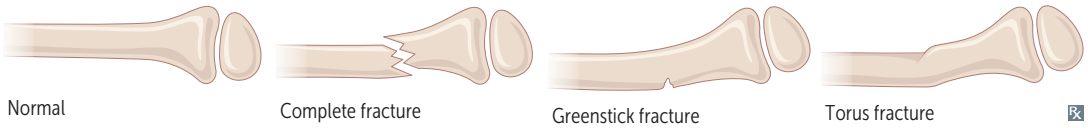
Classically presents in an obese young adolescent with hip/knee pain and altered gait. Increased axial force on femoral head → epiphysis displaces relative to femoral neck (like a scoop of ice cream slipping off a cone). Diagnosed via x-ray.

Common pediatric fractures

Greenstick fracture — Incomplete fracture extending partway through width of bone A following bending stress; bone fails on tension side; compression side intact (compare to torus fracture). Bone is bent like a green twig.

Torus (buckle) fracture — Axial force applied to immature bone → cortex buckles on compression (concave) side and fractures B. Tension (convex) side remains solid (intact).

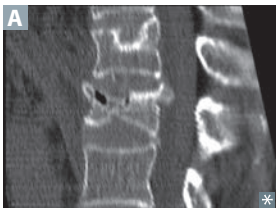




Achondroplasia

Failure of longitudinal bone growth (endochondral ossification) → short limbs. Membranous ossification is not affected → large head relative to limbs. Constitutive activation of fibroblast growth factor receptor (FGFR3) actually inhibits chondrocyte proliferation. > 85% of mutations occur sporadically; autosomal dominant with full penetrance (homozygosity is lethal). Associated with ↑ paternal age. Most common cause of short-limbed dwarfism.

Osteoporosis



Trabecular (spongy) and cortical bone lose mass despite normal bone mineralization and lab values (serum Ca^{2+} and PO_4^{3-}).

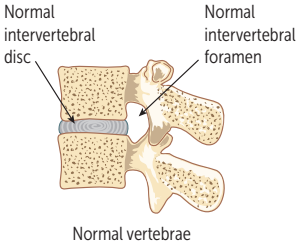
Most commonly due to ↑ bone resorption related to ↓ estrogen levels and old age. Can be 2° to drugs (eg, steroids, alcohol, anticonvulsants, anticoagulants, thyroid replacement therapy) or other conditions (eg, hyperparathyroidism, hyperthyroidism, multiple myeloma, malabsorption syndromes, anorexia).

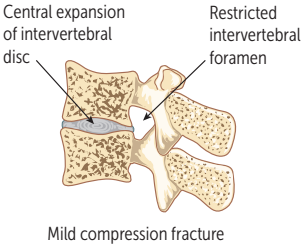
Diagnosed by bone mineral density measurement by DEXA (dual-energy X-ray absorptiometry) at the lumbar spine, total hip, and femoral neck, with a T-score of ≤ –2.5 or by a fragility fracture (eg, fall from standing height, minimal trauma) at hip or vertebra. One-time screening recommended in females ≥ 65 years old.

Prophylaxis: regular weight-bearing exercise and adequate Ca^{2+} and vitamin D intake throughout adulthood.

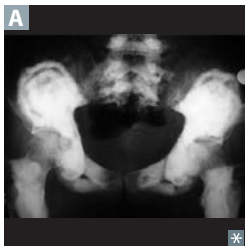
Treatment: bisphosphonates, teriparatide, SERMs, rarely calcitonin; denosumab (monoclonal antibody against RANKL).

Can lead to vertebral compression fractures A—acute back pain, loss of height, kyphosis. Also can present with fractures of femoral neck, distal radius (Colles fracture).





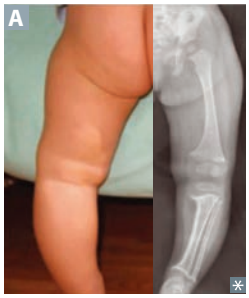
Osteopetrosis



Failure of normal bone resorption due to defective osteoclasts → thickened, dense bones that are prone to fracture. Mutations (eg, carbonic anhydrase II) impair ability of osteoclast to generate acidic environment necessary for bone resorption. Overgrowth of cortical bone fills marrow space → pancytopenia, extramedullary hematopoiesis. Can result in cranial nerve impingement and palsies due to narrowed foramina.

X-rays show diffuse symmetric sclerosis (bone-in-bone, "stone bone" A). Bone marrow transplant is potentially curative as osteoclasts are derived from monocytes.

Osteomalacia/rickets

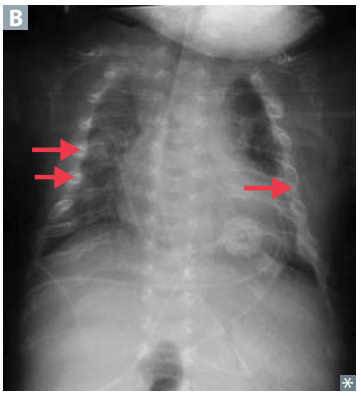


Defective mineralization of osteoid (osteomalacia) or cartilaginous growth plates (rickets, only in children). Most commonly due to vitamin D deficiency.

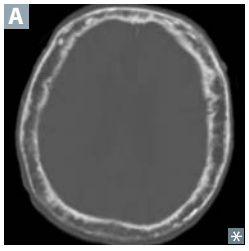
X-rays show osteopenia and pseudofractures in osteomalacia, epiphyseal widening and metaphyseal cupping/fraying in rickets. Children with rickets have pathologic bow legs (genu varum A), bead-like costochondral junctions (rachitic rosary B), craniotabes (soft skull).

↓ vitamin D → ↓ serum Ca^{2+} → ↑ PTH secretion → ↓ serum PO_4^{3-}.

Hyperactivity of osteoblasts → ↑ ALP.



Osteitis deformans



Also called Paget disease of bone. Common, localized disorder of bone remodeling caused by ↑ osteoclastic activity followed by ↑ osteoblastic activity that forms poor-quality bone. Serum Ca^{2+}, phosphorus, and PTH levels are normal. ↑ ALP. Mosaic pattern of woven and lamellar bone (osteocytes within lacunae in chaotic juxtapositions); long bone chalk-stick fractures. ↑ blood flow from ↑ arteriovenous shunts may cause high-output heart failure. ↑ risk of osteosarcoma.

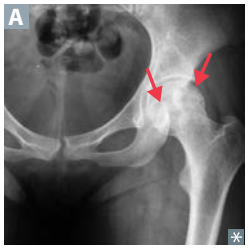
Hat size can be increased due to skull thickening A; hearing loss is common due to skull deformity.

Stages of Paget disease:

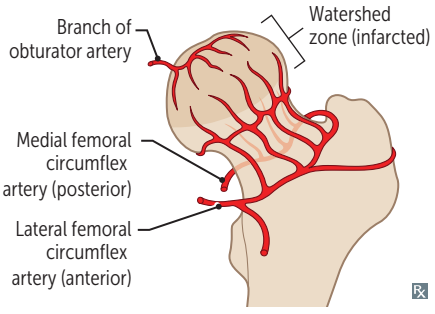
- Lytic—osteoclasts
- Mixed—osteoclasts + osteoblasts
- Sclerotic—osteoblasts
- Quiescent—minimal osteoclast/osteoblast activity

Treatment: bisphosphonates.

Avascular necrosis of bone



Infarction of bone and marrow, usually very painful. Most common site is femoral head (watershed zone) A (due to insufficiency of medial circumflex femoral artery). Causes include Corticosteroids, chronic Alcohol overuse, Sickle cell disease, Trauma, SLE, "the Bends" (caisson/decompression disease), LEgg-Calvé-Perthes disease (idiopathic), Gaucher disease, Slipped capital femoral epiphysis—CASTS Bend LEGS.



Lab values in bone disorders

DISORDER	SERUM Ca^{2+}	PO_4^{3-}	ALP	PTH	COMMENTS
Osteoporosis	—	—	—	—	↓ bone mass
Osteopetrosis	—/↓	—	—	—	Dense, brittle bones. Ca^{2+} ↓ in severe, malignant disease
Paget disease of bone	—	—	↑	—	Abnormal "mosaic" bone architecture
Osteitis fibrosa cystica Primary hyperparathyroidism	↑	↓	↑	↑	"Brown tumors" due to fibrous replacement of bone, subperiosteal thinning Idiopathic or parathyroid hyperplasia, adenoma, carcinoma
Secondary hyperparathyroidism	↓	↑	↑	↑	Often as compensation for CKD (↓ PO_4^{3-} excretion and production of activated vitamin D)
Osteomalacia/rickets	↓	↓	↑	↑	Soft bones; vitamin D deficiency also causes 2° hyperparathyroidism
Hypervitaminosis D	↑	↑	—	↓	Caused by oversupplementation or granulomatous disease (eg, sarcoidosis)

↑ ↓ = 1° change.

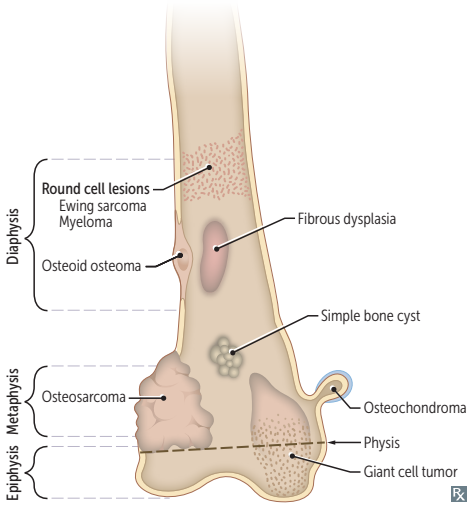
Primary bone tumors

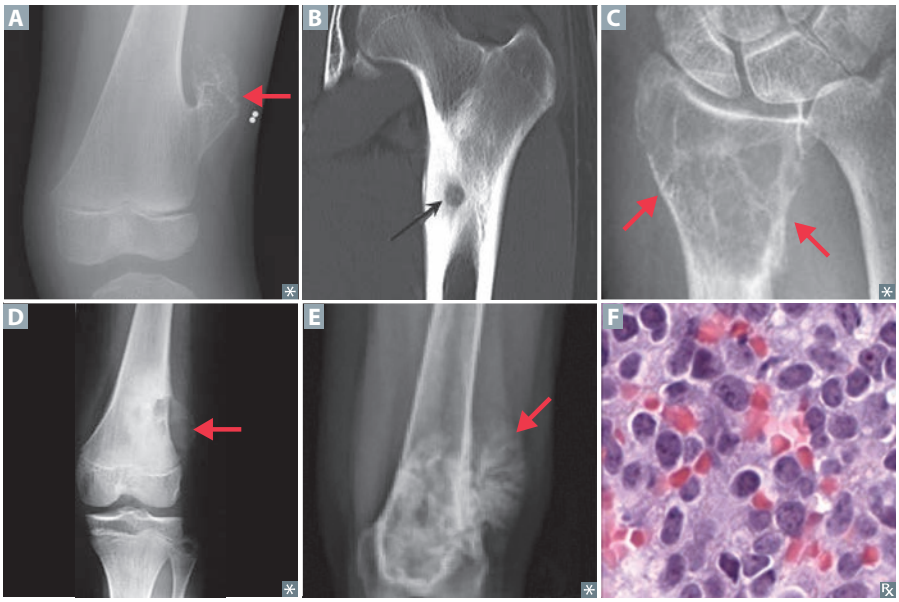
Metastatic disease is more common than 1° bone tumors. Benign bone tumors that start with o are more common in boys.

TUMOR TYPE	EPIDEMIOLOGY	LOCATION	CHARACTERISTICS
Benign tumors			
Osteochondroma	Most common benign bone tumor Males < 25 years old	Metaphysis of long bones	Lateral bony projection of growth plate (continuous with marrow space) covered by cartilaginous cap A Rarely transforms to chondrosarcoma
Osteoma	Middle age	Surface of facial bones	Associated with Gardner syndrome
Osteoid osteoma	Adults < 25 years old Males > females	Cortex of long bones	Presents as bone pain (worse at night) that is relieved by NSAIDs Bony mass (< 2 cm) with radiolucent osteoid core B
Osteoblastoma	Males > females	Vertebrae	Similar histology to osteoid osteoma Larger size (> 2 cm), pain unresponsive to NSAIDs
Chondroma		Medulla of small bones of hand and feet	Benign tumor of cartilage
Giant cell tumor	20–40 years old	Epiphysis of long bones (often in knee region)	Locally aggressive benign tumor Neoplastic mononuclear cells that express RANKL and reactive multinucleated giant (osteoclast-like) cells. "Osteoclastoma" "Soap bubble" appearance on x-ray C

Primary bone tumors *(continued)*

TUMOR TYPE	EPIDEMIOLOGY	LOCATION	CHARACTERISTICS
Malignant tumors			
Osteosarcoma (osteogenic sarcoma)	Accounts for 20% of 1° bone cancers. Peak incidence of 1° tumor in males < 20 years. Less common in elderly; usually 2° to predisposing factors, such as Paget disease of bone, bone infarcts, radiation, familial retinoblastoma, Li-Fraumeni syndrome.	Metaphysis of long bones (often in knee region).	Pleomorphic osteoid-producing cells (malignant osteoblasts). Presents as painful enlarging mass or pathologic fractures. Codman triangle D (from elevation of periosteum) or sunburst pattern on x-ray E (think of an osteocod [bone fish] swimming in the sun). Aggressive. 1° usually responsive to treatment (surgery, chemotherapy), poor prognosis for 2°.
Chondrosarcoma		Medulla of pelvis, proximal femur and humerus.	Tumor of malignant chondrocytes.
Ewing sarcoma	Most common in White patients. Generally males < 15 years old.	Diaphysis of long bones (especially femur), pelvic flat bones.	Anaplastic small blue cells of neuroectodermal origin (resemble lymphocytes) F. Differentiate from conditions with similar morphology (eg, lymphoma, chronic osteomyelitis) by testing for t(11;22) (fusion protein EWS-FLI1). "Onion skin" periosteal reaction in bone. Aggressive with early metastases, but responsive to chemotherapy. 11 + 22 = 33 (Patrick Ewing's jersey number).

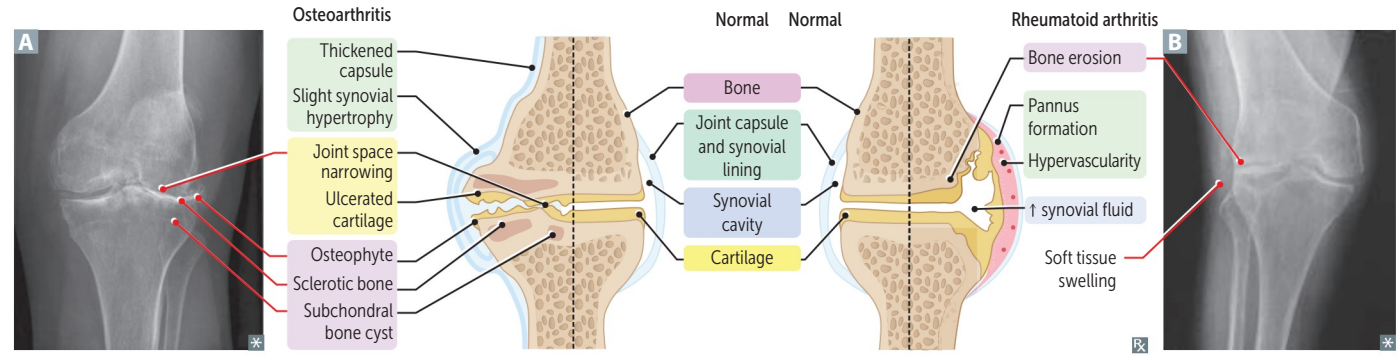


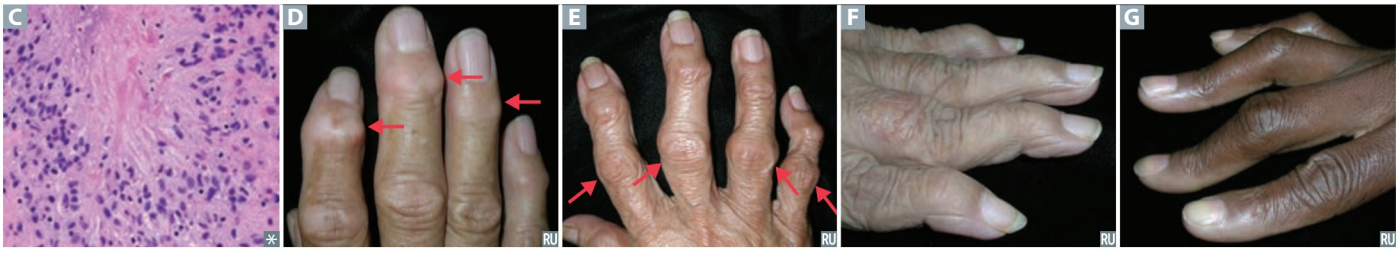


Osteoarthritis vs rheumatoid arthritis

	Osteoarthritis A	Rheumatoid arthritis B
PATHOGENESIS	Mechanical—wear and tear destroys articular cartilage (degenerative joint disorder) → inflammation with inadequate repair. Chondrocytes mediate degradation and inadequate repair.	Autoimmune—inflammation C induces formation of pannus (proliferative granulation tissue), which erodes articular cartilage and bone.
PREDISPOSING FACTORS	Age, female, obesity, joint trauma.	Female, HLA-DR4 (4-walled "rheum"), tobacco smoking. ⊕ rheumatoid factor (IgM antibody that targets IgG Fc region; in 80%), anti-cyclic citrullinated peptide antibody (more specific).
PRESENTATION	Pain in weight-bearing joints after use (eg, at the end of the day), improving with rest. Asymmetric joint involvement. Knee cartilage loss begins medially ("bowlegged"). No systemic symptoms.	Pain, swelling, and morning stiffness lasting > 1 hour, improving with use. Symmetric joint involvement. Systemic symptoms (fever, fatigue, weight loss). Extraarticular manifestations common.*
JOINT FINDINGS	Osteophytes (bone spurs), joint space narrowing, subchondral sclerosis and cysts. Synovial fluid noninflammatory (WBC < 2000/mm^3). Development of Heberden nodes D (at DIP) and Bouchard nodes E (at PIP), and 1st CMC; not MCP.	Erosions, juxta-articular osteopenia, soft tissue swelling, subchondral cysts, joint space narrowing. Deformities: cervical subluxation, ulnar finger deviation, swan neck F, boutonniere G. Involves MCP, PIP, wrist; not DIP or 1st CMC.
TREATMENT	Activity modification, acetaminophen, NSAIDs, intra-articular glucocorticoids.	NSAIDs, glucocorticoids, disease-modifying agents (eg, methotrexate, sulfasalazine), biologic agents (eg, TNF-α inhibitors).

*Extraarticular manifestations include rheumatoid nodules (fibrinoid necrosis with palisading histiocytes) in subcutaneous tissue and lung (+ pneumoconiosis → Caplan syndrome), interstitial lung disease, pleuritis, pericarditis, anemia of chronic disease, neutropenia + splenomegaly (Felty syndrome), AA amyloidosis, Sjögren syndrome, scleritis, carpal tunnel syndrome.





Gout

FINDINGS

Acute inflammatory monoarthritis caused by precipitation of monosodium urate crystals in joints A. Risk factors: male sex, hypertension, obesity, diabetes, dyslipidemia, alcohol use. Strongest risk factor is hyperuricemia, which can be caused by:

- Underexcretion of uric acid (90% of patients)—largely idiopathic, potentiated by renal failure; can be exacerbated by certain medications (eg, thiazide diuretics).
- Overproduction of uric acid (10% of patients)—Lesch-Nyhan syndrome, PRPP excess, ↑ cell turnover (eg, tumor lysis syndrome), von Gierke disease.

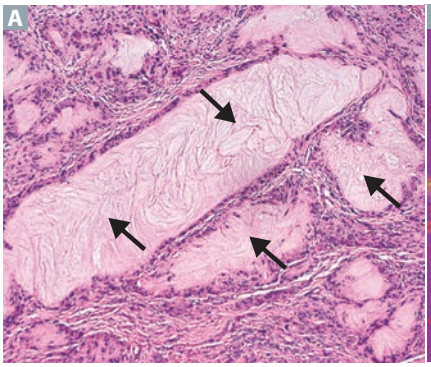
Crystals are needle shaped and ⊖ birefringent under polarized light (yellow under parallel light, blue under perpendicular light B). Serum uric acid levels may be normal during an acute attack.

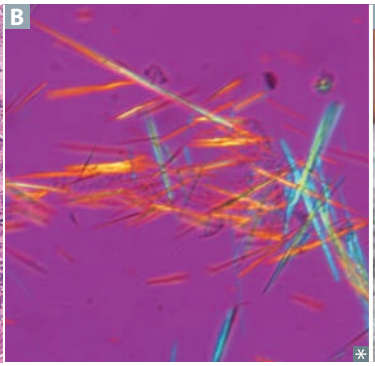
SYMPTOMS

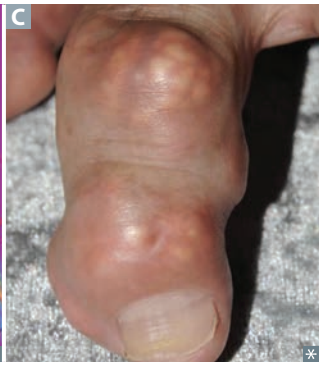
Asymmetric joint distribution. Joint is swollen, red, and painful. Classic manifestation is painful MTP joint of big toe (podagra). Tophus formation C (often on external ear, olecranon bursa, or Achilles tendon). Acute attack tends to occur after a large meal with foods rich in purines (eg, red meat, seafood), trauma, surgery, dehydration, diuresis, or alcohol consumption (alcohol metabolites compete for same excretion sites in kidney as uric acid → ↓ uric acid secretion and subsequent buildup in blood).

TREATMENT

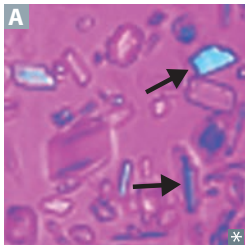
Acute: NSAIDs (eg, indomethacin), glucocorticoids, colchicine.
Chronic (preventive): xanthine oxidase inhibitors (eg, allopurinol, febuxostat).







Calcium pyrophosphate deposition disease



Previously called pseudogout. Deposition of calcium pyrophosphate crystals within the joint space. Occurs in patients > 50 years old; both sexes affected equally. Usually idiopathic, sometimes associated with hemochromatosis, hyperparathyroidism, joint trauma.

Pain and swelling with acute inflammation (pseudogout) and/or chronic degeneration (pseudo-osteoarthritis). Most commonly affected joint is the knee.

Chondrocalcinosis (cartilage calcification) on x-ray.

Crystals are rhomboid and weakly ⊕ birefringent under polarized light (blue when parallel to light) A.

Acute treatment: NSAIDs, colchicine, glucocorticoids.

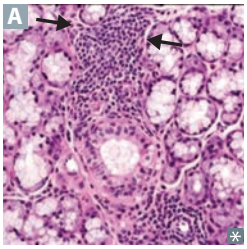
Prophylaxis: colchicine.

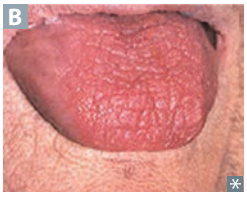
The blue P's—blue (when parallel), positive birefringence, calcium pyrophosphate, pseudogout

Systemic juvenile idiopathic arthritis

Systemic arthritis seen in < 16 year olds. Usually presents with daily spiking fevers, salmon-pink macular rash, arthritis (commonly 2+ joints). Associated with anterior uveitis. Frequently presents with leukocytosis, thrombocytosis, anemia, ↑ ESR, ↑ CRP. Treatment: NSAIDs, steroids, methotrexate, TNF inhibitors.

Sjögren syndrome





Autoimmune disorder characterized by destruction of exocrine glands (especially lacrimal and salivary) by lymphocytic infiltrates A. Predominantly affects females 40–60 years old.

Findings:

- Inflammatory joint pain
- Keratoconjunctivitis sicca (↓ tear production and subsequent corneal damage)
- Xerostomia (↓ saliva production) → mucosal atrophy, fissuring of the tongue B
- Presence of antinuclear antibodies, rheumatoid factor (can be positive in the absence of rheumatoid arthritis), antiribonucleoprotein antibodies: SS-A (anti-Ro) and/or SS-B (anti-La)
- Bilateral parotid enlargement

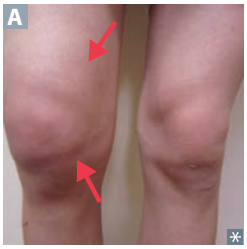
Anti-SSA and anti-SSB may also be seen in SLE.

A common 1° disorder or a 2° syndrome associated with other autoimmune disorders (eg, rheumatoid arthritis, SLE, systemic sclerosis).

Complications: dental caries; mucosa-associated lymphoid tissue (MALT) lymphoma (may present as parotid enlargement); ↑ risk of giving birth to baby with neonatal lupus.

Focal lymphocytic sialadenitis on labial salivary gland biopsy can confirm diagnosis.

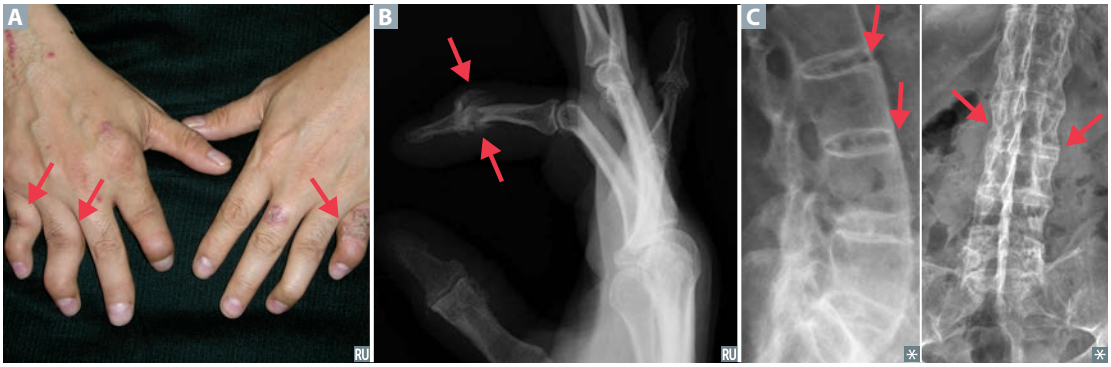
Septic arthritis



S aureus, *Streptococcus*, and *Neisseria gonorrhoeae* are common causes. Affected joint is swollen A, red, and painful. Synovial fluid purulent (WBC > 50,000/mm^3).

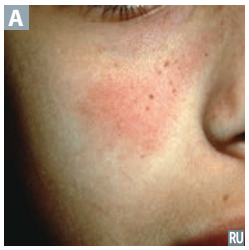
Disseminated gonococcal infection—STI that presents as either purulent arthritis (eg, knee) or triad of polyarthralgia, tenosynovitis (eg, hand), dermatitis (eg, pustules).

Seronegative spondyloarthritis	Arthritis without rheumatoid factor (no anti-IgG antibody). Strong association with HLA-B27 (MHC class I serotype). Subtypes (PAIR) share variable occurrence of inflammatory back pain (associated with morning stiffness, improves with exercise), peripheral arthritis, enthesitis (inflamed insertion sites of tendons, eg, Achilles), dactylitis ("sausage fingers"), uveitis.	
Psoriatic arthritis	Associated with skin psoriasis and nail lesions. Asymmetric and patchy involvement A. Dactylitis and "pencil-in-cup" deformity of DIP on x-ray B.	Seen in fewer than ⅓ of patients with psoriasis.
Ankylosing spondylitis	Symmetric involvement of spine and sacroiliac joints → ankylosis (joint fusion), uveitis, aortic regurgitation.	Bamboo spine (vertebral fusion) C. Costovertebral and costosternal ankylosis may cause restrictive lung disease. Monitor degree of reduced chest wall expansion to assess disease severity. More common in males.
Inflammatory bowel disease	Crohn disease and ulcerative colitis are often associated with spondyloarthritis.	
Reactive arthritis	Classic triad: ▪ Conjunctivitis ▪ Urethritis ▪ Arthritis	"Can't see, can't pee, can't bend my knee." Associated with infections by *Shigella*, *Campylobacter*, *E coli*, *Salmonella*, *Chlamydia*, *Yersinia*. "She Caught Every Student Cheating Yesterday and overreacted."



Systemic lupus erythematosus

Systemic, remitting, and relapsing autoimmune disease. Organ damage primarily due to a type III hypersensitivity reaction and, to a lesser degree, a type II hypersensitivity reaction. Associated with deficiency of early complement proteins (eg, C1q, C4, C2) → ↓ clearance of immune complexes. Classic presentation: rash, joint pain, and fever in a female of reproductive age. ↑ prevalence in Black, Caribbean, Asian, and Hispanic populations.



Libman-**S**acks **E**ndocarditis—nonbacterial, verrucous thrombi usually on mitral or aortic valve and can be present on either surface of the valve (but usually on undersurface). **LSE** in **SLE**.

Lupus nephritis (glomerular deposition of DNA-anti-DNA immune complexes) can be nephritic or nephrotic (causing hematuria or proteinuria). Most common and severe type is diffuse proliferative.

Common causes of death in SLE: **i**nfections, **c**ardiovascular disease (accelerated CAD), **k**idney disease (most common). **I**mmune **c**omplexes **k**ill.

In an anti-SSA ⊕ pregnant patient, ↑ risk of newborn developing neonatal lupus → congenital heart block, periorbital/diffuse rash, transaminitis, and cytopenias at birth.

RASH OR PAIN:
- **R**ash (malar A or discoid B)
- **A**rthritis (nonerosive)
- **S**erositis (eg, pleuritis, pericarditis)
- **H**ematologic disorders (eg, cytopenias)
- **O**ral/nasopharyngeal ulcers (usually painless)
- **R**enal disease
- **P**hotosensitivity
- **A**ntinuclear antibodies
- **I**mmunologic disorder (anti-dsDNA, anti-Sm, antiphospholipid)
- **N**eurologic disorders (eg, seizures, psychosis)

Mixed connective tissue disease

Features of SLE, systemic sclerosis, and/or polymyositis. Associated with anti-U1 RNP antibodies (speckled ANA).

Antiphospholipid syndrome

1° or 2° autoimmune disorder (most commonly in SLE).

Diagnosed based on clinical criteria including history of thrombosis (arterial or venous) or spontaneous abortion along with laboratory findings of lupus anticoagulant, anticardiolipin, anti-β_2 glycoprotein I antibodies.

Treatment: systemic anticoagulation.

Anticardiolipin antibodies can cause false-positive VDRL/RPR.

Lupus anticoagulant can cause prolonged PTT that is not corrected by the addition of normal platelet-free plasma.

Polymyalgia rheumatica

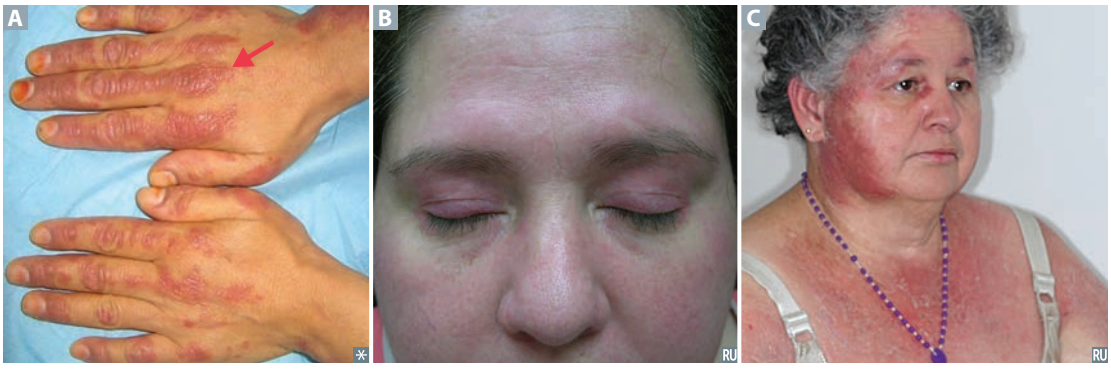
SYMPTOMS	Pain and stiffness in proximal muscles (eg, shoulders, hips), often with fever, malaise, weight loss. Does not cause muscular weakness. More common in females > 50 years old; associated with giant cell (temporal) arteritis.
FINDINGS	↑ ESR, ↑ CRP, normal CK.
TREATMENT	Rapid response to low-dose corticosteroids.

Fibromyalgia — Most common in females 20–50 years old. Chronic, widespread musculoskeletal pain associated with "tender points," stiffness, paresthesias, poor sleep, fatigue, cognitive disturbance ("fibro fog"). Treatment: regular exercise, antidepressants (TCAs, SNRIs), neuropathic pain agents (eg, gabapentin).

Polymyositis/dermatomyositis — Nonspecific: ⊕ ANA, ↑ CK. Specific: ⊕ anti-Jo-1 (histidyl-tRNA synthetase), ⊕ anti-SRP (signal recognition particle), ⊕ anti-Mi-2 (helicase).

Polymyositis — Progressive symmetric proximal muscle weakness, characterized by endomysial inflammation with CD8+ T cells. Most often involves shoulders.

Dermatomyositis — Clinically similar to polymyositis, but also involves Gottron papules A, photodistributed facial erythema (eg, heliotrope [violaceous] edema of the eyelids B), "shawl and face" rash C, darkening and thickening of fingertips and sides resulting in irregular, "dirty"-appearing marks. ↑ risk of occult malignancy. Perimysial inflammation and atrophy with CD4+ T cells.



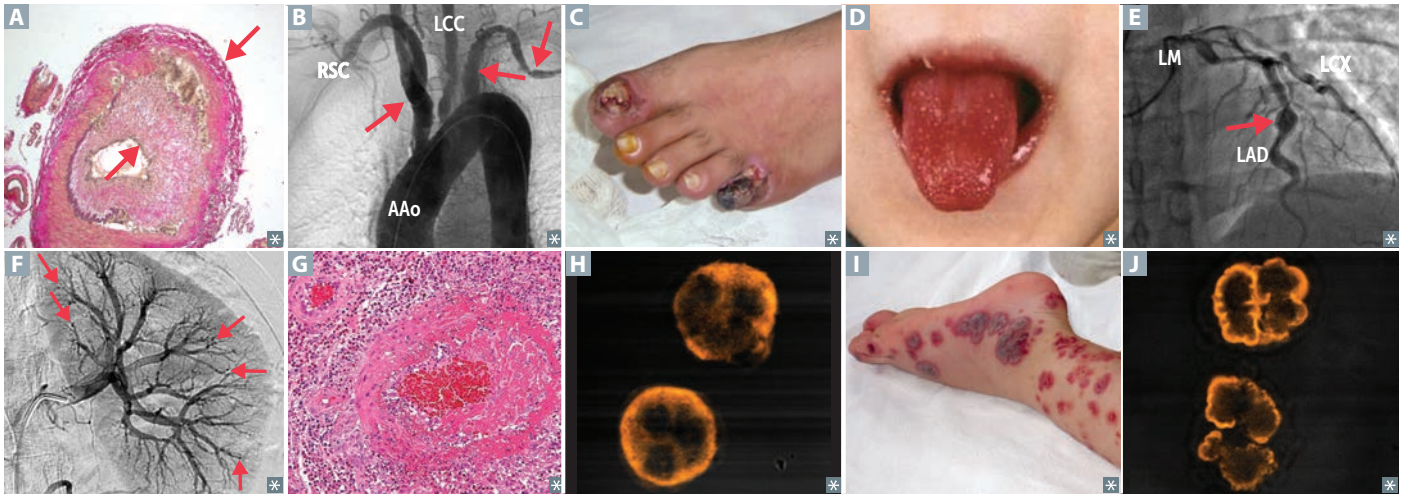
Myositis ossificans — Heterotopic ossification involving skeletal muscle (eg, quadriceps). Associated with blunt muscle trauma. Presents as painful soft tissue mass. Imaging shows eggshell calcification. Histology shows metaplastic bone surrounding area of fibroblastic proliferation. Benign, but may be mistaken for sarcoma.

Vasculitides

	EPIDEMIOLOGY/PRESENTATION	NOTES
Large-vessel vasculitis		
Giant cell (temporal) arteritis	Females > 50 years old. Unilateral headache, possible temporal artery tenderness, jaw claudication. May lead to irreversible blindness due to anterior ischemic optic neuropathy. Associated with polymyalgia rheumatica.	Most commonly affects branches of carotid artery. Focal granulomatous inflammation A. ↑ ESR. Treat with high-dose corticosteroids prior to temporal artery biopsy to prevent blindness.
Takayasu arteritis	Usually Asian females < 40 years old. "Pulseless disease" (weak upper extremity pulses), fever, night sweats, arthritis, myalgias, skin nodules, ocular disturbances.	Granulomatous thickening and narrowing of aortic arch and proximal great vessels B. ↑ ESR. Treatment: corticosteroids.
Medium-vessel vasculitis		
Buerger disease (thromboangiitis obliterans)	Heavy tobacco smoking history, males < 40 years old. Intermittent claudication. May lead to gangrene C, autoamputation of digits, superficial nodular phlebitis. Raynaud phenomenon is often present.	Segmental thrombosing vasculitis with vein and nerve involvement. Treatment: smoking cessation.
Kawasaki disease (mucocutaneous lymph node syndrome)	Usually Asian children < 4 years old. Conjunctival injection, Rash (polymorphous → desquamating), Adenopathy (cervical), Strawberry tongue (oral mucositis) D, Hand-foot changes (edema, erythema), fever.	CRASH and burn on a Kawasaki. May develop coronary artery aneurysms E; thrombosis or rupture can cause death. Treatment: IV immunoglobulin and aspirin.
Polyarteritis nodosa	Usually middle-aged males. Hepatitis B seropositivity in 30% of patients. Fever, weight loss, malaise, headache. GI: abdominal pain, melena. Hypertension, neurologic dysfunction, cutaneous eruptions, renal damage.	Typically involves renal and visceral vessels, not pulmonary arteries. Different stages of transmural inflammation with fibrinoid necrosis. Innumerable renal microaneurysms F and spasms on arteriogram (string of pearls appearance). Treatment: corticosteroids, cyclophosphamide.
Small-vessel vasculitis		
Behçet syndrome	↑ incidence in people of Turkish and eastern Mediterranean descent. Recurrent aphthous ulcers, genital ulcerations, uveitis, erythema nodosum. Can be precipitated by HSV or parvovirus. Flares last 1–4 weeks.	Immune complex vasculitis. Associated with HLA-B51.
Cutaneous small-vessel vasculitis	Occurs 7-10 days after certain medications (penicillin, cephalosporins, phenytoin, allopurinol) or infections (eg, HCV, HIV). Palpable purpura, no visceral involvement.	Immune complex–mediated leukocytoclastic vasculitis; late involvement indicates systemic vasculitis.

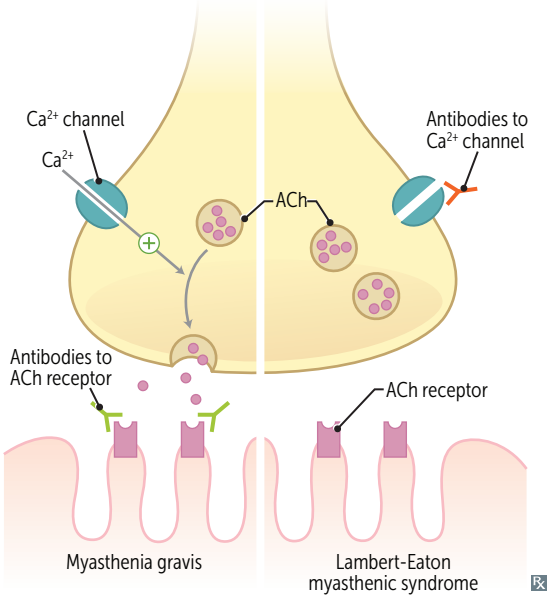
Vasculitides *(continued)*

	EPIDEMIOLOGY/PRESENTATION	NOTES
Small-vessel vasculitis *(continued)*		
Eosinophilic granulomatosis with polyangiitis	Asthma, sinusitis, skin nodules or purpura, peripheral neuropathy (eg, wrist/foot drop). Can also involve heart, GI, kidneys (pauci-immune glomerulonephritis).	Formerly called Churg-Strauss syndrome. Granulomatous, necrotizing vasculitis with eosinophilia G. MPO-ANCA/p-ANCA, ↑ IgE level.
Granulomatosis with polyangiitis	Upper respiratory tract: perforation of nasal septum, chronic sinusitis, otitis media, mastoiditis. Lower respiratory tract: hemoptysis, cough, dyspnea. Renal: hematuria, red cell casts.	Triad: ▪ Focal necrotizing vasculitis ▪ Necrotizing granulomas in lung and upper airway ▪ Necrotizing glomerulonephritis PR3-ANCA/c-ANCA H (anti-proteinase 3). CXR: large nodular densities. Treatment: corticosteroids in combination with rituximab or cyclophosphamide.
Immunoglobulin A vasculitis	Most common childhood systemic vasculitis. Often follows URI. Classic triad of Henoch-Schönlein purpura ▪ Hinge pain (arthralgias) ▪ Stomach pain (abdominal pain associated with intussusception) ▪ Palpable purpura on buttocks/legs I	Formerly called Henoch-Schönlein purpura. Vasculitis 2° to IgA immune complex deposition. Associated with IgA nephropathy (Berger disease). Treatment: supportive care, possibly corticosteroids.
Microscopic polyangiitis	Necrotizing vasculitis commonly involving lung, kidneys, and skin with pauci-immune glomerulonephritis and palpable purpura. Presentation similar to granulomatosis with polyangiitis but without nasopharyngeal involvement.	No granulomas. MPO-ANCA/p-ANCA J (anti-myeloperoxidase). Treatment: cyclophosphamide, corticosteroids.
Mixed cryoglobulinemia	Often due to viral infections, especially HCV. Triad of palpable purpura, weakness, arthralgias. May also have peripheral neuropathy and renal disease (eg, glomerulonephritis).	Cryoglobulins are immunoglobulins that precipitate in the Cold. Vasculitis due to mixed IgG and IgM immune complex deposition.

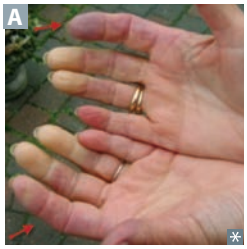


Neuromuscular junction diseases

	Myasthenia gravis	Lambert-Eaton myasthenic syndrome
FREQUENCY	Most common NMJ disorder	Uncommon
PATHOPHYSIOLOGY	Autoantibodies to postsynaptic ACh receptor	Autoantibodies to presynaptic Ca^{2+} channel → ↓ ACh release
CLINICAL	Fatigable muscle weakness—ptosis; diplopia; proximal weakness; respiratory muscle involvement → dyspnea; bulbar muscle involvement → dysphagia, difficulty chewing Spared reflexes Worsens with muscle use	Proximal muscle weakness, autonomic symptoms (dry mouth, constipation, impotence) Hyporeflexia Improves with muscle use
ASSOCIATED WITH	Thymoma, thymic hyperplasia	Small cell lung cancer
AChE INHIBITOR ADMINISTRATION	Reverses symptoms (pyridostigmine for treatment)	Minimal effect



Raynaud phenomenon



↓ blood flow to skin due to arteriolar (small vessel) vasospasm in response to cold or stress: color change from white (ischemia) to blue (hypoxia) to red (reperfusion). Most often in the fingers A and toes. Called Raynaud disease when 1° (idiopathic), Raynaud syndrome when 2° to a disease process such as mixed connective tissue disease, SLE, or CREST syndrome (limited form of systemic sclerosis). Digital ulceration (critical ischemia) seen in 2° Raynaud syndrome. Treat with calcium channel blockers.