



Arthritis

Pathogenesis, morphology, and clinicopathologic differentiation

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Learning objectives: Interpret joint disease by mechanism

- Explain how synovium and articular cartilage maintain normal joint function.
- Separate degenerative, autoimmune, infectious, and crystal-induced pathways.
- Recognize the distinctive joint lesions of OA, RA, infection, gout, and CPPD.
- Use joint distribution and tissue pathology to frame the differential diagnosis.

Joints: Stability and mobility require different anatomy

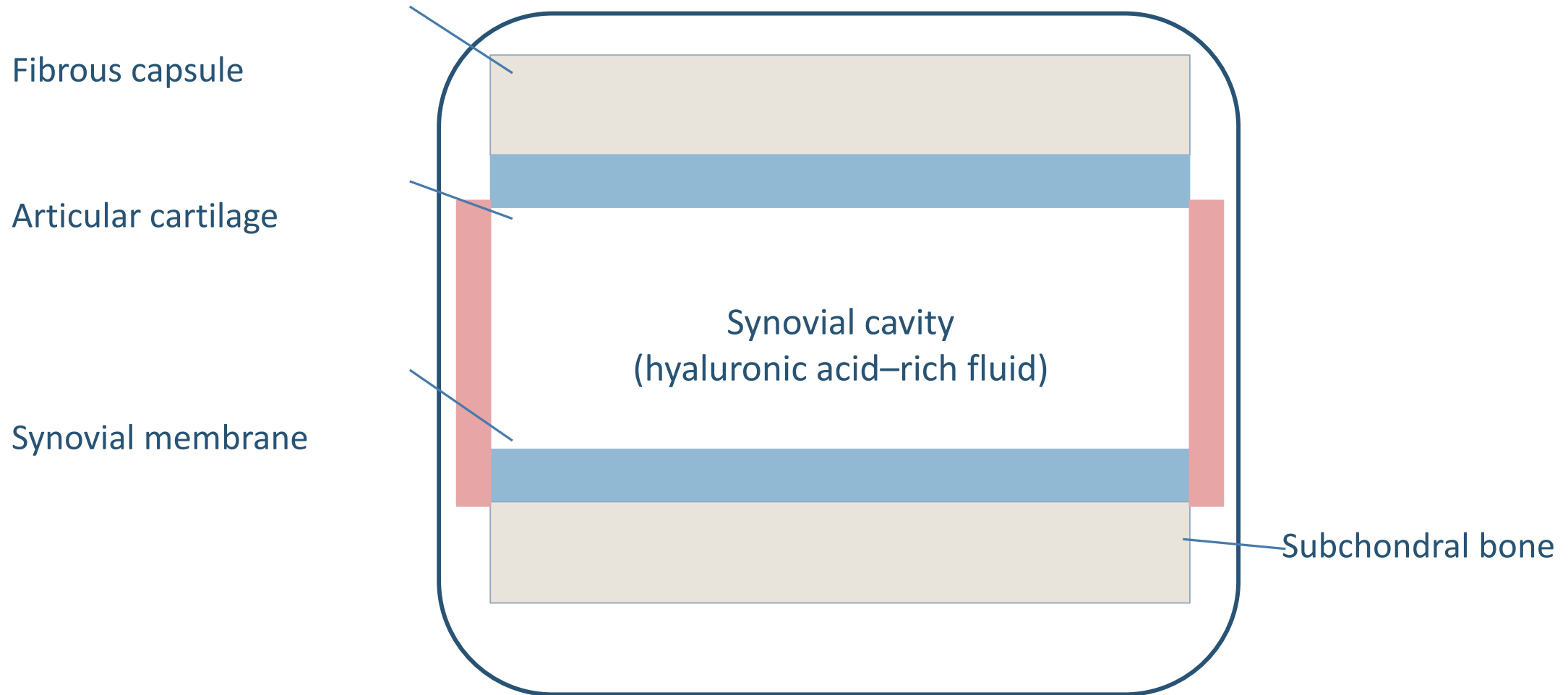
Solid (nonsynovial) joints

- No joint cavity; Minimal movement.
- Fibrous connections include sutures and tooth–jaw attachments.
- Cartilaginous connections include pubic symphysis.

Synovial joints

- A cavity permits a broad range of motion.
- Synovial membrane encloses joint within a fibrous capsule.
- Cartilage surfaces transmit load and limit friction.

Synovial joint: Structures vulnerable to arthritis



Schematic—not a histologic section

Two synoviocyte populations perform complementary tasks

Type A synoviocytes

- Specialized macrophage-like cells.
- Phagocytose debris within the synovial environment.

Type B synoviocytes

- Fibroblast-like cells.
- Synthesize hyaluronic acid and synovial proteins.

Synovial fluid is a nutrient and lubricant medium

- The synovial lining lacks a basement membrane.
- Exchange of gases, nutrients, and waste occurs across synovium.
- Synovial fluid is a hyaluronic acid–rich plasma filtrate.
- It lubricates surfaces and supports avascular articular cartilage.

Hyaline cartilage: Structure supports mechanical function

Water

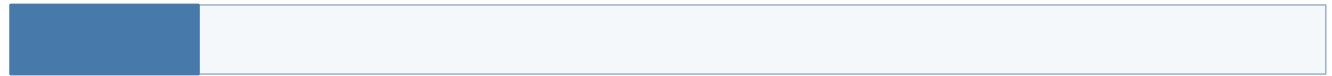
70%



Resists compression with proteoglycans

Type II collagen

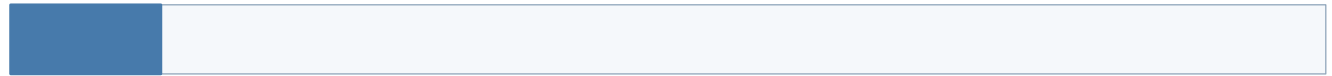
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Tensile integrity and load transmission

Proteoglycans

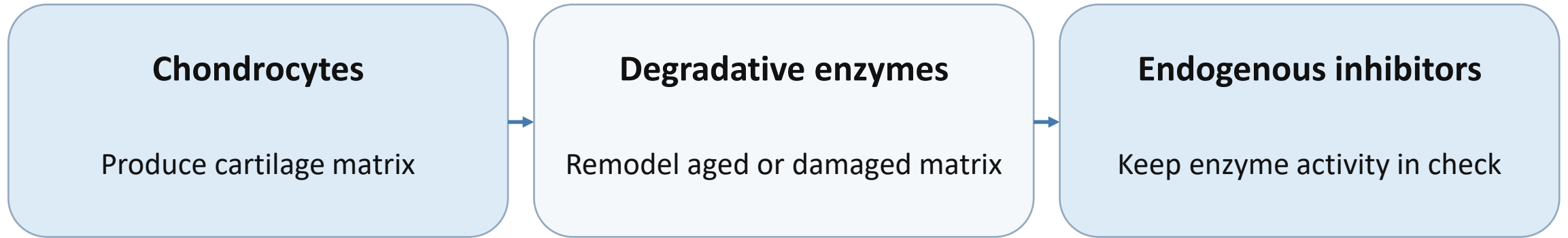
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Hydration and resistance to compression

Chondrocytes maintain this avascular, aneural, and alymphatic matrix.

Articular cartilage: Maintained by regulated turnover



Pathologic interpretation

- Joint disease disturbs the balance between matrix synthesis and destruction.
- Cytokines such as IL-1 and TNF may accelerate matrix degradation.

Arthritis: Four major pathogenetic families

Degenerative

Osteoarthritis
Cartilage damage and failed repair

Autoimmune / immune-mediated

Rheumatoid arthritis; Spondyloarthritis
Synovitis or enthesitis

Infectious

Suppurative, tuberculous, viral, Lyme
Organisms or infection-associated inflammation

Crystal-mediated

Gout and calcium pyrophosphate deposition
Crystal-triggered innate inflammation

The tissue compartment predicts the dominant lesion

Cartilage-centered degeneration

- OA begins with chondrocyte and extracellular matrix dysfunction.
- Cartilage fissures precede exposed subchondral bone.

Inflammation-centered disorders

- RA produces cellular synovitis and invasive pannus.
- Spondyloarthropathies often involve entheses.
- Crystals activate leukocytes; Infection introduces organisms.

Clinical pattern helps classify arthritis

- Distribution: Monoarticular, oligoarticular, or polyarticular.
- Tempo: Abrupt attack, persistent inflammation, or gradual progression.
- Tissue response: Effusion, erosions, osteophytes, or ankylosis.
- Associated findings: Infection, autoantibodies, enthesitis, or tophi.

Osteoarthritis: Degenerative cartilage failure

- Osteoarthritis (OA) is the commonest joint disease.
- Its primary lesion is degeneration of articular cartilage.
- Cartilage damage compromises whole-joint structure and function.
- Low-grade inflammation contributes secondarily rather than defining the initial lesion.

Primary and secondary OA differ in predisposing context

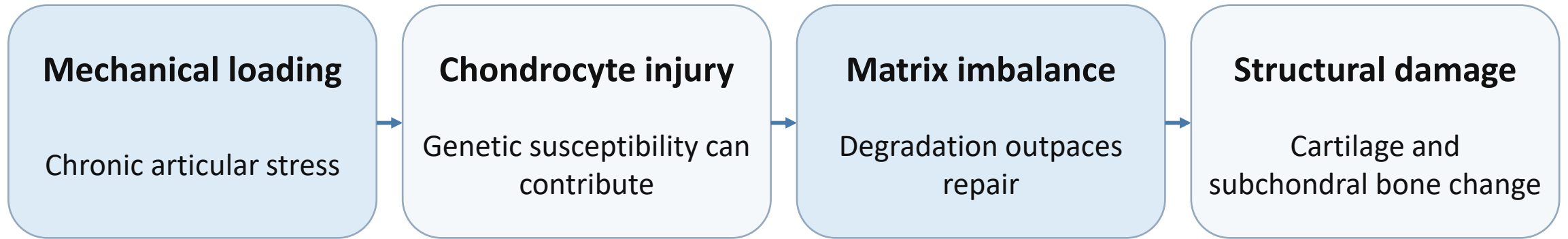
Primary (idiopathic) OA

- Usually insidious onset with age.
- Typically oligoarticular; May become generalized.
- No specific precipitating abnormality recognized.

Secondary OA

- Associated with previous trauma or joint deformity.
- Systemic predispositions include obesity, diabetes, and ochronosis.
- Consider underlying causes when OA presents in a younger patient.

OA pathogenesis: Stress exceeds reparative capacity



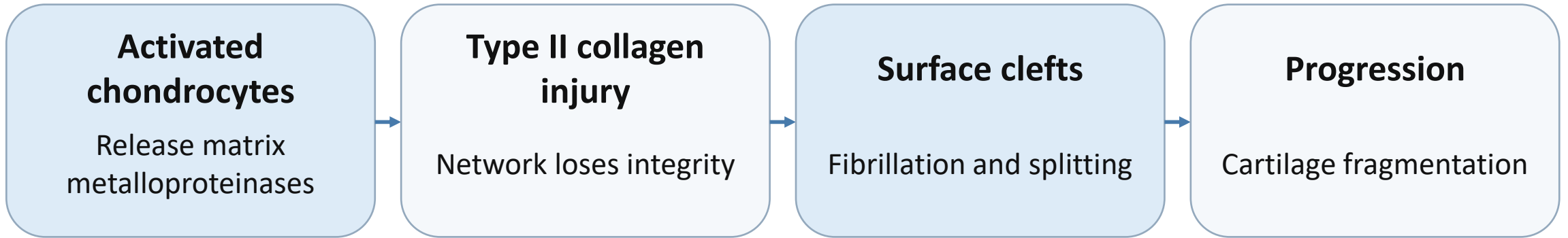
Pathologic interpretation

- Mechanical stress is central; Inflammatory mediators amplify progression.
- Susceptibility polymorphisms may involve matrix and signaling proteins.

Early OA: Chondrocyte proliferation does not restore matrix

- Chondrocytes form proliferative clusters as an attempted repair response.
- Proteoglycan synthesis continues, but degradation exceeds replacement.
- Cartilage matrix water content increases.
- Surface integrity deteriorates despite compensatory cell activity.

MMP-mediated collagen cleavage creates cartilage fissures



Pathologic interpretation

- Loss of the tensile collagen network permits clefts at the articular surface.

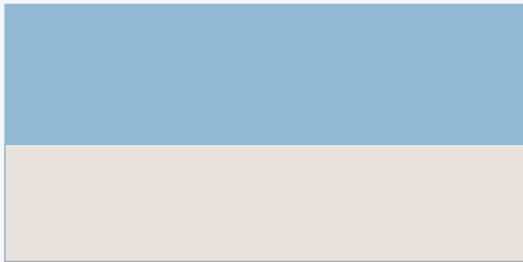
OA inflammatory mediators aggravate structural damage

- TGF- β , IL-1, IL-6, prostaglandins, and nitric oxide are implicated.
- Chondrocytes and synovial cells participate in local signaling.
- TGF- β can promote matrix metalloproteinase production.
- Bone morphogenetic proteins and TGF- β contribute to osteophyte formation.

Osteoarthritis: A progression of structural injury

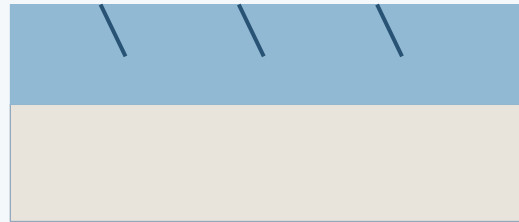
Maintained cartilage

Intact articular matrix
And chondrocytes



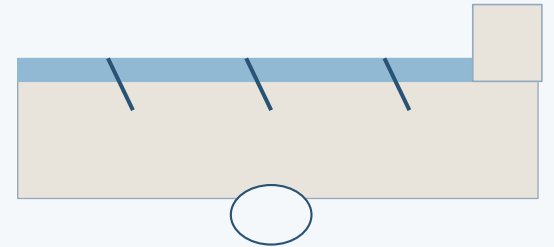
Early degeneration

Fibrillation and fissures
With repair attempts



Advanced cartilage loss

Eburnation, osteophytes
And subchondral changes



Advanced OA: Exposed bone and loose cartilage fragments

- Full-thickness cartilage can detach to form loose bodies (“joint mice”).
- Exposed subchondral bone becomes a friction-polished articular surface.
- This ivory-like change is termed bone eburnation.
- Subchondral bone damage contributes to pain and functional limitation.

Osteophytes and subchondral cysts have distinct mechanisms

- Peripheral bony outgrowths are capped by fibrocartilage and hyaline cartilage.
- Chondral caps may later ossify: The mature lesion is an osteophyte.
- Microfractures in subarticular bone permit joint fluid entry.
- A ball-valve mechanism can expand fibrous-walled subchondral cysts.

OA radiographic–pathologic correspondence

Imaging feature	Structural substrate
Joint-space narrowing	Loss of hyaline articular cartilage
Subchondral sclerosis	Reactive dense bone beneath damaged surface
Marginal osteophytes	Bony outgrowths at articular margins
Subchondral cysts	Fluid enters damaged subarticular bone

OA symptom pattern reflects mechanical loading

- Deep joint pain typically worsens with use.
- Stiffness improves as the joint begins moving.
- Crepitus and restricted range of motion are characteristic.
- Spinal osteophytes can impinge nerve roots and cause radicular symptoms.

OA favors selected weight-bearing and hand joints

Predominant location	Characteristic involvement
Axial or weight-bearing	Knees, hips, cervical and lumbar spine
Hand	Distal and proximal interphalangeal joints
Thumb base	First carpometacarpal articulation
Foot	First tarsometatarsal articulation

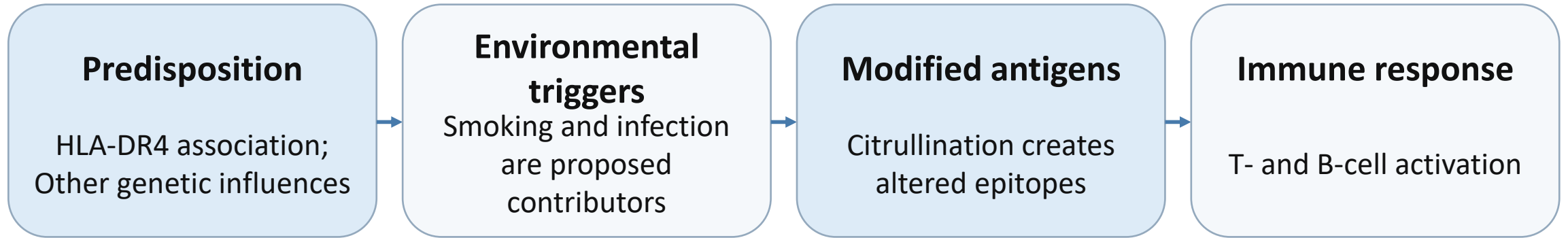
OA: Structural severity and symptoms may diverge

- Radiographic disease burden does not correlate closely with pain or disability.
- Heberden nodes reflect osteophytes at distal interphalangeal joints.
- Joint deformities occur, but OA does not characteristically cause ankylosis.
- In typical advanced disease, radiography is diagnostically informative without tissue biopsy.

RA: Systemic autoimmunity centered on destructive synovitis

- Rheumatoid arthritis (RA) produces chronic nonsuppurative proliferative synovitis.
- Inflammatory synovium can erode cartilage and adjacent bone.
- Progression may lead to fibrous or bony ankylosis.
- Extraarticular lesions may affect skin, lungs, vessels, heart, and eyes.

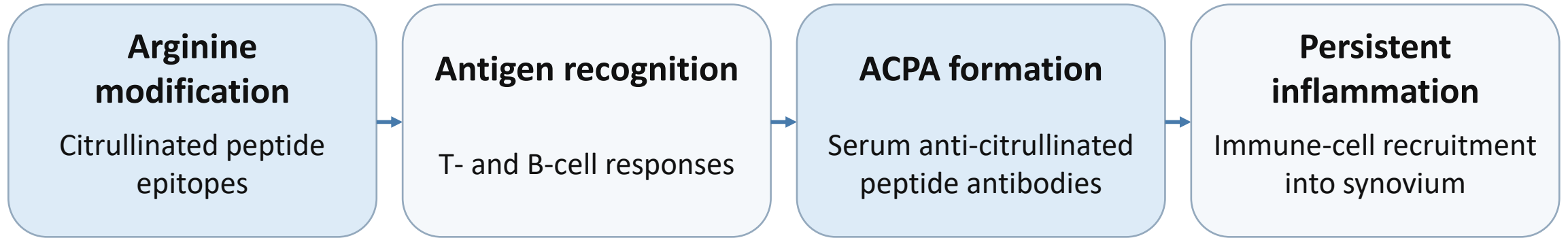
RA initiation requires susceptibility and immune activation



Pathologic interpretation

- The initiating joint antigen is not definitively identified.
- Environmental contribution is plausible but not fully defined in the source.

Citrullination connects altered self-antigens to ACPA



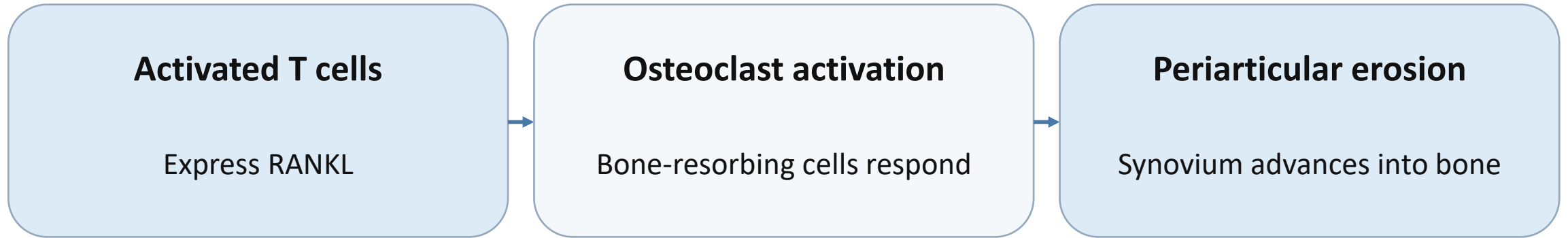
Pathologic interpretation

- ACPA aids diagnosis but is not present in all patients.

RA cytokines have different targets

Mediator	Major pathologic action
TNF, IL-1, IL-6	Recruit leukocytes; induce synovial proteases
IL-17	Recruit neutrophils and monocytes
RANKL	Stimulate osteoclast-mediated bone resorption
IFN- γ	Activate macrophages and synovial cells

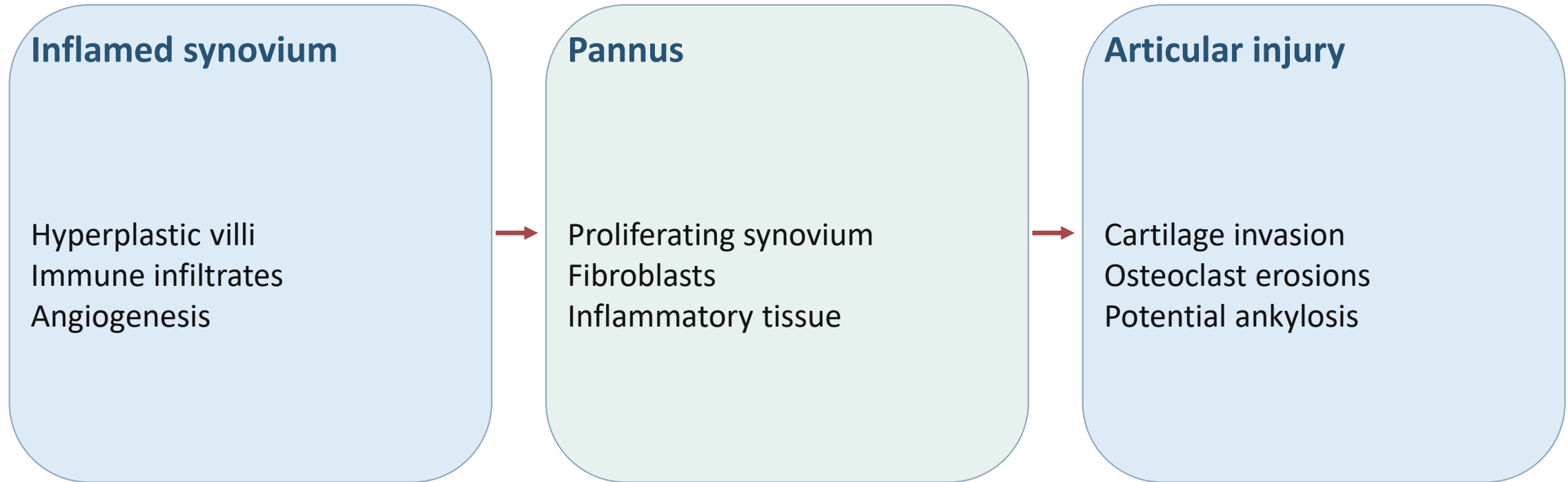
RANKL links immune activation to marginal bone erosion



Pathologic interpretation

- Bone erosion is a defining destructive element of RA.
- TNF signaling sustains inflammation and joint damage.

Rheumatoid pannus: Destructive proliferative synovitis



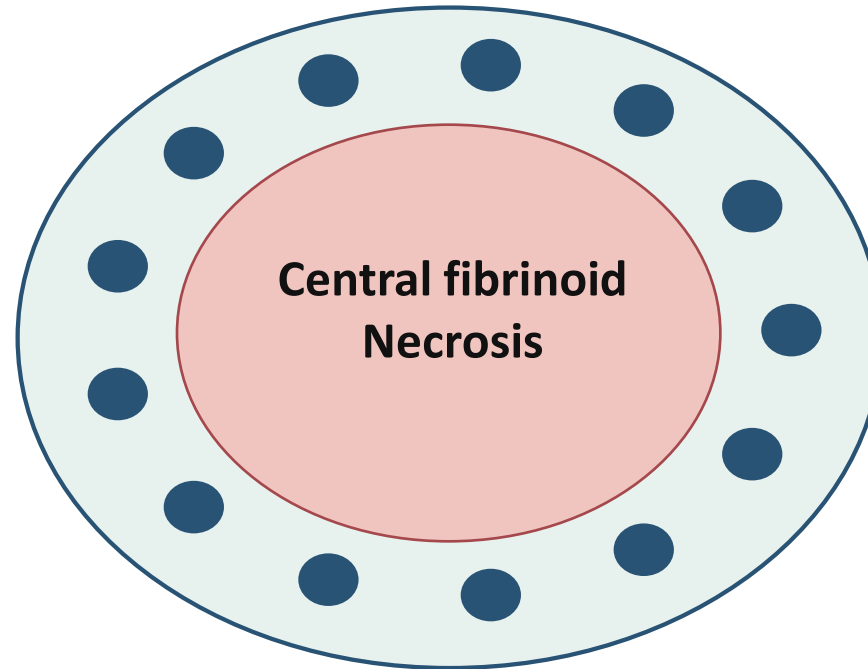
Pannus is tissue, not simply joint fluid: It invades cartilage and erodes bone.

RA synovium: Hyperplasia, follicles, and vascular growth

- Hyperplastic synoviocytes create villous synovial contours.
- CD4+ T cells, B cells, plasma cells, macrophages, and dendritic cells infiltrate.
- B cells may form lymphoid follicles; New vessels reflect angiogenesis.
- Fibrin-rich surface exudates may contain neutrophils.

Rheumatoid nodule: Palisading around fibrinoid necrosis

Palisaded activated
Macrophages



Peripheral lymphocytes
And plasma cells

RA distribution: Small-joint symmetric inflammatory arthritis

- Metacarpophalangeal and proximal interphalangeal joints are characteristic.
- Hand and foot joints typically precede wrists and larger articulations.
- Warm, swollen, painful joints are prominent.
- Stiffness and pain are most pronounced after inactivity or in the morning.

RA serology: Informative but not universally positive

ACPA

- Targets citrullinated protein epitopes.
- Supports diagnosis and can be associated with more persistent disease.
- Negative ACPA does not exclude RA.

Rheumatoid factor

- Often IgM or IgA binding the Fc portion of IgG.
- Not specific to RA and not present in all patients.
- Seronegative RA is a clinical–radiologic diagnosis.

RA imaging captures inflammatory bone and cartilage injury

- Periarticular osteopenia accompanies chronic inflammatory arthritis.
- Marginal erosions reflect osteoclast-mediated bone resorption.
- Joint-space loss reflects cartilage destruction.
- Late disease can develop destructive deformities and ankylosis.

Extraarticular RA arises beyond articular synovium

- Subcutaneous rheumatoid nodules have fibrinoid necrosis and macrophage rims.
- Vasculitic injury may involve arterial walls.
- Pleural, pericardial, and pulmonary inflammatory lesions may occur.
- Ocular complications include uveitis and keratoconjunctivitis.

Osteoarthritis versus rheumatoid arthritis

Feature	Osteoarthritis	Rheumatoid arthritis
Primary injury	Mechanical cartilage degeneration	Autoimmune synovitis
Inflammation	Usually secondary and mild	Primary and often severe
Articular pathology	Fibrillation, osteophytes, cysts	Pannus, erosions, ankylosis
Serology	No characteristic autoantibodies	ACPA or rheumatoid factor may occur
Systemic lesions	Not typical	May occur in multiple organs

Why OA and RA produce different late morphology

OA: Failed cartilage maintenance

- Articular cartilage fragments.
- Eburnation and sclerosis appear.
- Osteophytes develop at joint margins.
- Inflamed pannus is not the dominant lesion.

RA: Proliferative synovial destruction

- Immune-rich villous synovium expands.
- Pannus invades articular cartilage.
- Bone erosions accompany inflammation.
- Ankylosis may follow progressive destruction.

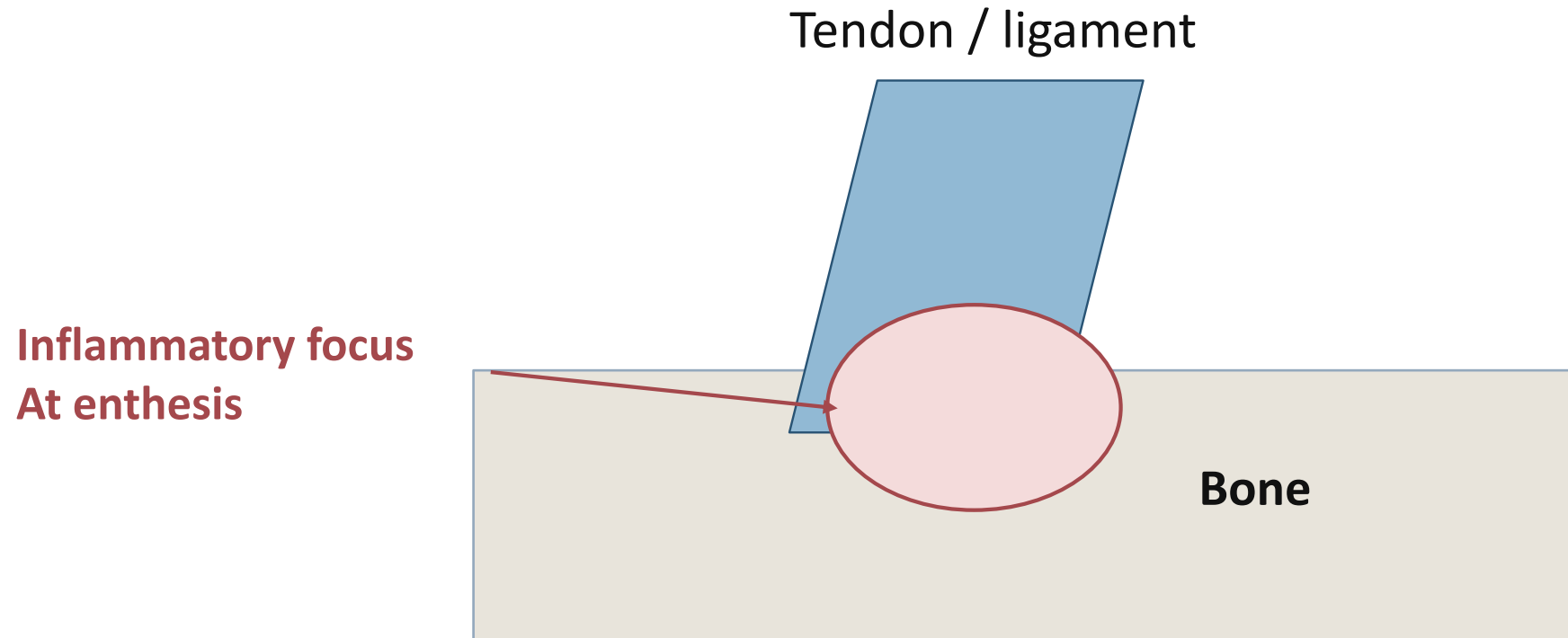
Juvenile idiopathic arthritis is a heterogeneous childhood group

- Onset occurs before age 16 and arthritis persists at least six weeks.
- Oligoarthritis and large-joint involvement are relatively common.
- Systemic inflammatory manifestations occur in some subgroups.
- ANA positivity is common; Rheumatoid nodules are usually absent.

Seronegative spondyloarthropathies target entheses

- Rheumatoid factor is typically absent.
- Inflammation concentrates at ligament and tendon insertions.
- Sacroiliac and vertebral joints are frequently involved.
- HLA-B27 association and new bone formation with ankylosis are shared features.

Enthesitis: Inflammation at tendon–bone attachment

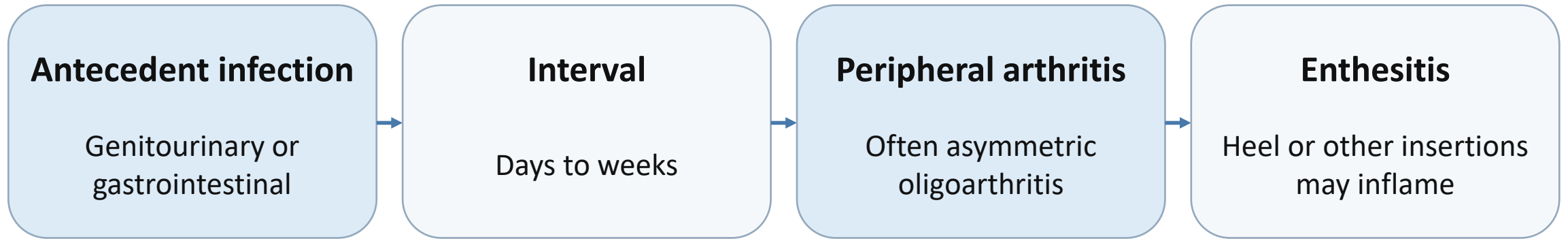


Inflammation at insertion sites helps distinguish spondyloarthropathy from primary synovitis.

Ankylosing spondylitis: Axial inflammation and fusion

- Sacroiliac and vertebral apophyseal joints are prominent targets.
- Patients often present with inflammatory low back pain and reduced mobility.
- Articular destruction and new bone formation may cause bony ankylosis.
- HLA-B27 is associated, but its precise pathogenic role remains uncertain.

Reactive arthritis follows an extraarticular infection



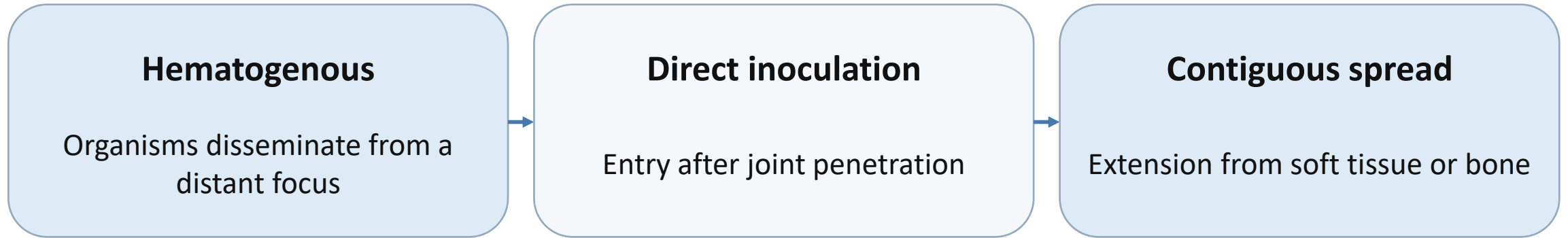
Pathologic interpretation

- Triggers mentioned include Chlamydia and enteric bacterial infections.
- Joint symptoms are postinfectious; The classic triad need not be complete.

Reactive arthritis: Recognize the peripheral–extraarticular cluster

- Asymmetric lower-limb arthritis often affects the knee.
- Achilles tendon or plantar fascial enthesitis may produce heel swelling.
- Dactylitis produces diffuse “sausage-like” digit swelling in some patients.
- Conjunctivitis, uveitis, urethritis, cervicitis, and mucosal lesions may coexist.

Infectious arthritis: Three routes to the joint



Pathologic interpretation

- Articular cartilage regenerates poorly after rapid infectious destruction.
- The affected joint may become permanently damaged.

Suppurative bacterial arthritis is a destructive emergency

- An acute bacterial joint infection often arises through bloodstream spread.
- *S. Aureus* is the dominant cause in the United States.
- Host factors and exposure settings influence other likely organisms.
- Delay in recognition can permit rapid permanent cartilage damage.

Suppurative arthritis: Clinical context suggests organisms

Setting	Source-associated consideration
Neonate	Group B Streptococcus; spread from osteomyelitis
Sickle cell disease	Salmonella susceptibility
Terminal complement C5–C9 deficiency	Disseminated gonococcal infection
Immunodeficiency or injected substance use	Increased risk of septic arthritis

Acute suppurative arthritis: Aspirate the inflamed joint

- Typically presents abruptly with intense pain and limited movement.
- Warmth, swelling, fever, leukocytosis, and high CRP are common.
- Most cases are monoarticular; Large joints are frequent sites.
- Purulent aspirate with an identifiable organism supports diagnosis.

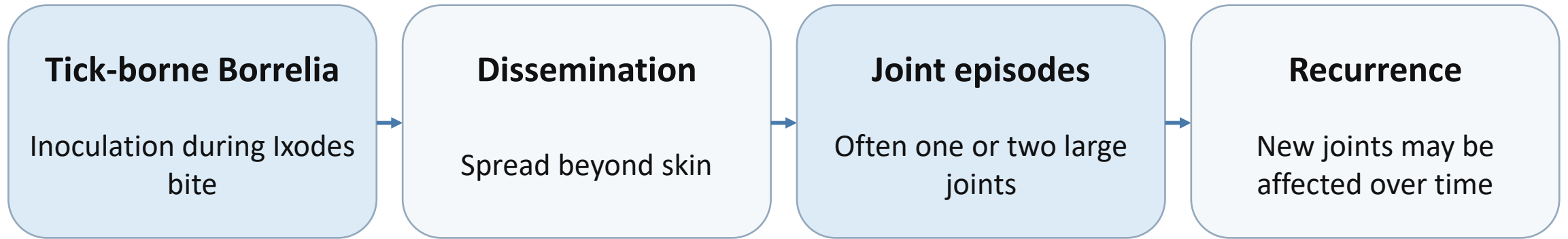
Mycobacterial arthritis: Granulomatous chronic damage

- M. Tuberculosis can reach a joint through blood or adjacent osteomyelitis.
- The course is insidious, with progressively increasing pain.
- Confluent caseating granulomas form in infected synovium.
- Erosive pannus and eventual fibrous ankylosis may obliterate the joint space.

Viral arthritis can be infectious or immune-mediated

- Reported causes include alphaviruses, parvovirus B19, and rubella.
- Epstein–Barr virus and hepatitis B or C also can be associated.
- The course varies from acute to subacute.
- Joint symptoms may reflect direct infection or immune responses triggered by infection.

Lyme arthritis: A joint manifestation after dissemination



Pathologic interpretation

- The knee is a particularly common site.
- Earlier treatment of infection reduces subsequent arthritis risk.

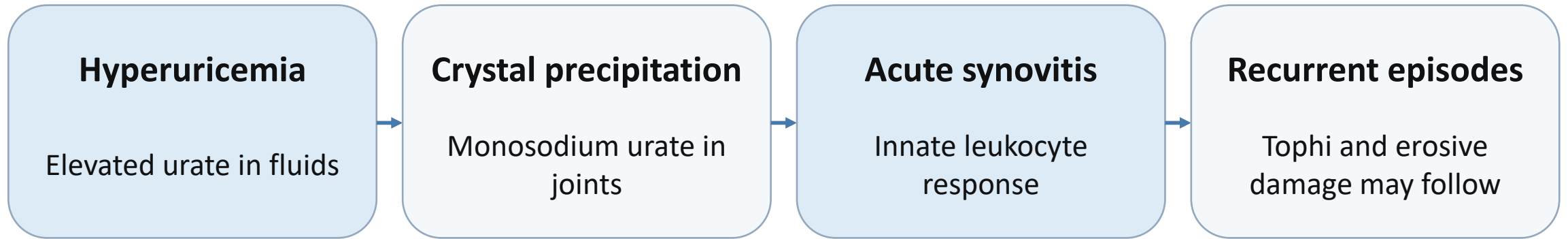
Lyme arthritis: Serology and persistent inflammation

- Serologic anti-Borrelia antibody testing is central to diagnosis.
- Borrelia DNA may also be detected in synovial fluid using PCR.
- Most cases respond to appropriate antimicrobial treatment.
- Persistent arthritis after treatment may reflect a postinfectious immune process.

Crystal-induced arthritis is an innate inflammatory response

- Monosodium urate crystals cause gout.
- Calcium pyrophosphate crystals produce CPP deposition disease (CPPD).
- Basic calcium phosphate and prosthetic wear debris are additional triggers.
- Crystal deposits provoke joint inflammation that can damage cartilage.

Gout requires urate excess plus joint crystallization



Pathologic interpretation

- Urate elevation is necessary but insufficient for clinical gout.
- Not every person with hyperuricemia develops symptomatic disease.

Urate can increase through production or impaired excretion

Overproduction

- Uric acid is the terminal product of purine catabolism.
- High cell turnover and purine salvage defects increase urate synthesis.
- HGPRT defects illustrate disturbed purine salvage.

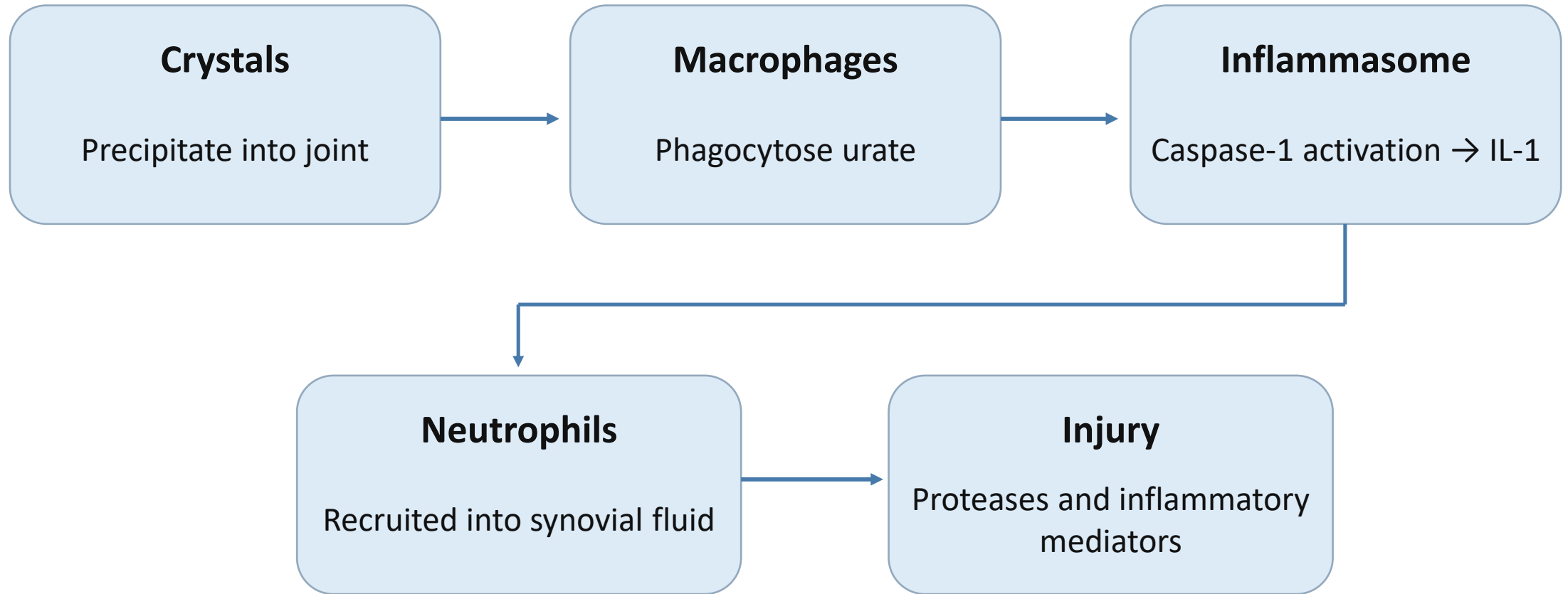
Underexcretion

- Reduced renal clearance is common in primary gout.
- Transport genes contribute to urate homeostasis.
- Chronic renal disease and some medications reduce excretion.

Factors influencing symptomatic gout

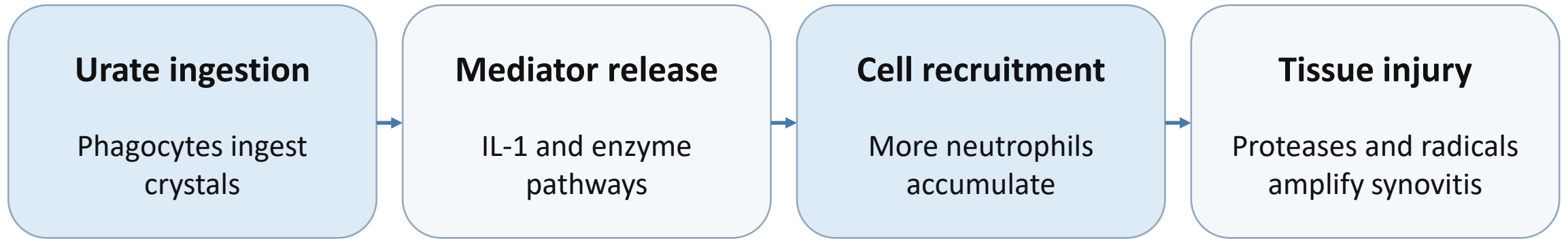
- Prolonged elevation of serum urate increases the opportunity for crystallization.
- Genetic variants can influence transport, ion handling, and inflammation.
- Obesity and alcohol exposure are associated with risk.
- Diuretic use may reduce renal urate excretion.

Urate crystals amplify acute innate inflammation



Recurring neutrophil recruitment sustains the acute flare.

Acute gout becomes self-amplifying after neutrophil influx



Pathologic interpretation

- Phagolysosome damage and complement contribute to inflammation.

Acute gout pathology is neutrophil-rich crystal synovitis

- Synovial fluid and membrane contain dense neutrophilic infiltrates.
- Slender urate needles may be found within aspirated neutrophils.
- Crystals display negative birefringence with compensated polarized microscopy.
- Inflammation subsides as crystallization episodes resolve.

Tophaceous gout represents persistent crystal burden

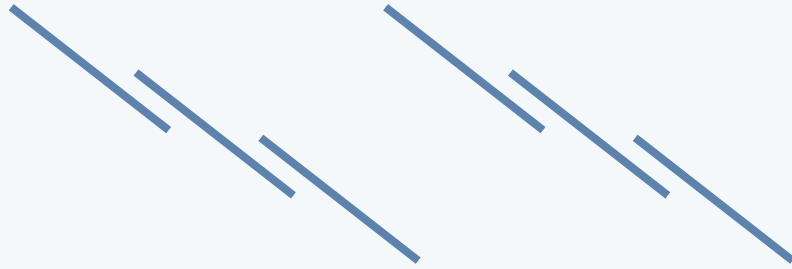
- Tophi are aggregates of urate surrounded by foreign-body giant cells.
- Deposits may involve synovium, cartilage, tendons, bursae, and soft tissue.
- Tophaceous synovitis causes juxtaarticular erosions and cartilage loss.
- Extraarticular deposits can be associated with renal complications.

Gout: Four clinical phases

Stage	Clinical–pathologic phenotype
Asymptomatic hyperuricemia	Excess serum urate without acute synovitis
Acute gouty arthritis	Abrupt, severe, often monoarticular inflammation
Intercritical gout	Symptom-free interval between attacks
Chronic tophaceous gout	Persistent tophi with structural erosive damage

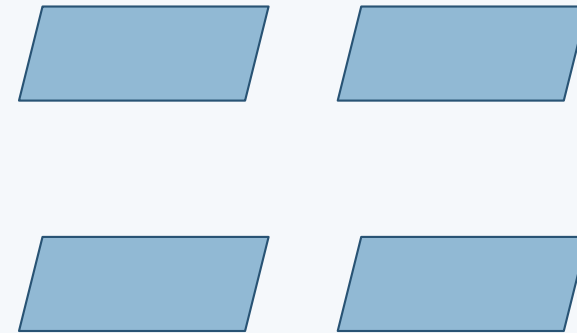
Crystal morphology: Urate versus calcium pyrophosphate

Monosodium urate (gout)



Slender needle-shaped crystals
Negative birefringence

Calcium pyrophosphate (CPPD)



Rhomoid crystals
Positive birefringence

CPPD: Crystallization within cartilage precedes synovitis

- CPP crystals accumulate in hyaline cartilage and fibrocartilage.
- Proteoglycan loss is thought to favor mineral deposition around chondrocytes.
- Deposits can disrupt the matrix even without overt inflammation.
- Crystals entering the joint activate the inflammasome and IL-1 pathways.

CPPD is not synonymous with a symptomatic attack

- CPPD may be silent despite cartilage crystal deposits.
- Acute or subacute attacks commonly affect the knee or wrist.
- Chronic joint pain may resemble OA or RA.
- Chondrocalcinosis on imaging identifies calcification, not necessarily clinical arthritis.

Gout versus CPPD: Microscopy and joint pattern

Characteristic	Gout (urate)	CPPD
Crystal morphology	Needle-shaped	Rhomboid
Compensated polarization	Negative birefringence	Positive birefringence
Primary deposition	Synovial / periarticular urate	Cartilage / fibrocartilage CPP
Typical acute site	First MTP joint common	Knee and wrist common
Distinctive chronic finding	Tophi and erosions	Chondrocalcinosis ± joint damage

CPPD associations may point to an underlying condition

- Many cases are age-associated and sporadic.
- Secondary CPPD can be associated with prior joint damage.
- Reported systemic associations include hyperparathyroidism and hemochromatosis.
- Hypomagnesemia, hypothyroidism, ochronosis, and diabetes are also listed.

An acutely swollen joint: Mechanism-based triage

Acute painful joint with swelling

Infection

Abrupt monoarthritis
Identify organism in aspirate

Crystal disease

Identify urate or CPP crystals
By polarization

Immune-mediated

Pattern of chronic synovitis
And other-organ findings

Suspected suppurative arthritis requires prompt aspiration and evaluation.

Mechanism-based differential: Identify the decisive lesion

Pattern	Leading pathology clue
Slow mechanical pain	Cartilage fibrillation, osteophytes, eburnation
Symmetric small-joint inflammation	Hyperplastic immune-rich synovium and pannus
Axial pain with enthesitis	Insertion-site inflammation and possible ankylosis
Explosive hot monoarthritis	Exclude bacterial seeding; evaluate joint aspirate
Episodic crystal arthritis	Synovial crystals with neutrophilic inflammation

Illustrative case: Mechanical versus immune-mediated symptoms

- A 69-year-old develops knee pain with walking and gradually worsening crepitus.
- Finger radiographs show prominent distal interphalangeal osteophytes.
- There is no sustained inflammatory small-joint swelling.
- Question: Which cartilage and bone lesions should be expected?

Case interpretation: Degenerative architecture is expected

- The presentation favors osteoarthritis over rheumatoid arthritis.
- Expected pathology: Fissured cartilage, chondrocyte clusters, and eventual eburnation.
- Peripheral osteophytes and subchondral cysts may develop.
- ACPA or rheumatoid factor are not central to this degenerative diagnosis.

Illustrative case: An acutely painful swollen knee

- A patient develops sudden severe monoarticular knee pain with fever.
- The joint is warm and movement is markedly restricted.
- The history also includes previous gout attacks.
- Question: What competing mechanisms must be considered immediately?

Case interpretation: Do not overlook suppurative arthritis

- Bacterial infection may rapidly destroy articular cartilage.
- Joint aspiration can identify an organism in purulent fluid.
- Crystal-associated synovitis also causes abrupt neutrophilic inflammation.
- Urgent exclusion of infection takes precedence over assuming a gout flare.

Arthritis: Anchor the diagnosis to the mechanism

Category	Primary lesion	Highest-value clue
Osteoarthritis	Cartilage breakdown	Osteophytes and eburnation
Rheumatoid arthritis	Immune proliferative synovitis	Pannus with marginal erosion
Spondyloarthritis	Enthesis / axial inflammation	Enthesitis and ankylosis
Infectious arthritis	Microbial joint injury	Organism in inflammatory aspirate
Crystal disease	Crystal-driven innate inflammation	Urate or CPP crystals

Source reference and further reading

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Elsevier; 2026. Chapter 26, “Bones, Joints, and Soft Tissue Tumors,” pp. 1088–1097.
- Sections: Joints; Arthritis; Osteoarthritis; Rheumatoid Arthritis; Spondyloarthropathies; Infectious Arthritis; Crystal-Induced Arthritis.
- Chapter 26, Table 26.5: Comparative Features of Osteoarthritis and Rheumatoid Arthritis.
- Chapter 26, Figs. 26.30–26.39: mechanisms and morphology of arthritis.