

# 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

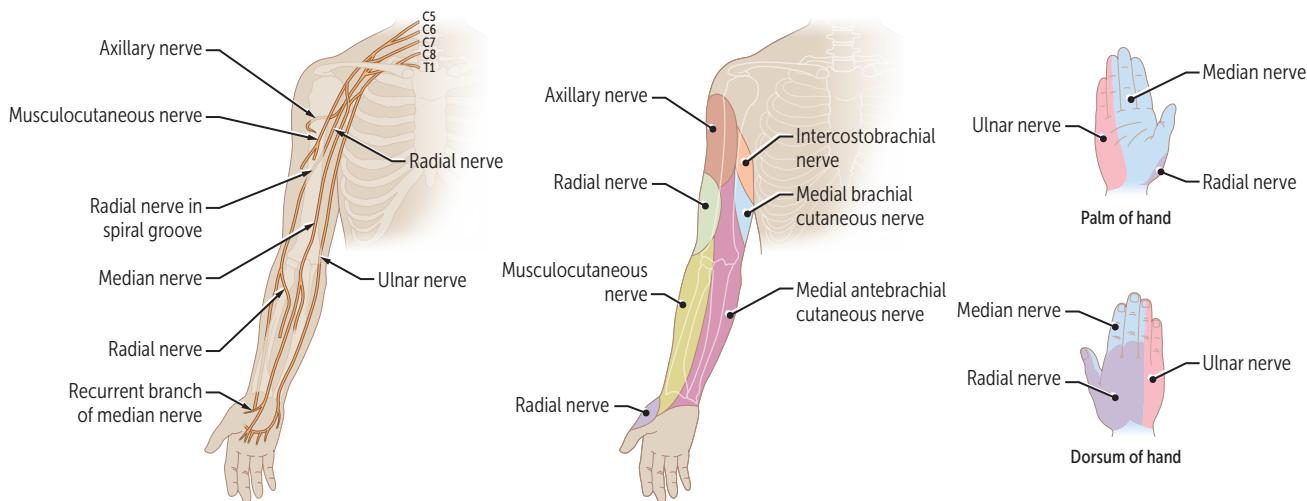
This chapter provides information you will need to understand common anatomic dysfunctions, orthopedic conditions, rheumatic diseases, and dermatologic conditions. Be able to interpret 3D anatomy in the context of radiologic imaging. For the rheumatic diseases, create instructional cases that include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

► Anatomy and Physiology	450
► Pathology	462
► Dermatology	481
► Pharmacology	494

## ► MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—ANATOMY AND PHYSIOLOGY

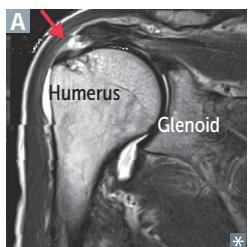
**Upper extremity nerves**

NERVE	CAUSES OF INJURY	PRESENTATION
<b>Axillary (C5-C6)</b>	Fractured surgical neck of humerus Anterior dislocation of humerus	Flattened deltoid Loss of arm abduction at shoulder ( $> 15^\circ$ ) Loss of sensation over deltoid and lateral arm
<b>Musculocutaneous (C5-C7)</b>	Upper trunk compression	$\downarrow$ biceps (C5-C6) reflex Loss of forearm flexion and supination Loss of sensation over radial and dorsal forearm
<b>Radial (C5-T1)</b>	Compression of axilla, eg, due to crutches or sleeping with arm over chair (“Saturday night palsy”) Midshaft fracture of humerus Repetitive pronation/supination of forearm, eg, due to screwdriver use (“finger drop”)	Injuries above the elbow cause loss of sensation over posterior arm/forearm and dorsal hand, wrist drop (loss of elbow, wrist, and finger extension) with $\downarrow$ grip strength (wrist extension necessary for maximal action of flexors) Injuries below the elbow can cause paresthesias of the dorsal forearm (superficial radial nerve) or wrist drop (posterior interosseous nerve) Tricep function and posterior arm sensation spared in midshaft fracture
<b>Median (C5-T1)</b>	Supracondylar fracture of humerus → proximal lesion of the nerve Carpal tunnel syndrome and wrist laceration → distal lesion of the nerve	“Ape hand” and “Hand of benediction” Loss of wrist flexion and function of the lateral two <b>Lumbri</b> cals, <b>Opon</b> ens pollicis, <b>Abdu</b> ctor pollicis brevis, <b>Flexor</b> pollicis brevis ( <b>LOAF</b> ) Loss of sensation over thenar eminence and dorsal and palmar aspects of lateral 3 1/2 fingers with proximal lesion
<b>Ulnar (C8-T1)</b>	Fracture of medial epicondyle of humerus (proximal lesion) Fractured hook of hamate (distal lesion) from fall on outstretched hand Compression of nerve against hamate as the wrist rests on handlebar during cycling	“Ulnar claw” on digit extension Radial deviation of wrist upon flexion (proximal lesion) $\downarrow$ flexion of ulnar fingers, abduction and adduction of fingers (interossei), thumb adduction, actions of ulnar 2 lumbrical muscles Loss of sensation over ulnar 1 1/2 fingers including hypotenar eminence
<b>Recurrent branch of median nerve (C5-T1)</b>	Superficial laceration of palm	“Ape hand” Loss of thenar muscle group: opposition, abduction, and flexion of thumb No loss of sensation
Humerus fractures, proximally to distally, follow the <b>ARM</b> (Axillary → Radial → Median) nerves		



Rx

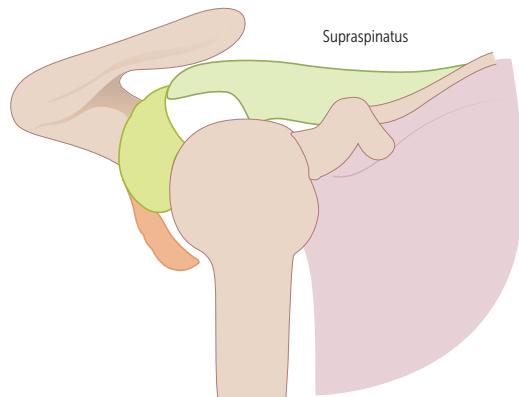
### Rotator cu muscles



Shoulder muscles that form the rotator cuff:

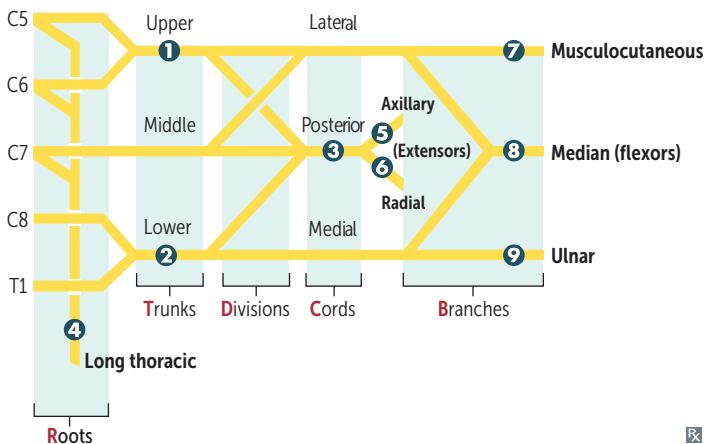
- **Supraspinatus** (suprascapular nerve)—abducts arm initially (before the action of the deltoid); most common rotator cuff injury (trauma or degeneration and impingement → tendinopathy or tear [arrow in A]), assessed by “empty/full can” test
  - **Infraspinatus** (suprascapular nerve)—externally rotates arm; pitching injury
  - **teres minor** (axillary nerve)—adducts and externally rotates arm
  - **Subscapularis** (upper and lower subscapular nerves)—internally rotates and adducts arm
- Innervated primarily by C5-C6.

**SItS** (small t is for teres **minor**).



**Brachial plexus lesions**

- ① Erb palsy ("waiter's tip")
- ② Klumpke palsy (claw hand)
- ③ Wrist drop
- ④ Winged scapula
- ⑤ Deltoid paralysis
- ⑥ "Saturday night palsy" (wrist drop)
- ⑦ Difficulty flexing elbow, variable sensory loss
- ⑧ Decreased thumb function, "hand of benediction"
- ⑨ Intrinsic muscles of hand, claw hand



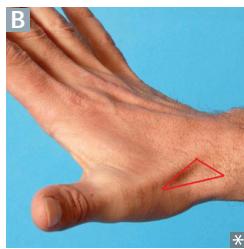
Divisions of brachial plexus:

**R**emember  
**T**o  
**D**rink  
**C**old  
**B**eer

Trunks of brachial plexus and the subclavian artery pass between anterior and middle scalene muscles. Subclavian vein passes anteromedial to the scalene triangle.



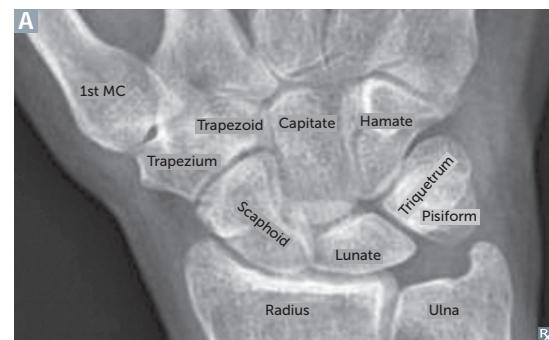
CONDITION	INJURY	CAUSES	MUSCLE DEFICIT	FUNCTIONAL DEFICIT	PRESERVATION
Erb palsy ("waiter's tip")	Traction or tear of upper trunk: C5-C6 roots	Infants—lateral traction on neck during delivery Adults—trauma leading to neck traction (eg, falling on head and shoulder in motorcycle accident)	Deltoid, supraspinatus  Infraspinatus, supraspinatus  Biceps brachii Herb gets DIBs on tips	Abduction (arm hangs by side)  Lateral rotation (arm medially rotated)  Flexion, supination (arm extended and pronated)	
Klumpke palsy	Traction or tear of lower trunk: C8-T1 roots	Infants—upward force on arm during delivery Adults—trauma (eg, grabbing a tree branch to break a fall)	Intrinsic hand muscles: lumbricals, interossei, thenar, hypothenar	Claw hand: lumbricals normally flex MCP joints and extend DIP and PIP joints	
Thoracic outlet syndrome	Compression of lower trunk and subclavian vessels, most commonly within the scalene triangle	Cervical/ anomalous first ribs (arrows in A), Pancoast tumor	Same as Klumpke palsy	Atrophy of intrinsic hand muscles; ischemia, pain, and edema due to vascular compression	
Winged scapula	Lesion of long thoracic nerve, roots C5-C7 ("wings of heaven")	Axillary node dissection after mastectomy, stab wounds	Serratus anterior	Inability to anchor scapula to thoracic cage → cannot abduct arm above horizontal position B	

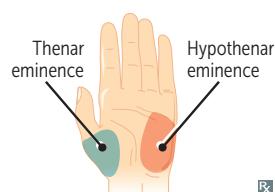
**Wrist region**

Scaphoid, lunate, triquetrum, pisiform, hamate, capitate, trapezoid, trapezium **A**. (So long to pinky, here comes the thumb)

Scaphoid (palpable in anatomic snuff box **B**) is the most commonly fractured carpal bone, typically due to a fall on an outstretched hand. Complications of proximal scaphoid fractures include avascular necrosis and nonunion due to retrograde blood supply from a branch of the radial artery. Occult fracture not always seen on initial x-ray.

Dislocation of lunate may impinge median nerve and cause carpal tunnel syndrome. Fracture of the hook of the hamate can cause ulnar nerve compression—**Guyon canal syndrome**.



**Hand muscles**

Thenar (median)—**O**pponens pollicis, **A**bductor pollicis brevis, **F**lexor pollicis brevis—superficial head (deep head by ulnar nerve).

Hypotenar (ulnar)—**O**pponens digiti minimi, **A**bductor digiti minimi, **F**lexor digiti minimi brevis.

Dorsal interossei (ulnar)—abduct the fingers.

Palmar interossei (ulnar)—adduct the fingers.

Lumbricals (1st/2nd, median; 3rd/4th, ulnar)—flex at the MCP joint, extend PIP and DIP joints.

Both groups perform the same functions:  
**O**ppose, **A**bduct, and **F**lex (**OAF**).

**DAB** = **D**orsals **A**Bduct.

**PAD** = **P**almars **AD**duct.

**Distortions of the hand**

At rest, a balance exists between the extrinsic flexors and extensors of the hand, as well as the intrinsic muscles of the hand—particularly the lumbrical muscles (flexion of MCP, extension of DIP and PIP joints).

“Clawing” **A**—seen best with **distal** lesions of median or ulnar nerves. Remaining extrinsic flexors of the digits exaggerate the loss of the lumbricals → fingers extend at MCP, flex at DIP and PIP joints.

Deficits less pronounced in **proximal** lesions; deficits present during voluntary flexion of the digits.

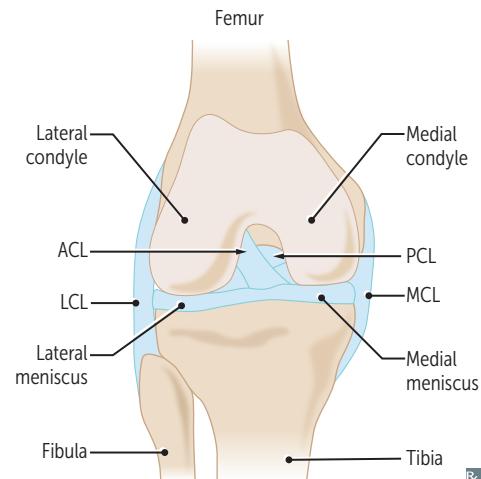
SIGN	“Ulnar claw”	“Hand of benediction”	“Median claw”	“Trouble making a st”
PRESENTATION				

**Actions of hip muscles**

ACTION	MUSCLES
<b>Abductors</b>	Gluteus medius, gluteus minimus
<b>Adductors</b>	Adductor magnus, adductor longus, adductor brevis
<b>Extensors</b>	Gluteus maximus, semitendinosus, semimembranosus, long head of biceps femoris
<b>Flexors</b>	Iliopsoas (iliacus and psoas), rectus femoris, tensor fascia lata, pectenius, sartorius
<b>Internal rotation</b>	Gluteus medius, gluteus minimus, tensor fascia latae
<b>External rotation</b>	Iliopsoas, gluteus maximus, piriformis, obturator internus, obturator externus

**Knee exam**Lateral femoral condyle to anterior tibia: **ACL**.Medial femoral condyle to posterior tibia: **PCL**.**LAMP**.

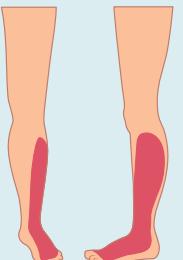
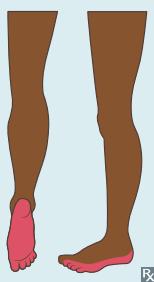
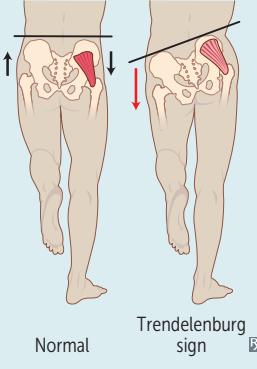
TEST	PROCEDURE
<b>Anterior drawer sign</b>	Positive in ACL tear. Tibia glides anteriorly (relative to femur) when knee is at 90° angle. Alternatively, Lachman test done (places knee at 30° angle).
<b>Posterior drawer sign</b>	Bending knee at 90° angle, ↑ posterior gliding of tibia due to PCL injury.
<b>Valgus stress test</b>	AbnoA



## Lower extremity nerves

NERVE	INNERVATION	CAUSE OF INJURY	PRESNTATION/COMMENTS
Iliohypogastric (T12-L1)	Sensory—suprapubic region Motor—transversus abdominis and internal oblique	Abdominal surgery	Burning or tingling pain in surgical incision site radiating to inguinal and suprapubic region
Genitofemoral nerve (L1-L2)	Sensory—scrotum/labia majora, medial thigh Motor—cremaster	Laparoscopic surgery	↓ upper medial thigh and anterior thigh sensation beneath the inguinal ligament (lateral part of the femoral triangle); absent cremasteric reflex
Lateral femoral cutaneous (L2-L3)	Sensory—anterior and lateral thigh	Tight clothing, obesity, pregnancy, pelvic procedures	↓ thigh sensation (anterior and lateral) <b>Meralgia paresthetica</b> — compression of lateral femoral cutaneous nerve → tingling, numbness, burning pain in anterolateral thigh
Obturator (L2-L4)	Sensory—medial thigh Motor—obturator externus, adductor longus, adductor brevis, gracilis, pectenue, adductor magnus	Pelvic surgery	↓ thigh sensation (medial) and adduction
Femoral (L2-L4)	Sensory—anterior thigh, medial leg Motor—quadriceps, iliacus, pectenue, sartorius	Pelvic fracture, compression from retroperitoneal hematoma or psoas abscess	↓ leg extension (↓ patellar reflex)
Sciatic (L4-S3)	Motor—semitendinosus, semimembranosus, biceps femoris, adductor magnus	Herniated disc, posterior hip dislocation, piriformis syndrome	Splits into common peroneal and tibial nerves

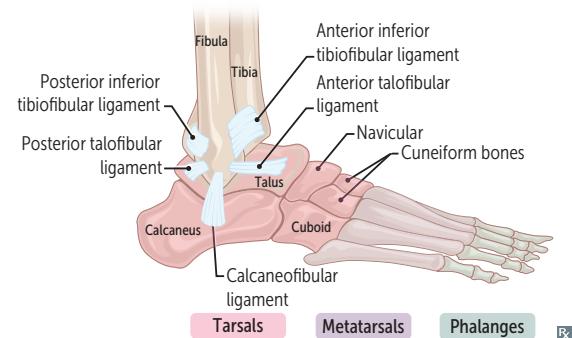
Lower extremity nerves (*continued*)

NERVE	INNERVATION	CAUSE OF INJURY	PRESENTATION/COMMENTS
<b>Common (lateral) peroneal (L4-S2)</b> 	Superficial peroneal nerve: <ul style="list-style-type: none"><li>▪ Sensory—dorsum of foot (except webspace between hallux and 2nd digit)</li><li>▪ Motor—peroneus longus and brevis</li></ul> Deep peroneal nerve: <ul style="list-style-type: none"><li>▪ Sensory—webspace between hallux and 2nd digit</li><li>▪ Motor—tibialis anterior</li></ul>	Trauma or compression of lateral aspect of leg, fibular neck fracture	<b>PED</b> = Peroneal Everts and Dorsiflexes; if injured, foot drop <b>PED</b> Loss of sensation on dorsum of foot <b>Foot drop</b> —inverted and plantarflexed at rest, loss of eversion and dorsiflexion; “steppage gait”
<b>Tibial (L4-S3)</b> 	Sensory—sole of foot Motor—biceps femoris (long head), triceps surae, plantaris, popliteus, flexor muscles of foot	Knee trauma, Baker cyst (proximal lesion); tarsal tunnel syndrome (distal lesion)	<b>TIP</b> = Tibial Inverts and Plantarflexes; if injured, can't stand on <b>TIP</b> toes Inability to curl toes and loss of sensation on sole; in proximal lesions, foot everted at rest with weakened inversion and plantar flexion
<b>Superior gluteal (L4-S1)</b> 	Motor—gluteus medius, gluteus minimus, tensor fascia latae	Iatrogenic injury during intramuscular injection to superomedial gluteal region (prevent by choosing superolateral quadrant, preferably anterolateral region)	Trendelenburg sign/gait—pelvis tilts because weight-bearing leg cannot maintain alignment of pelvis through hip abduction Lesion is contralateral to the side of the hip that drops, ipsilateral to extremity on which the patient stands
<b>Inferior gluteal (L5-S2)</b>	Motor—gluteus maximus	Posterior hip dislocation	Difficulty climbing stairs, rising from seated position; loss of hip extension
<b>Pudendal (S2-S4)</b>	Sensory—perineum Motor—external urethral and anal sphincters	Stretch injury during childbirth, prolonged cycling, horseback riding	↓ sensation in perineum and genital area; can cause fecal and/or urinary incontinence Can be blocked with local anesthetic during childbirth using ischial spine as a landmark for injection

**Ankle sprains**

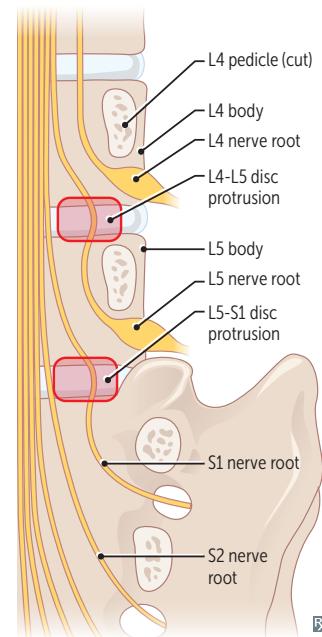
**Anterior talofibular ligament**—most common ankle sprain overall, classified as a low ankle sprain. Due to overinversion/supination of foot.  
Always tears first.

**Anterior inferior tibiofibular ligament**—most common high ankle sprain.

**Signs of lumbosacral radiculopathy**

Paresthesia and weakness related to specific lumbosacral spinal nerves. Intervertebral disc (nucleus pulposus) herniates posterolaterally through annulus fibrosus (outer ring) into spinal canal due to thin posterior longitudinal ligament and thicker anterior longitudinal ligament along midline of vertebral bodies. Nerve affected is usually below the level of herniation.  $\oplus$  straight leg raise,  $\oplus$  contralateral straight leg raise,  $\oplus$  reverse straight leg raise (femoral stretch).

Disc level herniation Nerve root affected	L3-L4	L4-L5	L5-S1
	L4	L5	S1
Dermatome affected			
Clinical findings	Weakness of knee extension $\downarrow$ patellar reflex	Weakness of dorsiflexion Difficulty in heel walking	Weakness of plantar flexion Difficulty in toe walking $\downarrow$ Achilles reflex

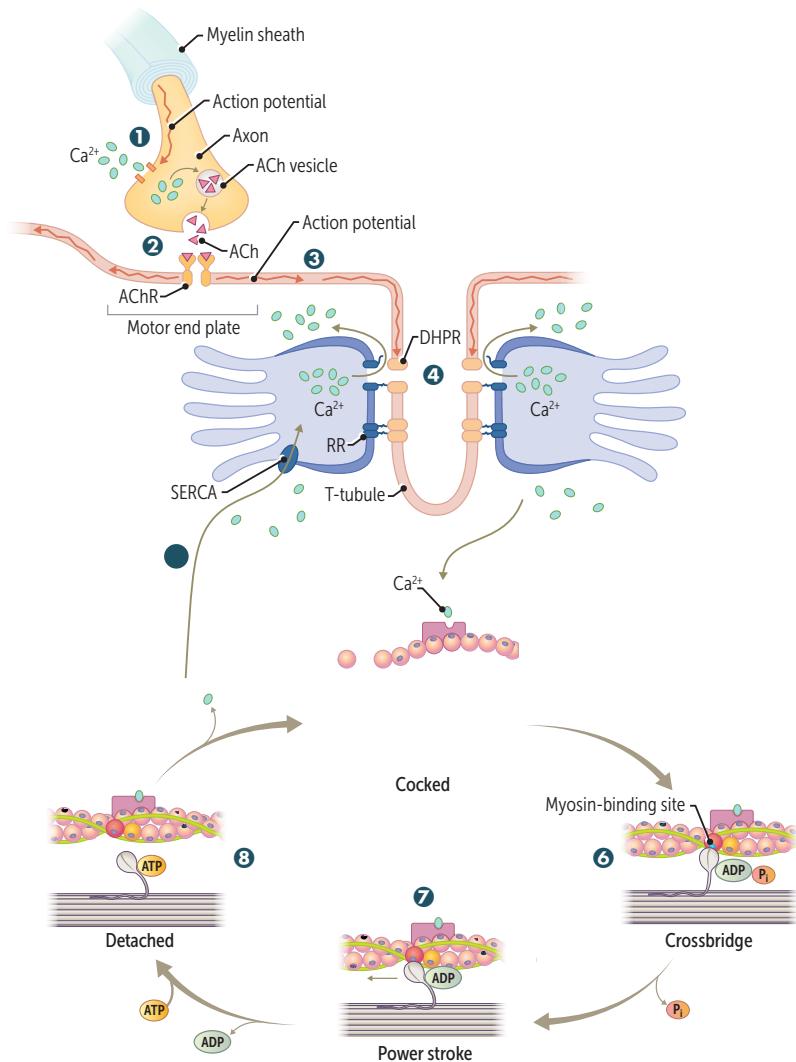
**Neurovascular pairing**

Nerves and arteries are frequently named together by the bones/regions with which they are associated. The following are exceptions to this naming convention.

LOCATION	NERVE	ARTERY
Axilla/lateral thorax	Long thoracic	Lateral thoracic
Surgical neck of humerus	Axillary	Posterior circumflex
Midshaft of humerus	Radial	Deep brachial
Distal humerus/cubital fossa	Median	Brachial
Popliteal fossa	Tibial	Popliteal
Posterior to medial malleolus	Tibial	Posterior tibial

**Motoneuron action potential to muscle contraction**

T-tubules are extensions of plasma membrane in contact with the sarcoplasmic reticulum, allowing for coordinated contraction of striated muscles.



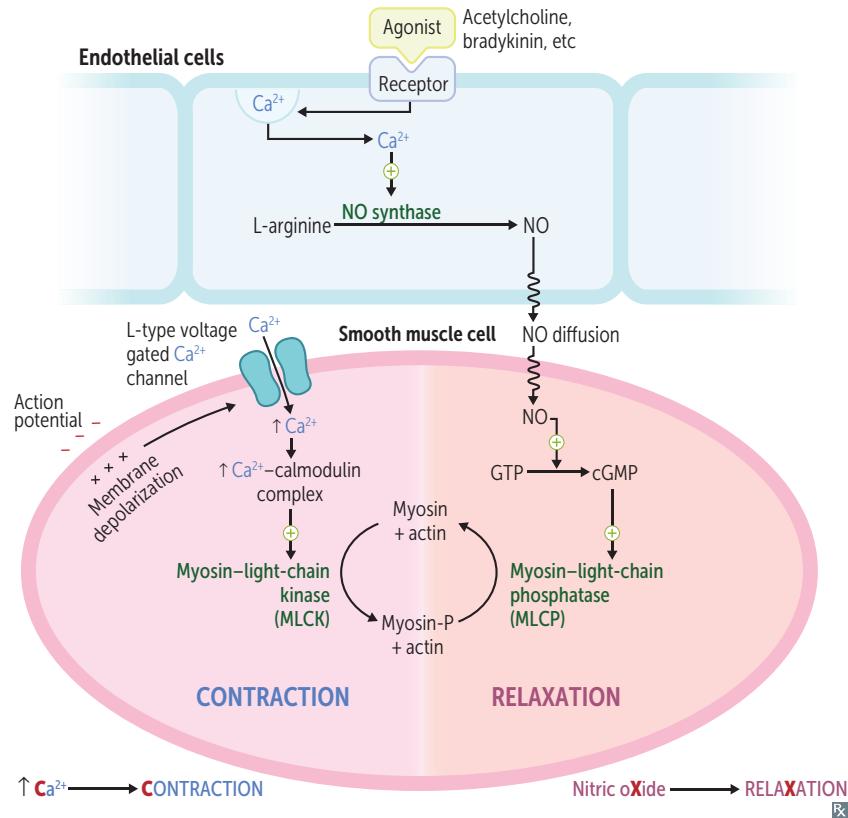
**Types of skeletal muscle fibers** Two types, normally distributed randomly within muscle. Muscle fiber type grouping commonly occurs due to reinnervation of denervated muscle fibers in peripheral nerve damage.

	Type I	Type II
CONTRACTION VELOCITY	Slow	Fast
FIBER COLOR	Red	White
PREDOMINANT METABOLISM	Oxidative phosphorylation → sustained contraction	Anaerobic glycolysis
MITOCHONDRIA, MYOGLOBIN	↑	↓
TYPE OF TRAINING	Endurance training	Weight/resistance training, sprinting
NOTES	Think “1 slow red ox”	Think “2 fast white antelopes”

### Skeletal muscle adaptations

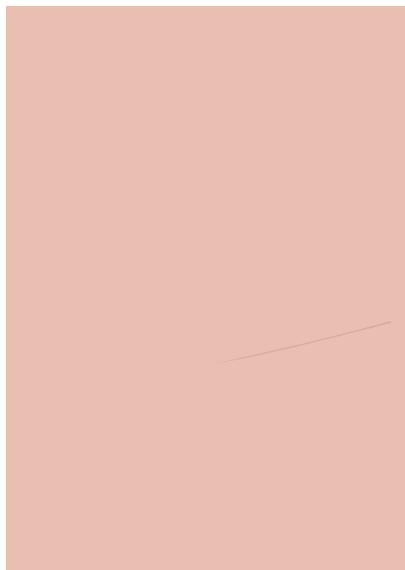
	Atrophy	Hypertrophy
MYOFIBRILS	↓ (removal via ubiquitin-proteasome system)	↑ (addition of sarcomeres in parallel)
MYONUCLEI	↓ (selective apoptosis)	↑ (fusion of satellite cells, which repair damaged myofibrils; absent in cardiac muscles)

### Vascular smooth muscle contraction and relaxation



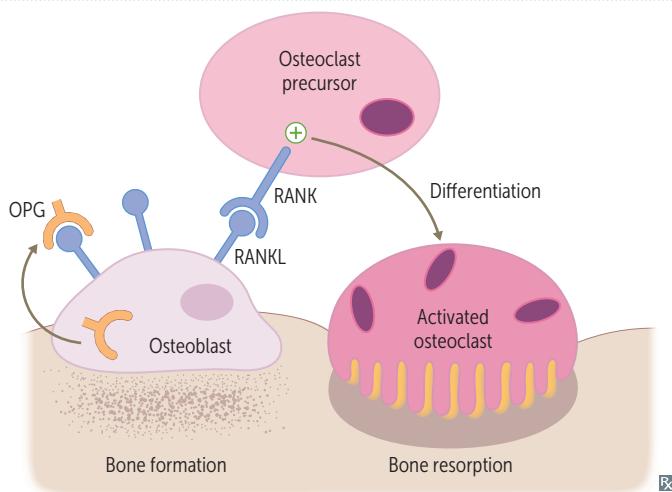
**Muscle proprioceptors** Specialized sensory receptors that relay information about muscle dynamics.

	<b>Muscle stretch receptors</b>	<b>Golgi tendon organ</b>
<b>PATHWAY</b>	<b>①</b> ↑ length and speed of stretch → <b>②</b> via dorsal root ganglion (DRG) → <b>③</b> activation of inhibitory interneuron and $\alpha$ motor neuron → <b>④</b> simultaneous inhibition of antagonist muscle (prevents overstretching) and activation of agonist muscle (contraction).	<b>①</b> ↑ tension → <b>②</b> via DRG → <b>③</b> activation of inhibitory interneuron → <b>④</b> inhibition of agonist muscle (reduced tension within muscle and tendon)
<b>LOCATION/INNERVATION</b>	Body of muscle/type Ia and II sensory axons	Tendons/type Ib sensory axons
<b>ACTIVATION BY</b>	↑ muscle stretch. Responsible for deep tendon reflexes	↑ muscle tension



### Cell biology of bone

<b>Osteoblast</b>	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.
<b>Osteoclast</b>	Dissolves (“crushes”) bone by secreting H <sup>+</sup> 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.
<b>Parathyroid hormone</b>	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).
<b>Estrogen</b>	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

<b>Medial (golfer's) elbow tendinopathy</b>	Repetitive wrist flexion or idiopathic → pain near medial epicondyle.
<b>Lateral (tennis) elbow tendinopathy</b>	Repetitive wrist 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.

May also be seen with fracture/dislocation of the hook of hamate.

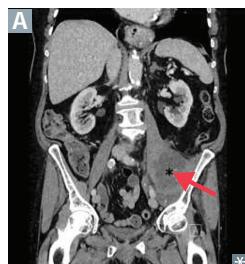
**Carpal tunnel syndrome**

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 but sensation spared, because palmar cutaneous branch enters hand external to carpal tunnel.

Suggested by  $\oplus$  Tinel sign (percussion of wrist causes tingling) and Phalen maneuver ( $90^\circ$  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 [A].

**Psoas abscess**

Collection of pus in iliopsoas compartment. May spread from blood (hematogenous) or from adjacent structures (eg, vertebral osteomyelitis, tuberculous spondylitis [also called Pott disease], pyelonephritis). Associated with Crohn disease, diabetes, and immunocompromised states.

*Staphylococcus aureus* most commonly isolated, but may also occur  $2^\circ$  to tuberculosis. Findings: flank pain, fever, inguinal mass,  $\oplus$  psoas sign (hip extension exacerbates lower abdominal pain).

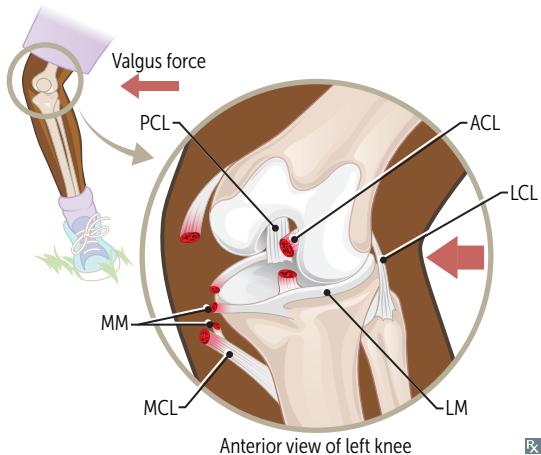
Labs: leukocytosis. Imaging (CT/MRI) will show focal hypodense lesion within the muscle plane (red arrow in [A]).

Treatment: abscess drainage, antibiotics.

### Common knee conditions

#### "Unhappy triad"

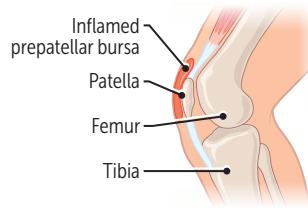
Common injury in contact sports due to lateral force impacting the knee when foot is planted on the ground. Consists of damage to the ACL **A**, MCL, and medial meniscus (attached to MCL). However, lateral meniscus involvement is more common than medial meniscus involvement in conjunction with ACL and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



Rx

#### Prepatellar bursitis

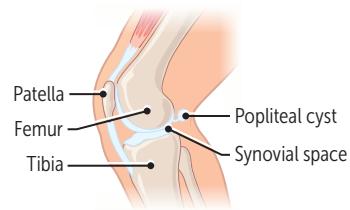
Inflammation of the prepatellar bursa in front of the kneecap (red arrow in **B**). Can be caused by repeated trauma or pressure from excessive kneeling (also called "housemaid's knee").



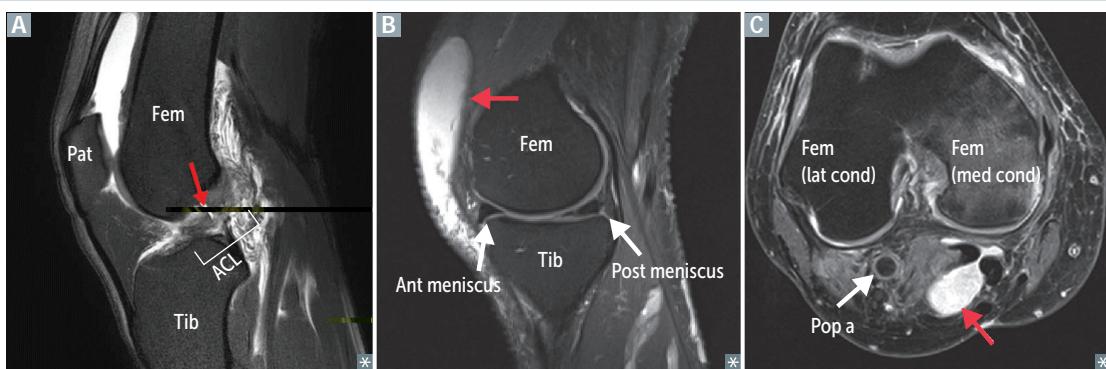
Rx

#### 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).

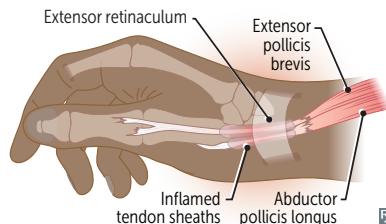


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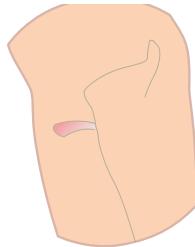
### Common musculoskeletal conditions

<b>Costochondritis</b>	Inflammation of costochondral or costosternal junctions. Presents with sharp, positional chest pain and focal tenderness to palpation. More common in younger female patients. May mimic cardiac (eg, MI) or pulmonary (eg, pulmonary embolism) diseases.
<b>De Quervain tenosynovitis</b>	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 mothers (lifting baby), golfers, racquet sport players, “thumb” texters.
<b>Dupuytren contracture</b>	Caused by fibroblastic proliferation and thickening of superficial palmar fascia. Typically involves the fascia at the base of the ring and little fingers. Unknown etiology; most frequently seen in males > 50 years old of Northern European descent.
<b>Ganglion cyst</b>	Fluid-filled swelling overlying joint or tendon sheath, most commonly at dorsal side of wrist. Usually resolves spontaneously.
<b>Iliotibial band syndrome</b>	Overuse injury of lateral knee that occurs primarily in runners. Pain develops 2° to friction of iliotibial band against lateral femoral epicondyle.
<b>Limb compartment syndrome</b>	↑ pressure within fascial compartment of a limb → venous outflow obstruction and arteriolar collapse → anoxia, necrosis, rhabdomyolysis → acute tubular necrosis. Causes include significant long bone fractures (eg, tibia), 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. <b>5 P's:</b> pain, pallor, paresthesia, pulselessness, paralysis.
<b>Medial tibial stress syndrome</b>	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.
<b>Plantar fascitis</b>	Inflammation of plantar aponeurosis characterized by heel pain (worse with first steps in the morning or after period of inactivity) and tenderness. Associated with obesity, prolonged standing or jumping (eg, dancers, runners), and flat feet. Heel spurs often coexist.
<b>Temporomandibular disorders</b>	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).



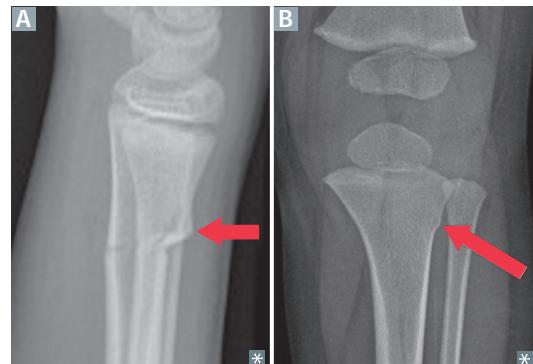
**Childhood musculoskeletal conditions**

Radial head  
subluxation



**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  $\text{Ca}^{2+}$  and  $\text{PO}_4^{3-}$ ).

Most commonly due to ↑ bone resorption ( $\uparrow$  osteoclast number and activity) related to ↓ estrogen levels, old age, and cigarette smoking. Can be  $2^\circ$  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  $\leq -2.5$  or by a fragility fracture (eg, fall from standing height, minimal trauma) at hip or vertebra. One-time screening recommended in females  $\geq 65$  years old.

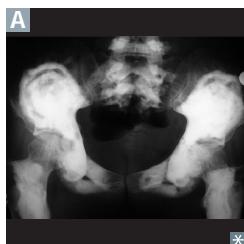
Prophylaxis: regular weight-bearing exercise and adequate  $\text{Ca}^{2+}$  and vitamin D intake throughout adulthood.

Treatment: bisphosphonates, teriparatide, SERMs, 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).



Normal vertebrae

**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**

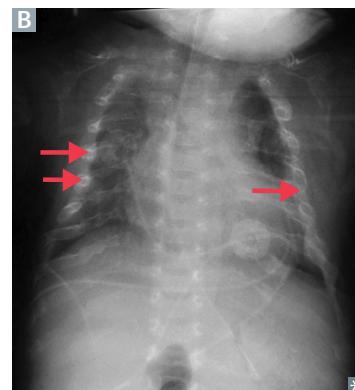
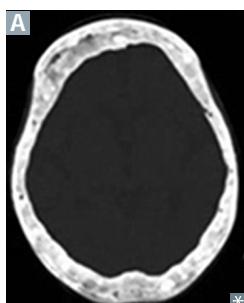
Defective mineralization of osteoid (osteomalacia) or cartilaginous growth plates (rickets, only in children). Most commonly due to vitamin D deficiency.

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**), beadlike costochondral junctions (rachitic rosary **B**), craniotabes (soft skull).

↓ vitamin D → ↓ serum  $\text{Ca}^{2+}$  → ↑ PTH secretion  
→ ↓ serum  $\text{PO}_4^{3-}$ .

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  $\text{Ca}^{2+}$ , 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.

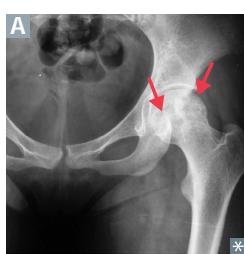
Hat size can be increased due to skull thickening **A**; hearing loss is common due to skull deformity.

Stages of Paget disease:

- Early destructive (lytic): osteoclasts
- Intermediate (mixed): osteoclasts + osteoblasts
- Late (sclerotic/blastic): osteoblasts

May enter quiescent phase.

Treatment: bisphosphonates.

**Avascular necrosis of bone**

Infarction of bone and marrow, usually very painful. Most common site is femoral head (watershed area) **A** (due to insufficiency of medial circumflex femoral artery). Causes include glucocorticoids, 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 <sup>2+</sup>	PO <sub>4</sub> <sup>3-</sup>	ALP	PTH	COMMENTS
Osteoporosis	—	—	—	—	↓ bone mass
Osteopetrosis	—/↓	—	—	—	Dense, brittle bones. Ca <sup>2+</sup> ↓ in severe, malignant disease
Paget disease of bone	—	—	↑	—	Abnormal “mosaic” bone architecture
Osteitis brosa 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 <sub>4</sub> <sup>3-</sup> 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
<b>Benign tumors</b>			
<b>Osteochondroma</b>	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 <b>A</b> Rarely transforms to chondrosarcoma
<b>Osteoma</b>	Middle age	Surface of facial bones	Associated with Gardner syndrome
<b>Osteoid osteoma</b>	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>B</b>
<b>Osteoblastoma</b>	Males > females	Vertebrae	Similar histology to osteoid osteoma Larger size (> 2 cm), pain unresponsive to NSAIDs
<b>Chondroma</b>		Medulla of small bones of hand and feet	Benign tumor of cartilage
<b>Giant cell tumor</b>	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 (osteoclastlike) cells. “Osteoclastoma” “Soap bubble” appearance on x-ray <b>C</b>

**Malignant tumors****Osteosarcoma  
(osteogenic sarcoma)**

Accounts for 20% of 1° bone cancers.  
Peak incidence of 1° tumor in males < 20 years.  
Less common in older adults; 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).

Pleiomorphic 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**

Most common in adults > 50 years old.

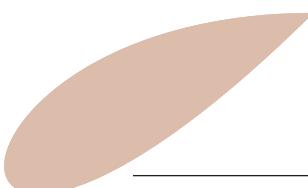
Medulla of pelvis, proximal femur and humerus.

Tumor of malignant chondrocytes. Lytic (> 50%) cases with intralesional calcifications, endosteal erosion, cortex breach.

**Ewing sarcoma**

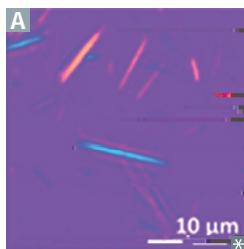
Most common in White patients, generally males < 15 years old.

Diaphyseal (5 (a)-4.8 (r)-14 (s o)14. mp5 (a). m1is6sillhim512.1 (p)9.3 (e)-9.6 (a o)3.m



**Osteoarthritis vs rheumatoid arthritis**

	Osteoarthritis A	Rheumatoid arthritis B
PATHOGENESIS	Mechanical—wear and tear destroys articular cartilage (degenerative joint disorder) → inflammation with inadequate repair (mediated by chondrocytes).	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”), HLA-DRB1, tobacco smoking. $\oplus$ 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 (r)-13 (i)129. (o)3.4 (3)13.6 (l)2.49(o)3.48(e)-7. (e)00.9 (e)0.66(n)14.8 (t)-29.4 (. )]TK7 (h(n )].1 (e)	

**Gout****FINDINGS**

Acute inflammatory monoarthritis caused by precipitation of monosodium urate crystals in joints. 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 alcohol and 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 **A**). Serum uric acid levels may be normal during an acute attack.

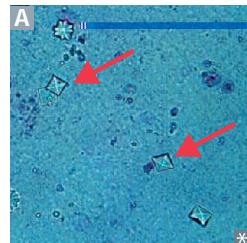
**SYMPOMTS**

Asymmetric joint distribution. Joint is swollen, red, and painful. Classic manifestation is painful MTP joint of big toe (podagra). Tophus formation **B** (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 [beer > spirits] 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**

Formerly 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** of CPPD—**blue** (when parallel), positive birefringence, calcium **pyrophosphate**, **pseudogout**.

**Systemic juvenile idiopathic arthritis**

Systemic arthritis seen in < 16 years of age. 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.

**Sjögren syndrome**

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

## Findings:

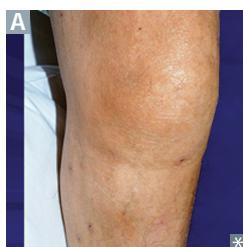
- Inflammatory joint pain
- Keratoconjunctivitis sicca (decreased tear production and subsequent corneal damage) → gritty or sandy feeling in eyes
- Xerostomia (↓ saliva production) → mucosal atrophy, fissuring of the tongue **A**
- Presence of antinuclear antibodies, rheumatoid factor (can be positive 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. Usually monoarticular.

Affected joint is often swollen **A**, red, and painful. Synovial fluid purulent (WBC > 50,000/mm<sup>3</sup>).

Complications: osteomyelitis, chronic pain, irreversible joint damage, sepsis. Treatment: antibiotics, aspiration, and drainage (+/- debridement) to prevent irreversible joint damage.

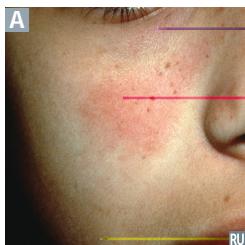
**Disseminated gonococcal infection**—STI that presents as either purulent arthritis (eg, knee) or triad of polyarthralgia, tenosynovitis (eg, hand), dermatitis (eg, pustules).

<b>Seronegative spondyloarthritis</b>	Arthritis without rheumatoid factor (no anti-IgG antibody). Strong association with HLA-B27 (MHC class I serotype). Subtypes ( <b>PAIR</b> ) 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.	
<b>Psoriatic arthritis</b>	Associated with skin psoriasis and nail lesions. Asymmetric and patchy involvement <b>A</b> . Dactylitis and “pencil-in-cup” deformity of DIP on x-ray <b>B</b> .	Seen in fewer than 1/3 of patients with psoriasis.
<b>Ankylosing spondylitis</b>	Symmetric involvement of spine and sacroiliac joints → ankylosis (joint fusion), uveitis, aortic regurgitation.	Bamboo spine (vertebral fusion) <b>C</b> . Costovertebral and costosternal ankylosis may cause restrictive lung disease. More common in males, with age of onset usually 20–40 years.
<b>Inflammatory bowel disease</b>	Crohn disease and ulcerative colitis are often associated with spondyloarthritis.	
<b>Reactive arthritis</b>	Classic triad: <ul style="list-style-type: none"><li>▪ <b>Conjunctivitis</b></li><li>▪ <b>Urethritis</b></li><li>▪ <b>Arthritis</b></li></ul>	“Can’t <b>see</b> , can’t <b>pee</b> , can’t <b>bend my knee</b> .” Associated with infections by <b>Shigella</b> , <b>Campylobacter</b> , <b>E coli</b> , <b>Salmonella</b> , <b>Chlamydia</b> , <b>Yersinia</b> . “She Caught Every Student Cheating Yesterday and over <b>reacted</b> .”



**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, Clq, C4, C2) → ↓ clearance of immune complexes. Classic presentation: facial rash (spares nasolabial folds), joint pain, and fever in a female of reproductive age. ↑ prevalence in Black, Caribbean, Asian, and Hispanic populations in the US.

**Libman-Sacks Endocarditis (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: renal disease (most common), infections, cardiovascular disease (accelerated CAD). Lupus patients die with redness in their cheeks.

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:**

Rash (malar **A** or discoid **B**)

Arthritis (nonerosive)

Serositis (eg, pleuritis, pericarditis)

Hematologic disorders (eg, cytopenias)

Oral/nasopharyngeal ulcers (usually painless)

Renal disease

Photosensitivity

Antinuclear antibodies

Immunologic disorder (anti-dsDNA, anti-Sm, antiphospholipid)

Neurologic 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 recurrent abortion along with laboratory findings of lupus anticoagulant, anticardiolipin, anti-β<sub>2</sub> 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 glucocorticoids.

**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”). Normal inflammatory markers like ESR. Treatment: regular exercise, antidepressants (TCAs, SNRIs), neuropathic pain agents (eg, gabapentinoids).

<b>Polymyositis/ dermatomyositis</b>	Nonspecific: + ANA, ↑ CK. Specific: + anti-Jo-1 (histidyl-tRNA synthetase), + anti-SRP (signal recognition particle), + anti-Mi-2 (helicase).
<b>Polymyositis</b>	Progressive symmetric proximal muscle weakness, characterized by endomysial inflammation with CD8+ T cells. Most often involves shoulders.
<b>Dermatomyositis</b>	Clinically similar to polymyositis, but also involves Gottron papules <b>A</b> , photodistributed facial erythema (eg, heliotrope [violaceous] edema of the eyelids <b>B</b> ), “shawl and face” rash <b>C</b> , mechanic’s hands (thickening, cracking, irregular “dirty”-appearing marks due to hyperkeratosis of digital skin <b>D</b> ). ↑ risk of occult malignancy. Perimysial inflammation and atrophy with CD4+ T cells.

**Myositis ossi cans**

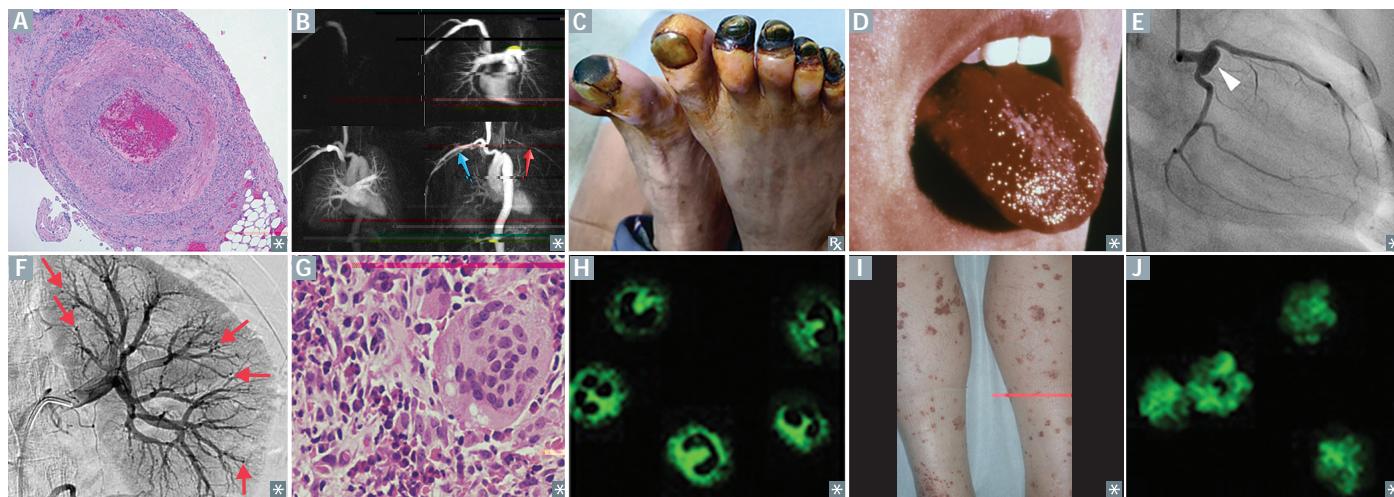
Heterotopic ossification involving skeletal muscle (eg, quadriceps). Associated with blunt muscle trauma. Presents as painful soft tissue mass. Imaging: eggshell calcification. Histology: metaplastic bone surrounding area of fibroblastic proliferation. Benign, but may be mistaken for sarcoma.

**Vasculitides**

	EPIDEMIOLOGY/PRESENTATION	NOTES
<b>Large-vessel vasculitis</b>		
<b>Giant cell (temporal) arteritis</b>	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 carotid artery branches.	May also cause aortitis or vertebral artery infarct. Focal granulomatous inflammation <b>A</b> . ↑↑ ESR. IL-6 levels correlate with disease activity. Treat with high-dose glucocorticoids prior to temporal artery biopsy to prevent blindness.
<b>Takayasu arteritis</b>	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>B</b> . ↑ ESR. Treatment: glucocorticoids.
<b>Medium-vessel vasculitis</b>		
<b>Buerger disease (thromboangiitis obliterans)</b>	Heavy tobacco smoking history, males < 40 years old. Intermittent claudication. May lead to gangrene <b>C</b> , autoamputation of digits, superficial nodular phlebitis.	Raynaud phenomenon is often present. Segmental thrombosing vasculitis with vein and nerve involvement. Treatment: smoking cessation.
<b>Kawasaki disease</b>	Usually Asian children < 4 years old. Bilateral nonexudative bulbar Conjunctivitis, Rash (polymorphous → desquamating), Adenopathy (cervical), Strawberry tongue (oral mucositis) <b>D</b> , Hand-foot changes (edema, erythema), <b>fever</b> .	Formerly called mucocutaneous lymph node syndrome. <b>CRASH</b> and <b>burn</b> on a <b>Kawasaki</b> . May develop coronary artery aneurysms <b>E</b> ; thrombosis or rupture can cause death. Treatment: IV immunoglobulin and aspirin.
<b>Polyarteritis nodosa</b>	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, spares pulmonary arteries.	Different stages of transmural inflammation with fibrinoid necrosis. Innumerable renal microaneurysms <b>F</b> and spasms on arteriogram (string of pearls appearance). Treatment: glucocorticoids, cyclophosphamide. PAN usually affects the <b>SKIN</b> : Skin, <b>Kidneys</b> , <b>Intestines</b> (GI), <b>Nerves</b> .
<b>Small-vessel vasculitis</b>		
<b>Behçet syndrome</b>	↑ 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.
<b>Cutaneous small-vessel vasculitis</b>	Occurs 7–10 days after certain medications (penicillins, cephalosporins, sulfonamides, phenytoin, allopurinol) or infections (eg, HCV, HIV). Palpable purpura, no visceral involvement.	Immune complex-mediated leukocytoclastic vasculitis; late involvement indicates systemic vasculitis.

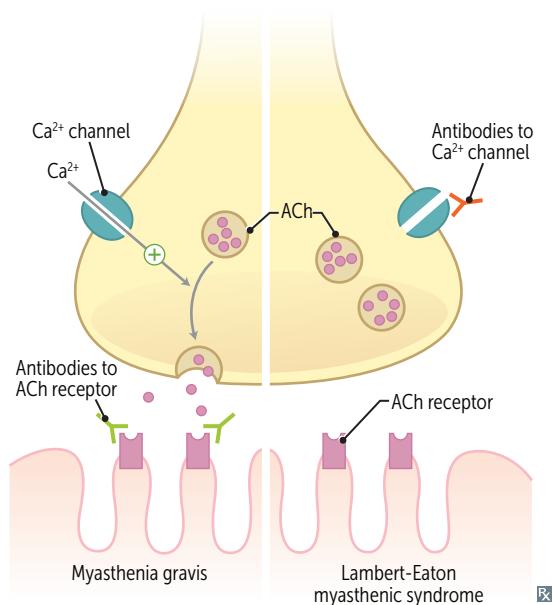
## Vasculitides (continued)

	EPIDEMIOLOGY/PRESENTATION	NOTES
<b>Small-vessel vasculitis (continued)</b>		
<b>Eosinophilic granulomatosis with polyangiitis</b>	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 <b>G</b> . MPO-ANCA/p-ANCA, ↑ IgE level.
<b>Granulomatosis with polyangiitis</b>	Upper respiratory tract: perforation of nasal septum, chronic sinusitis, otitis media, mastoiditis. Lower respiratory tract: hemoptysis, cough, dyspnea. Renal: pauci-immune rapidly progressive glomerulonephritis (hematuria, red cell casts).	Triad: <ul style="list-style-type: none"><li>▪ Focal necrotizing vasculitis</li><li>▪ Necrotizing granulomas in lung and upper airway</li><li>▪ Necrotizing glomerulonephritis</li></ul> PR3-ANCA/c-ANCA <b>H</b> (anti-proteinase 3). CXR: large nodular densities. Treatment: glucocorticoids in combination with rituximab or cyclophosphamide.
<b>Immunoglobulin A vasculitis</b>	Most common childhood systemic vasculitis. Often follows URI. Classic triad: <ul style="list-style-type: none"><li>▪ <b>H</b>inge pain (arthralgias)</li><li>▪ <b>S</b>tomach pain (abdominal pain associated with intussusception)</li><li>▪ <b>P</b>alpable purpura on buttocks/legs <b>I</b></li></ul>	Formerly called <b>H</b> enoch-Schönlein purpura. Vasculitis 2° to IgA immune complex deposition. Associated with IgA nephropathy (Berger disease). Treatment: supportive care, possibly glucocorticoids.
<b>Microscopic polyangiitis</b>	Necrotizing vasculitis commonly involving lung, kidneys, and skin with pauci-immune glomerulonephritis <b>J</b> and palpable purpura. Presentation similar to granulomatosis with polyangiitis but without nasopharyngeal involvement.	No granulomas. MPO-ANCA/p-ANCA (anti-myeloperoxidase). Treatment: cyclophosphamide, glucocorticoids.
<b>Mixed cryoglobulinemia</b>	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 <b>C</b> old. 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 <b>post</b> synaptic ACh receptor	Autoantibodies to <b>presynaptic</b> Ca <sup>2+</sup> channel → ↓ ACh release; <b>L</b> comes before <b>M</b>
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.





**Dermatologic macroscopic terms**

LESION	CHARACTERISTICS	EXAMPLES
<b>Macule</b>	Flat lesion with well-circumscribed change in skin color < 1 cm	Freckle (ephelis), labial macule <b>A</b>
<b>Patch</b>	Macule > 1 cm	Vitiligo <b>B</b>
<b>Papule</b>	Elevated solid skin lesion < 1 cm	Neurofibroma <b>C</b> , acne
<b>Plaque</b>	Papule > 1 cm	Psoriasis <b>D</b>
<b>Vesicle</b>	Small fluid-containing blister < 1 cm	Chickenpox (varicella), shingles (zoster) <b>E</b>
<b>Bulla</b>	Large fluid-containing blister > 1 cm	Bullous pemphigoid <b>F</b>
<b>Pustule</b>	Vesicle containing pus	Pustular psoriasis <b>G</b>
<b>Wheal</b>	Transient smooth papule or plaque	Hives (urticaria) <b>H</b>
<b>Scale</b>	Flaking off of stratum corneum	Eczema, psoriasis, SCC <b>I</b>
<b>Crust</b>	Dry exudate	Impetigo <b>J</b>

**Dermatologic microscopic terms**

LESION	CHARACTERISTICS	EXAMPLES
<b>Dyskeratosis</b>	Abnormal premature keratinization	Squamous cell carcinoma
<b>Hyperkeratosis</b>	↑ thickness of stratum corneum	Psoriasis, calluses
<b>Parakeratosis</b>	Retention of nuclei in stratum corneum	Psoriasis, actinic keratosis
<b>Hypergranulosis</b>	↑ thickness of stratum granulosum	Lichen planus
<b>Spongiosis</b>	Epidermal accumulation of edematous fluid in intercellular spaces	Eczematous dermatitis
<b>Acantholysis</b>	Separation of epidermal cells	Pemphigus vulgaris
<b>Acanthosis</b>	Epidermal hyperplasia (↑ spinosum)	Acanthosis nigricans, psoriasis

### Pigmented skin disorders

<b>Albinism</b>	Normal melanocyte number with ↓ melanin production <b>A</b> due to ↓ tyrosinase activity or defective tyrosine transport. ↑ risk of skin cancer.
<b>Melasma (chloasma)</b>	Acquired hyperpigmentation associated with pregnancy (“mask of pregnancy” <b>B</b> ) or OCP use. More common in patients with darker skin tones.
<b>Vitiligo</b>	Irregular patches of complete depigmentation <b>C</b> . Caused by destruction of melanocytes (believed to be autoimmune). Associated with other autoimmune disorders.
<b>Waardenburg syndrome</b>	Patchy depigmentation of skin, hair, and irises that can be associated with deafness. Caused by defects in the differentiation of neural crest cells into melanocytes.



### Seborrheic dermatitis



Erythematous, well-demarcated plaques **A** with greasy yellow scales in areas rich in sebaceous glands, such as scalp, face, and periocular region. Common in both infants (cradle cap) and adults, associated with Parkinson disease. Sebaceous glands are not inflamed, but play a role in disease development. Possibly associated with *Malassezia* spp. Treatment: topical antifungals and glucocorticoids.

## Common skin disorders

<b>Acne</b>	Multifactorial etiology—↑ sebum/androgen production, abnormal keratinocyte desquamation, <i>Cutibacterium acnes</i> colonization of the pilosebaceous unit (comedones), and inflammation (papules/pustules <b>A</b> , nodules, cysts). Treatment: retinoids, benzoyl peroxide, and antibiotics.
<b>Atopic dermatitis (eczema)</b>	Pruritic eruption associated with ichthyosis vulgaris and other atopic diseases (asthma, allergic rhinitis, food allergies); ↑ serum IgE. Often appears on face in infancy <b>B</b> and then on flexural surfaces <b>C</b> in children and adults.
<b>Allergic contact dermatitis</b>	Type IV hypersensitivity reaction secondary to contact allergen (eg, nickel <b>D</b> , poison ivy <b>E</b> , neomycin).
<b>Keratosis pilaris</b>	Follicular-based papules from keratin plugging, most often on extensor surfaces of arms and thighs.
<b>Melanocytic nevus</b>	Common mole. Benign, but melanoma can arise in congenital or atypical moles. Intradermal nevi are papular <b>F</b> . Junctional nevi are flat macules <b>G</b> .
<b>Pseudofolliculitis barbae</b>	Inflammatory reaction to hair penetrating the skin characterized by firm papules and pustules that are painful and pruritic. Commonly occurs near jawline as a result of shaving (“razor bumps”), more common with naturally curly hair.
<b>Psoriasis</b>	Papules and plaques with silvery scaling <b>H</b> , especially on knees and elbows. Acanthosis with parakeratotic scaling (nuclei still in stratum corneum), Munro microabscesses. ↑ stratum spinosum, ↓ stratum granulosum. Auspitz sign ( <b>I</b> )—pinpoint bleeding spots from exposure of dermal papillae when scales are scraped off. Associated with nail pitting and psoriatic arthritis.
<b>Rosacea</b>	Inflammatory facial skin disorder characterized by erythematous papules and pustules <b>J</b> , but no comedones. May be associated with facial flushing in response to external stimuli (eg, alcohol, heat). Complications include ocular involvement, rhinophyma (bulbous deformation of nose).
<b>Seborrheic keratosis</b>	Well-demarcated, verrucous, benign squamous epithelial proliferation of immature keratinocytes with keratin-filled cysts (horn cysts) <b>K</b> . Looks “stuck on.” Leser-Trélat sign <b>L</b> —rapid onset of multiple seborrheic keratoses, indicates possible malignancy (eg, GI adenocarcinoma).
<b>Verrucae</b>	Warts; caused by low-risk HPV strains. Soft, tan-colored, cauliflowerlike papules <b>M</b> . Epidermal hyperplasia, hyperkeratosis, koilicytosis. Condyloma acuminatum on anus or genitals <b>N</b> .
<b>Urticaria</b>	Hives. Pruritic wheals that form after mast cell degranulation <b>O</b> . Characterized by superficial dermal edema and lymphatic channel dilation.





**Skin infections****Bacterial infections**

<b>Impetigo</b>	Skin infection involving superficial epidermis. Usually from <i>S aureus</i> or <i>S pyogenes</i> . Highly contagious. Honey-colored crusting <b>A</b> .
<b>Erysipelas</b>	Bullous impetigo <b>B</b> has bullae and is usually caused by <i>S aureus</i> .
<b>Cellulitis</b>	Infection involving upper dermis and superficial lymphatics, usually from <i>S pyogenes</i> . Presents with well-defined, raised demarcation between infected and normal skin <b>C</b> .
<b>Abscess</b>	Acute, painful, spreading infection of deeper dermis and subcutaneous tissues. Usually from <i>S pyogenes</i> or <i>S aureus</i> . Often starts with a break in skin from trauma or another infection <b>D</b> .
<b>Necrotizing fasciitis</b>	Collection of pus from a walled-off infection within deeper layers of skin <b>E</b> . Offending organism is almost always <i>S aureus</i> .
<b>Staphylococcal scalded skin syndrome</b>	Deeper tissue injury, usually from anaerobic bacteria or <i>S pyogenes</i> . Pain may be out of proportion to exam findings. Results in crepitus from methane and CO <sub>2</sub> production. “Flesh-eating bacteria.” Causes bullae and skin necrosis → violaceous color of bullae, surrounding skin <b>F</b> . Surgical emergency.

**Viral infections**

<b>Herpes</b>	Herpes virus infections (HSV-1 and HSV-2) of skin can occur anywhere from mucosal surfaces to normal skin. These include herpes labialis, herpes genitalis, herpetic whitlow <b>H</b> (finger).
<b>Molluscum contagiosum</b>	Umbilicated papules <b>I</b> caused by a poxvirus. While frequently seen in children, it may be sexually transmitted in adults.
<b>Varicella zoster</b>	Causes varicella (chickenpox) and zoster (shingles). Varicella presents with multiple crops of lesions in various stages from vesicles to crusts. Zoster is a reactivation of the virus in dermatomal distribution (unless it is disseminated).
<b>Hairy leukoplakia</b>	Irregular, white, painless plaques on lateral tongue that cannot be scraped off <b>J</b> . EBV mediated. Occurs in patients living with HIV, organ transplant recipients. Contrast with thrush (scrapable) and leukoplakia (precancerous).

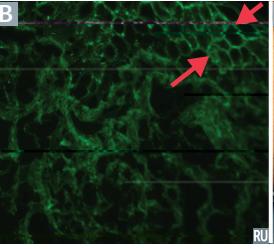
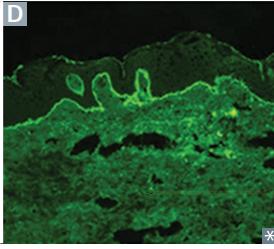
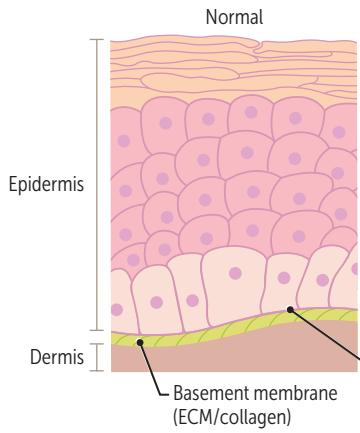
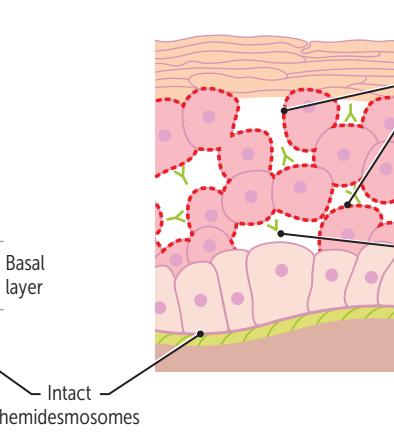
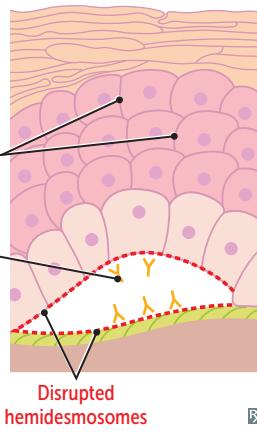


**Cutaneous mycoses**

<b>Tinea (dermatophytes)</b>	Clinical name for dermatophyte (cutaneous fungal) infections. Dermatophytes include <i>Microsporum</i> , <i>Trichophyton</i> , and <i>Epidermophyton</i> . Branching septate hyphae visible on KOH preparation with blue fungal stain <b>A</b> . Associated with pruritus.
<b>Tinea capitis</b>	Occurs on head, scalp. Associated with lymphadenopathy, alopecia, scaling <b>B</b> .
<b>Tinea corporis</b>	Occurs on body (usually torso). Characterized by enlarging erythematous, scaly rings (“ringworm”) with central clearing <b>C</b> . Can be acquired from contact with infected pets or farm animals.
<b>Tinea cruris</b>	Occurs in inguinal area (“jock itch”) <b>D</b> . Often does not show the central clearing seen in tinea corporis.
<b>Tinea pedis</b>	Three varieties (“athlete’s foot”): <ul style="list-style-type: none"> <li>▪ Interdigital <b>E</b>; most common</li> <li>▪ Moccasin distribution <b>F</b></li> <li>▪ Vesicular type</li> </ul>
<b>Tinea unguium</b>	Onychomycosis; occurs on nails.
<b>Tinea ( pityriasis) versicolor</b>	Caused by <i>Malassezia</i> spp. ( <i>Pityrosporum</i> spp.), a yeastlike fungus (not a dermatophyte despite being called tinea). Degradation of lipids produces acids that inhibit tyrosinase (involved in melanin synthesis) → hypopigmentation <b>G</b> ; hyperpigmentation and/or pink patches can also occur due to inflammatory response. Less pruritic than dermatophytes. Can occur any time of year, but more common in summer (hot, humid weather). “Spaghetti and meatballs” appearance on microscopy <b>H</b> . Treatment: selenium sulfide, topical and/or oral antifungal medications.



## Autoimmune blistering skin disorders

	Pemphigus vulgaris	Bullous pemphigoid	
PATHOPHYSIOLOGY	Potentially fatal. Most commonly seen in older adults. Type II hypersensitivity reaction. IgG antibodies against desmogelin 3 +/– desmoglein 1 (component of desmosomes, which connect keratinocytes in the stratum spinosum).	Less severe than pemphigus vulgaris. Most commonly seen in older adults. Type II hypersensitivity reaction. IgG antibodies against hemidesmosomes (epidermal basement membrane; antibodies are “bully” the epidermis).	
GROSS MORPHOLOGY	Flaccid intraepidermal bullae <b>A</b> caused by acantholysis (separation of keratinocytes, “row of tombstones” on H&E stain); oral mucosa is involved. Nikolsky sign $\oplus$ .	Tense blisters <b>C</b> containing eosinophils; oral mucosa spared. Nikolsky sign $\ominus$ .	
IMMUNOFLOURESCENCE	Reticular pattern around epidermal cells <b>B</b> .	Linear pattern at epidermal-dermal junction <b>D</b> .	
	 	 	
	 <p>Normal</p> <p>Epidermis</p> <p>Dermis</p> <p>Basement membrane (ECM/collagen)</p> <p>Basal layer</p> <p>Intact hemidesmosomes</p>	 <p>Disrupted desmosomes</p> <p>Intact desmosomes</p> <p>IgG antibodies</p> <p>Disrupted hemidesmosomes</p>	 <p>Intact desmosomes</p> <p>IgG antibodies</p> <p>Disrupted hemidesmosomes</p>
Epidermolysis bullosa simplex	Autosomal dominant defect in keratin filament assembly → cytoskeleton disruption → epithelial fragility. Presents early in life with friction-induced skin blistering that primarily affects palms and soles. Heals without scarring. Skin biopsy: intraepidermal cleavage.		

### Other blistering skin disorders

<b>Dermatitis herpetiformis</b>	Pruritic papules, vesicles, and bullae (often found on elbows, knees, buttocks) <b>A</b> . Deposits of IgA at tips of dermal papillae. Associated with celiac disease. Treatment: dapsone, gluten-free diet.
<b>Erythema multiforme</b>	Associated with infections (eg, <i>Mycoplasma pneumoniae</i> , HSV), drugs (eg, sulfa drugs, β-lactams, phenytoin). Presents with multiple types of lesions—macules, papules, vesicles, target lesions (look like targets with multiple rings and dusky center showing epithelial disruption) <b>B</b> .
<b>Stevens-Johnson syndrome</b>	Characterized by fever, bullae formation and necrosis, sloughing of skin at dermal-epidermal junction (⊕ Nikolsky), high mortality rate. Typically mucous membranes are involved <b>C</b> . Targetoid skin lesions may appear, as seen in erythema multiforme. Usually associated with adverse drug reaction. <b>Toxic epidermal necrolysis (TEN)</b> <b>D E</b> is more severe form of SJS involving > 30% body surface area. 10–30% involvement denotes SJS-TEN.



### Cutaneous ulcers

	Venous ulcer	Arterial ulcer	Neuropathic ulcer	Pressure injury
<b>ETIOLOGY</b>	Chronic venous insufficiency; most common ulcer type	Peripheral artery disease (eg, atherosclerotic stenosis)	Peripheral neuropathy (eg, diabetic foot)	Prolonged unrelieved pressure (eg, immobility)
<b>LOCATION</b>	Gaiter area (ankle to midcalf), typically over malleoli	Distal toes, anterior shin, pressure points	Bony prominences (eg, metatarsal heads, heel)	Weightbearing points (eg, sacrum, ischium, calcaneus)
<b>APPEARANCE</b>	Irregular border, shallow, exudative <b>A</b>	Symmetric with well-defined punched-out appearance <b>B</b>	Hyperkeratotic edge with undermined borders <b>C</b>	Varies based on stage from non-blanchable erythema to full-thickness skin loss <b>D</b>
<b>PAIN</b>	Mild to moderate	Severe	Absent	Present
<b>ASSOCIATED SIGNS</b>	Telangiectasias, varicose veins, edema, stasis dermatitis (erythematous eczematous patches)	Arterial insufficiency, cold and pale atrophic skin, hair loss, absent pulses	Claw toes, Charcot joints, absent reflexes	Soft tissue infection and osteomyelitis are frequent complications



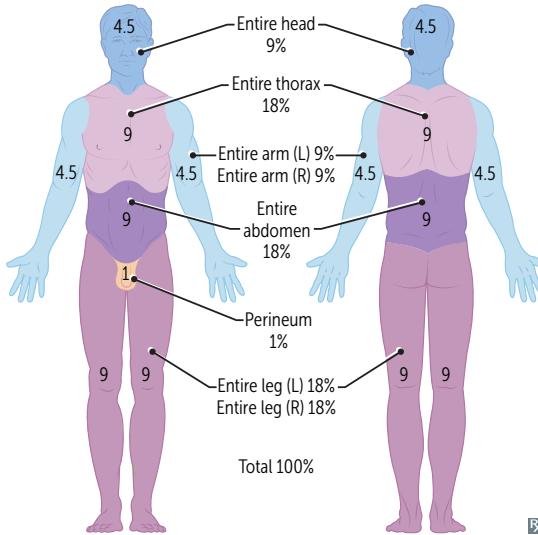
**Miscellaneous skin disorders**

<b>Acanthosis nigricans</b>	Epidermal hyperplasia causing symmetric, hyperpigmented thickening of skin, especially in axilla or on neck <b>A</b> . Associated with insulin resistance (eg, diabetes, obesity, Cushing syndrome, PCOS), visceral malignancy (eg, gastric adenocarcinoma).
<b>Erythema nodosum</b>	Painful, raised inflammatory lesions of subcutaneous fat (panniculitis), usually on anterior shins. Often idiopathic, but can be associated with sarcoidosis, coccidioidomycosis, histoplasmosis, TB, streptococcal infections <b>B</b> , leprosy <b>C</b> , inflammatory bowel disease.
<b>Ichthyosis vulgaris</b>	Disorder of defective keratinocyte desquamation due to filaggrin gene mutations resulting in diffuse scaling of the skin <b>D</b> most commonly on the extensor side of extremities and the trunk. Manifests in infancy or early childhood. Strong association with atopic dermatitis.
<b>Lichen Planus</b>	Pruritic, purple, polygonal planar papules and plaques are the <b>6 P's</b> of lichen Planus <b>E F</b> . Mucosal involvement manifests as Wickham striae (reticular white lines) and hypergranulosis. Sawtooth infiltrate of lymphocytes at dermal-epidermal junction. Associated with hepatitis C.
<b>Pityriasis rosea</b>	“Herald patch” <b>G</b> followed days later by other scaly erythematous plaques, often in a “Christmas tree” distribution on trunk <b>H</b> . Multiple pink plaques with collarette scale. Self-resolving in 6–8 weeks.
<b>Sunburn</b>	Acute cutaneous inflammatory reaction due to excessive UV irradiation. Causes DNA mutations, inducing apoptosis of keratinocytes. UVB is dominant in sunBurn, UVA in tAnning and photoAging. Exposure to UVA and UVB ↑ risk of skin cancer.



### Estimation of body surface area

Approximated by the rule of 9's. Used to assess the extent of burn injuries.



### Burn classification

DEPTH	INVOLVEMENT	APPEARANCE	SENSATION
Superficial burn	Epidermis only	Similar to sunburn; histamine release causes localized, dry, blanching redness without blisters	Painful
Superficial partial-thickness burn	Epidermis and papillary dermis	Blisters, blanches with pressure, swollen, warm	Painful to temperature and air
Deep partial-thickness burn	Epidermis and reticular dermis	Blisters (easily unroofed), does not blanch with pressure	Painless; perception of pressure only
Full-thickness burn	Epidermis and full-thickness dermis	White, waxy, dry, inelastic, leathery, does not blanch with pressure	Painless; perception of deep pressure only
Deeper injury burn	Epidermis, dermis, and involvement of underlying tissue (eg, fascia, muscle)	White, dry, inelastic, does not blanch with pressure	Painless; some perception of deep pressure

**Skin cancer**

Basal cell carcinoma (BCC) more common above **upper lip**.

Squamous cell carcinoma (SCC) more common below **lower lip**.



Sun exposure strongly predisposes to skin cancer.

**Basal cell carcinoma**

Most common skin cancer. Found in sun-exposed areas of body (eg, face). Locally invasive, but rarely metastasizes. Waxy, pink, pearly nodules, commonly with telangiectasias, rolled borders **A**, central crusting or ulceration. BCCs also appear as nonhealing ulcers with infiltrating growth **B** or as a scaling plaque (superficial BCC) **C**. Basal cell tumors have “palisading” (aligned) nuclei **D**.

**Squamous cell carcinoma**

Second most common skin cancer. Associated with immunosuppression, chronic nonhealing wounds, and occasionally arsenic exposure. **Marjolin ulcer**—SCC arising in chronic wounds or scars; usually develops > 20 years after insult. Commonly appears on face **E**, lower lip **F**, ears, hands. Locally invasive, may spread to lymph nodes, and will rarely metastasize. Ulcerative red lesions. Histopathology: keratin “pearls” **G**.

**Actinic keratosis**—Premalignant lesions caused by sun exposure. Small, rough, erythematous or brownish papules or plaques **H**. Risk of squamous cell carcinoma is proportional to degree of epithelial dysplasia.

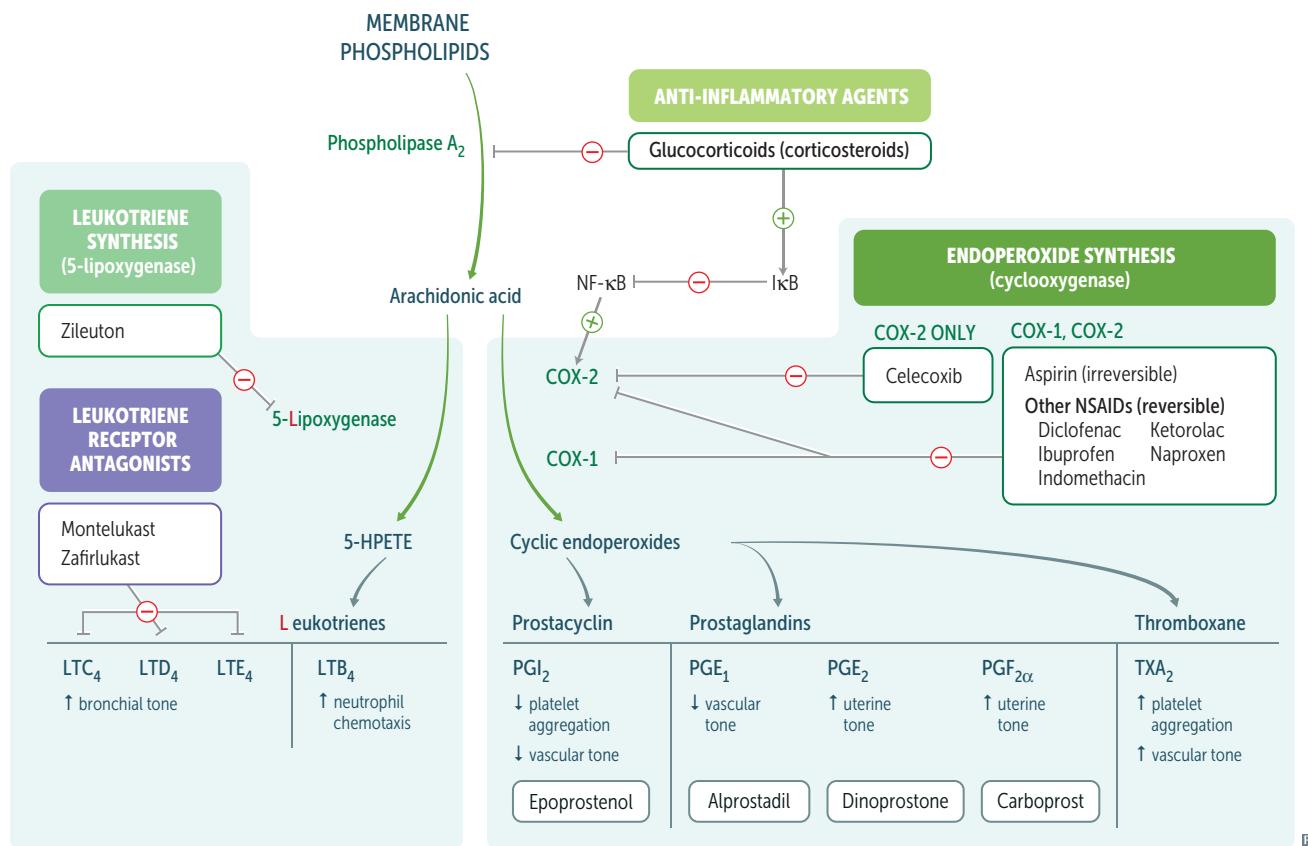
**Melanoma**

Common tumor with significant risk of metastasis. S-100 tumor marker. Associated with dysplastic nevi; people with lighter skin tones are at ↑ risk. Depth of tumor (Breslow thickness) correlates with risk of metastasis. Look for the **ABCDEs**: **A**symmetry, **B**order irregularity, **C**olor variation, **D**iameter > 6 mm, and **E**volution over time. At least 4 different types of melanoma, including superficial spreading **I**, nodular **J**, lentigo maligna **K**, and acral lentiginous (highest prevalence in people with darker skin tones) **L**. Often driven by activating mutation in BRAF kinase. Primary treatment is excision with appropriately wide margins. Advanced melanoma also treated with immunotherapy (eg, ipilimumab) and/or BRAF inhibitors (eg, vemurafenib).



## ► MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—PHARMACOLOGY

## Arachidonic acid pathways



LTB<sub>4</sub> is a neutrophil chemotactic agent.

PGI<sub>2</sub> is a vasodilator and platelet aggregation inhibitor.

Neutrophils arrive “B4” others.

Platelet-Gathering Inhibitor.

## Acetaminophen

MECHANISM	Reversibly inhibits cyclooxygenase, mostly in CNS. Inactivated peripherally.
CLINICAL USE	Antipyretic, analgesic, but not anti-inflammatory. Used instead of aspirin to avoid Reye syndrome in children with viral infection.
ADVERSE EFFECTS	Overdose produces hepatic necrosis; acetaminophen metabolite (NAPQI) depletes glutathione and forms toxic tissue byproducts in liver. N-acetylcysteine is antidote—regenerates glutathione.

**Aspirin**

MECHANISM	NSAID that <b>irreversibly</b> (Aspirin) inhibits cyclooxygenase (both COX-1 and COX-2) by covalent acetylation → ↓ synthesis of TXA <sub>2</sub> and prostaglandins. ↑ bleeding time. No effect on PT, PTT. Effect lasts until new platelets are produced.
CLINICAL USE	Low dose (< 300 mg/day): ↓ platelet aggregation. Intermediate dose (300–2400 mg/day): antipyretic and analgesic. High dose (2400–4000 mg/day): anti-inflammatory.
ADVERSE EFFECTS	Gastric ulceration, tinnitus (CN VIII), allergic reactions (especially in patients with asthma or nasal polyps). Chronic use can lead to acute kidney injury, interstitial nephritis, GI bleeding. Risk of Reye syndrome in children treated for viral infection. Toxic doses cause respiratory alkalosis early, but transitions to mixed metabolic acidosis-respiratory alkalosis. Overdose treatment: NaHCO <sub>3</sub> .

**Celecoxib**

MECHANISM	Reversibly and <b>selectively</b> inhibits the cyclooxygenase ( <b>COX</b> ) isoform 2 (“ <b>Selecoxib</b> ”), which is found in inflammatory cells and vascular endothelium and mediates inflammation and pain; spares COX-1, which helps maintain gastric mucosa. Thus, does not have the corrosive effects of other NSAIDs on the GI lining. Spares platelet function as TXA <sub>2</sub> production is dependent on COX-1.
CLINICAL USE	Rheumatoid arthritis, osteoarthritis.
ADVERSE EFFECTS	↑ risk of thrombosis, sulfa allergy.

**Nonsteroidal anti-inflammatory drugs**

MECHANISM	Reversibly inhibit cyclooxygenase (both COX-1 and COX-2). Block prostaglandin synthesis.
CLINICAL USE	Antipyretic, analgesic, anti-inflammatory. Indomethacin is used to close a PDA.
ADVERSE EFFECTS	Interstitial nephritis, gastric ulcer (prostaglandins protect gastric mucosa), renal ischemia (prostaglandins vasodilate afferent arteriole), aplastic anemia.

**Lefunomide**

MECHANISM	Reversibly inhibits dihydroorotate dehydrogenase, preventing pyrimidine synthesis. Suppresses T-cell proliferation.
CLINICAL USE	Rheumatoid arthritis, psoriatic arthritis.
ADVERSE EFFECTS	Diarrhea, hypertension, hepatotoxicity, teratogenicity.

**Bisphosphonates**

MECHANISM	Pyrophosphate analogs; bind hydroxyapatite in bone, inhibiting osteoclast activity.
CLINICAL USE	Osteoporosis, hypercalcemia, Paget disease of bone, metastatic bone disease, osteogenesis imperfecta.
ADVERSE EFFECTS	Esophagitis, osteonecrosis of jaw, atypical femoral stress fractures.



**TNF- $\alpha$  inhibitors**

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
<b>Etanercept</b>	Fusion protein (decoy receptor for TNF- $\alpha$ + IgG <sub>1</sub> Fc), produced by recombinant DNA.  Etanercept intercepts TNF.	Rheumatoid arthritis, psoriasis, ankylosing spondylitis.	Predisposition to infection, including reactivation of latent TB, since TNF is important in granuloma formation and stabilization.
<b>Adalimumab, certolizumab, golimumab, in iximab</b>	Anti-TNF- $\alpha$ monoclonal antibody.	Inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriasis.	Can also lead to drug-induced lupus.

**Imiquimod**

MECHANISM	Binds toll-like receptor 7 (TLR-7) of macrophages, monocytes, and dendritic cells to activate them → topical antitumor immune response modifier.
CLINICAL USE	Anogenital warts, actinic keratosis.
ADVERSE EFFECTS	Itching, burning pain at site of application, rashes.