Rheumatology

New - 2016

LABS

OVERVIEW

Know everything covered in this topic area about Labs! If this is your first time through the Rheumatology section, go over this topic several times before you continue. What you learn here will enable you to make better sense of lab references later in this section.

Remember: No single blood test makes any rheumatologic diagnosis. For example, ANA can be positive in many non-rheumatologic diseases and in healthy individuals. The key is whether the test results match the clinical picture.

To interpret a test result, it is important to understand the sensitivity and specificity of the test. **Sensitivity** is the proportion of those with a positive test result among patients with disease; tests that are very sensitive are useful for "ruling out" the disease. **Specificity** is the proportion of those with a negative test result among patients without disease; tests that are very specific are useful for "ruling in" the disease.

ANTINUCLEAR ANTIBODIES

ANA

Antinuclear antibodies (ANA) are autoimmune antibodies that attack components of the nucleus. They are found in many autoimmune disorders. The most common ANA tests:

- Indirect immunofluorescence
- Enzyme-linked immunosorbent assay (ELISA)

Indirect immunofluorescence is more sensitive; ELISA is less expensive.

Results are reported as titers (e.g., 1:320), with a particular pattern when positive.

Titers show the dilution at which the antibodies become undetectable. It is shown in doublings: 1:40, 1:80, 1:160, 1:320, 1:640, etc.—so, the higher the titer, the more antibodies in the serum.

Patterns are determined by looking at a specially prepared fluorescent stain slide to ascertain where the antibodies attack the nucleus. There are 6 different patterns: centromere, rim or peripheral, speckled, diffuse, homogenous, and nucleolar. While ANA patterns may provide some information, they do not identify the specific antibody present, nor are they specific for any particular disease. The homogenous and rim patterns can be observed in systemic lupus erythematosus (SLE). Anti-centromere patterns are suggestive of anti-centromere antibodies, which are seen with the limited form of systemic sclerosis (formerly known as **CREST**—**c**alcinosis, **R**aynaud's, **e**sophageal dysmotility, **s**clerodactyly, **t**elangiectasia).

ANA titers are considered positive only if > 1:80. Titers > 1:320 are considered clinically relevant for autoimmune diseases. Some rheumatologic diseases that are ANA+:

- Drug-induced lupus (100%)
- SLE (98–100%): Note that ANA-negative lupus is rare; so ANA is pretty useful for ruling out SLE!
- Mixed connective tissue disease (MCTD; 93–100%)
- Limited systemic sclerosis and diffuse systemic sclerosis (60–90%)
- Sjögren syndrome (48–70%)
- Polymyositis/dermatomyositis (60%)
- Rheumatoid arthritis (RA; 40%)

Example of ruling in vs. ruling out: The ANA is positive in almost all patients with SLE (high sensitivity) but also is positive in many other diseases (low specificity). So, a negative ANA test is helpful for ruling out SLE, but a positive test is poor for ruling it in.

The patterns found with fluorescent staining differ with the various types of ANA patterns. These different ANA attack different points in the nucleus, causing various diseases. We now have tests (below) that identify these antibodies far more precisely than with fluorescent staining.

When the ANA is positive and you suspect a specific rheumatologic disease, order the more specific antibody subtypes (ANA profile). Know which diseases are also associated with specific subtypes (Table 6-1 on page 6-2). Again, the general ANA test is not specific enough to diagnose any disease, only to rule one out.

Specific ANA Tests

Anti-dsDNA (in high titer) and **anti-Smith** (anti-Sm) are very specific for SLE. If one or both of these are strongly positive, the diagnosis of SLE is strongly supported. However, patients with drug-induced lupus can have antibodies to anti-dsDNA (hence, they are ANA positive also).

Anti-U1-RNP is very sensitive for MCTD but not very specific because it can be seen in SLE and other connective tissue diseases. In general, absence of the antibody excludes MCTD. Anti-U1-RNP and anti-dsDNA are often seen together because they bind to related antigens known as epitopes. An epitope, also known as antigenic determinant, is the part of an antigen that is recognized by the immune system. The term epitope is often used interchangeably when describing an antigenic component of a cell.

The clinical significance of **anti-ribosomal P protein** antibodies is their specificity for the diagnosis of SLE. These antibodies have not been found in normal controls and are rare in patients with other autoimmune diseases. There are studies suggesting an association and/or predisposition with CNS and liver disease in

Table 6-1: Antinuclear Antibody Disease Associations

Antibody	Subclass	Associated with:
Specific ANAs	Anti-dsDNA	Specific for SLE; an indicator of disease activity (as are complement levels) and identifies SLE patients with potential for significant renal disease. Absent in classic drug-induced SLE; sometimes develops in patients treated with TNF inhibitors.
	Anti-Sm	Specific for SLE.
	SSA (Ro)	SLE, neonatal SLE, Sjögren's, and sometimes myositis. Usually not found in scleroderma; passively transferred from mother to baby → neonatal heart block. DR3 is associated with SSA.
	SSB (La)	SLE and Sjögren's; sometimes found in patients with +SSA. Also passively transferred from mother to baby → neonatal heart block.
	Anti-U1-RNP	Sensitive for MCTD; also found in SLE—usually in association with anti-Sm or anti-dsDNA.
	Antihistone	Drug-induced lupus and SLE. Mainly used to rule out drug-induced lupus caused by procainamide, hydralazine, chlorpromazine, and quinidine.
	Anti-centromere	Limited scleroderma; identifies increased incidence of pulmonary arterial hypertension and improved survival.
	Anti-Scl-70 (Anti-topoisomerase I)	Progressive systemic sclerosis; identifies increased incidence of interstitial lung disease and reduced survival.
	Antisynthetases	Anti-Jo-1 = type of anti-synthetase antibody; associated with myositis; identifies increased incidence of interstitial lung disease. Anti- SRP (signal recognition protein) is associated with cardiomyopathy and refractory to treatment.

lupus patients. Do not confuse anti-ribosomal with anti-ribonucleoprotein antibodies (not the same)!

Antihistone antibody can be seen both in SLE and drug-induced lupus. The antihistone antibody test is very sensitive (> 95%) for drug-induced lupus (DIL). Drugs commonly associated with DIL include: procainamide, hydralazine, chlorpromazine, isoniazid, sulfasalazine, methyldopa, quinidine, minocycline, and anti-TNF agents. The absence of the antihistone antibody effectively rules out DIL in patients taking any of these agents, with the exception of patients who are on anti-TNF therapy or minocycline. It is rare to see antihistone antibodies in patients on anti-TNF biologics or minocycline, even though they manifest symptoms suggestive of DIL. Further information on DIL can be seen on page 6-17.

Anti-Scl-70 (a.k.a. **anti-topoisomerase I**) is specific for progressive systemic sclerosis, formerly known as diffuse scleroderma; it is present in ~ 75% of cases. Its presence supports a diagnosis of a systemic, diffuse process (not a limited cutaneous one) and is associated with progressive skin involvement, pulmonary fibrosis, and a higher mortality.

Before going further, let's clarify the terms **Ro** and **La**. Anti-Ro (or just "Ro") was the term given for the specific ANA antibody causing the "speckled" ANA pattern found mainly in SLE and Sjögren syndrome. During the same period, a serum antibody was discovered in these patients, which was named anti-SSA (or SSA). These 2 antibodies turned out to be the same antibody. So, these terms can be used interchangeably—you commonly see them together; e.g., Ro/SSA, SSA (Ro). Similarly, SSB is identical to La and commonly seen as La/SSB or SSB (La). The "SS" in SSA and SSB stands for Sjögren syndrome. The most important thing to remember about Ro and La is their association with congenital heart block. Patients with SLE who are pregnant or who plan to become pregnant should be tested for Ro and La antibodies.

ANCA

Anti-neutrophil cytoplasmic antibodies (ANCAs) are, as the term indicates, autoimmune antibodies against antigens in the cytoplasm of neutrophils. ANCAs are markers for vasculitis, including drug-induced vasculitis (Table 6-2).

It is thought that the vasculitis may be caused by the ANCA antibodies, which stimulate the release of lytic enzymes from neutrophils.

QuickQuiz

- What two ANA subtypes are specific for a diagnosis of SLE?
- Anti-U1-RNP is a very sensitive indicator for what rheumatologic disorder?
- Which antibody is associated with drug-induced lupus?
- Which drugs are associated with drug-induced lupus?
- Which rheumatologic disease is associated with a positive c-ANCA and anti-PR3?
- Name 2 diseases that are p-ANCA+ and anti-MPO+.

Two ANCAs are identified by their immunofluorescence (IF) pattern:

1) c-ANCA: Antibodies are diffuse in the cytoplasm.
2) p-ANCA: Antibodies are perinuclear.

These ANCAs can then be subdivided based on the antigen, or epitope, they are directed against: anti-proteinase 3 (anti-PR3; PR3 ANCA) or anti-myeloperoxidase (anti-MPO; MPO ANCA). Laboratories determine these antigens using an enzyme-linked immunosorbent assay (ELISA). This further analysis of the ANCA helps you narrow down a diagnosis.

So again, we have 2 ANCAs (c-ANCA and p-ANCA) that are further categorized, based on ELISA, into whether or not antibodies are directed against the PR3 or MPO antigens. (Proteinase 3 and myeloperoxidase are enzymes located in neutrophil cytoplasmic alpha granules.)

1) c-ANCA—anti-PR3
2) p-ANCA—anti-MPO

c-ANCA and anti-PR3 are strongly related while p-ANCA and anti-MPO are more loosely related. PR3 antigens usually cause the diffuse pattern seen in c-ANCA+ IF tests.

The combination of c-ANCA+ and anti-PR3+ is very specific for granulomatosis with polyangiitis (GPA; previously Wegener granulomatosis).

p-ANCA is less helpful because this IF pattern is nonspecific. Table 6-2 shows you that many diseases are p-ANCA+ (especially in the anti-MPO category). Further test any p-ANCA+ results with ELISA for anti-MPO antibodies.

If a patient is anti-MPO+, think vasculitis: microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), Churg-Strauss, pauci-immune rapidly progressive glomerulonephritis (RPGN), anti-GBM disease, and drug-induced ANCA-associated vasculitis.

The most common causes of anti-MPO+ drug-induced ANCA-associated vasculitis are the anti-thyroid drugs propylthiouracil (PTU) and methimazole. Many other drugs are much less commonly associated.

In summary:

- c-ANCA+ plus anti-PR3+: Think GPA.
- p-ANCA+ plus anti-MPO+: Think MPA, EGPA, Churg-Strauss, pauci-immune RPGN, Anti-GBM, and drug-induced.

The sensitivity and specificity of these antibody tests are, in general, not high enough for them to be used for screening. Pretest probability of the disease in question is important and should be considered before ordering ANCAs.

COMPLEMENT

The complement system is comprised of a variety of small proteins that function to enhance, or complement, the action of antibodies and phagocytic cells. Hypocomplementemia is seen in SLE, vasculitis, rheumatoid arthritis, and infective endocarditis.

There is more on the complement pathway in Allergy & Immunology, Book 4. But note: Complement components can be decreased due to a genetic deficiency, consumption during complement activation, or underproduction—as in eclampsia or **HELLP** syndrome (**h**emolysis, **e**levated **l**iver enzymes, **l**ow **p**latelets).

Table 6-2: ANCAs

IF ANCA	ELISA	Disease
c-ANCA	Anti-PR3+	GPA
p-ANCA	Anti-MPO+	MPA EGPA Churg-Strauss Pauci-immune RPGN Anti-GBM disease Drug-induced; e.g., PTU, methimazole
	Anti-MPO–	Crohn disease Ulcerative colitis Chronic active hepatitis Primary sclerosing cholangitis Primary biliary sclerosis Chronic arthritides

Know:

- **C2** or **C4**—usually a genetic allele deficiency.
- **C3** is consumed with any activation of the complement pathway (classical or alternative).
- **C4** is consumed only with activation of the classical pathway (as with SLE).
- **CH50** assay measures total hemolytic complement of the classical pathway and requires all components (C1–C9) of the classical pathway for a normal result.

The CH50 assay is most useful as a screening tool for disease states resulting in hypocomplementemia. A low CH50 should prompt you to order the individual complements listed above to help you in your diagnosis. For example, patients with recurrent or severe neisserial (meningococcal or gonococcal) infections may have terminal complement deficiency (C5–C9). Patients with SLE may have low C3 and C4; C3 is a more sensitive index of disease activity in SLE. Therefore, normalization of individual complement levels and CH50 can be used to follow disease activity.

RHEUMATOID FACTOR AND ANTI-CCP

Rheumatoid factor (RF) is an auto-antibody that binds to the Fc region of IgG. It is positive in 80–85% of patients with RA, which makes RF a fairly sensitive test for RA, but it is not specific because a positive RF can be seen in other diseases, including: chronic lung disease, chronic infections (e.g., TB, HIV, viral hepatitis), Sjögren's, SLE, infectious endocarditis, and hematologic malignancies.

The anti-citrullinated cyclic peptide (anti-CCP antibody), however, is highly specific for RA (specificity ~ 97%) and tends to portend a poorer prognosis. The presence of both RF and anti-CCP antibodies is associated with more aggressive RA and extra-articular manifestations (e.g., rheumatoid nodule, rheumatoid lung/interstitial lung disease).

Table 6-3: Incidence of HLA-B27

Ankylosing spondylitis	90%
Reactive arthritis; typically secondary to GU/GI infections	60–80%
C. jejuni and *C. trachomatis* arthropathy	50%
Uveitis	50%
Healthy Caucasian population	7–8%
Rheumatoid arthritis, osteoarthritis, rubella arthritis	10%

Although it does not cause reactive arthritis, *Klebsiella pneumoniae* has an enzyme (not encoded) that cross-reacts with the HLA-B27 test.

MAJOR HISTOCOMPATIBILITY COMPLEX: HUMAN LEUKOCYTE ANTIGENS

Overview

There are 2 main classes of major histocompatibility complex (MHC) human leukocyte antigens (HLA) antigens:

- Class I includes the HLA-A, HLA-B, and HLA-C antigens, which interact with CD8 or T suppressor cells.
- Class II includes the HLA-D antigens; e.g., DR2, DR3, and DR4, which interact with CD4 or T helper cells.
- Note: An easy way to remember this relationship between MHC and CD T cells is that both form a product of 8—MHCI x CD8 = 8, while MHCII x CD4 = 8.

HLA-B27

Know when HLA-B27 is found:

- Reactive arthritis: 60–80%, higher when sacroiliitis is present.
- Ankylosing spondylitis (AS): 90%.
- Psoriatic arthritis: up to 60% (particularly with spinal/axial disease).
- Inflammatory bowel disease (IBD) with associated axial joint arthritis: up to 60%. But there is no HLA-B27 association when only appendicular joint disease is present in IBD patients.

Note that if axial disease is present, HLA-B27 is typically positive. Keep in mind that 7–8% of the healthy Caucasian North American population carries this haplotype; therefore, an individual with HLA-B27 has only a 10–20% risk of developing an HLA-B27-related disease. Consequently, this test has limited clinical usefulness if not ordered in the right clinical scenario. A negative HLA-B27 test is useful in ruling out ankylosing spondylitis. See Table 6-3.

HLA-DR2, 3, 4

DR2 and DR3 are associated with SLE. DR3 is occasionally found in Sjögren syndrome and polymyositis. DR4 antigens are associated with severe RA. More in Allergy & Immunology, Book 4.

Other important general HLA associations to know:

1) HLA-B5701 is strongly associated with abacavir hypersensitivity reaction (see Infectious Disease, Book 1).
2) HLA-B51 is associated with Behçet disease.
3) HLA-DQ2/DQ8 is associated with celiac disease (see Gastroenterology, Book 1).

Quick Quiz

- Name 2 diseases that consume complement during a flare.
- Other than rheumatoid arthritis, a positive RF can be seen with what other diseases?
- What antibody test is more specific than RF for rheumatoid arthritis?
- Compare and contrast "normal," "noninflammatory," "inflammatory," and "septic" joint fluid. (See Table 6-4.)
- Describe gout crystals and their birefringence.

ERYTHROCYTE SEDIMENTATION RATE AND C-REACTIVE PROTEIN

The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the most common acute phase reactants (APRs; inflammatory markers) used in clinical medicine. They are most helpful in determining disease activity and response to therapy.

Unfortunately, they are of limited diagnostic utility. Although they are sensitive markers of inflammation in general, they are not specific for any particular disease. Diagnostically, they are most helpful in ruling out inflammatory disease, especially when the pretest likelihood is low to moderate. Note that an extreme elevation of the ESR (> 100 mm/hr) is almost always a hallmark of serious underlying disease, most commonly malignancy, infection, or vasculitis.

THE JOINT

SYNOVIAL FLUID AND CRYSTAL ANALYSIS

Synovium and synovial fluid: Type A cells of the synovial membrane are phagocytic, whereas type B cells probably synthesize hyaluronic acid. Chondrocytes make the cartilage. Cartilage is avascular and depends on the synovial fluid for nutrients. The chondrocytes can produce only a limited amount of collagen, so only slight damage is repairable.

Joint fluid is categorized based on the inflammatory response (WBC/mm^3). The WBC count in aspirated joint fluid decreases rapidly, so analyze it immediately. See Table 6-4.

Also, know that frank blood (hemorrhagic joint) can be caused by trauma, bleeding diathesis, tumor, and pigmented villonodular synovitis (PVNS).

Look for crystals in inflammatory fluid using the polarizing microscope. Look for monosodium urate crystals (gout) and calcium pyrophosphate dihydrate (CPPD) crystals (pseudogout). Both types have 2 colors: blue and yellow; hence, they are termed "birefringent." The crystals are identified, however, by the color of the crystals that are parallel to the microscope's color compensator. (Crystals perpendicular to the color compensator are the opposite color.) Be concerned only about the crystal color that is parallel! If the crystals are yellow when parallel to the compensator, they are termed "negatively birefringent," and when they are blue, they are "positively birefringent."

Uric acid (gout) crystals are yellow when parallel to the compensator (negatively birefringent), and they are needle-like. (Helpful hint: The double Ls in "yellow" are parallel to each other.)

Table 6-4: Synovial Fluid Analysis

Joint Fluid	WBC (cells/mm^3)	Other Findings	Disease Associations
Normal	0–200	None RBC	Normal or OA Internal derangement
Noninflammatory	200–2,000	None RBC	OA, trauma, neuropathic joints, hypertrophic arthropathy, TB, PVNS; occasionally SLE, scleroderma, and rheumatic fever.
Inflammatory	2,000–50,000	None Intracellular, strongly negatively birefringent crystals (yellow) Intraceullar, weakly positively birefringent crystals (blue) RBC	RA, gout, pseudogout, SLE, scleroderma, reactive arthritis, ankylosing spondylitis, TB or fungal infection
Septic	50,000–100,000	None Organisms on Gram stain	Septic joint (but gonococcal septic joint can be 10,000 cells/mm^3) RA (very inflammed), gout, pseudogout

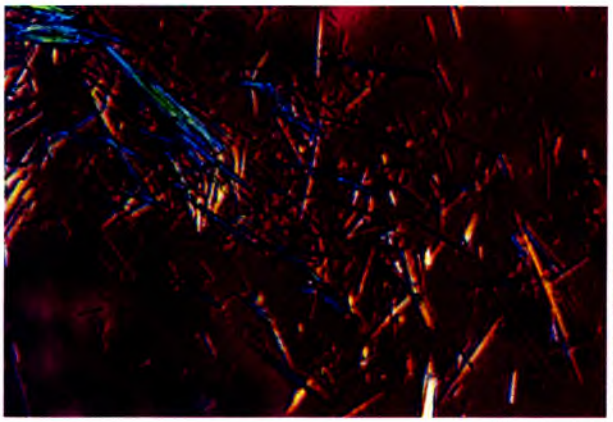


Image 6-1: Birefringent crystals

CPPD (pseudogout) crystals are blue (weakly positive birefringent) when parallel to the compensator; they appear as small, rhomboid structures.

CPPD crystals attract neutrophils and can cause a purulent joint similar to gout with high synovial fluid WBC count. To be very certain that the crystals are actually causing the inflammatory reaction in the joint, you must see intracellular crystals, which are crystals within the neutrophils, as opposed to crystals just floating around freely in the joint space. Important: Crystalline and infectious arthritis can coexist, so it is important to always send studies for both.

Again, you cannot simply look at a photo of a crystal and see whether it is positively or negatively birefringent; you must know the direction of the compensator dial. For instance, in Image 6-1, you see needle-shaped crystals (so probably uric acid), but you won't know they are negatively birefringent unless the compensator is vertical and the vertical crystals are yellow (yellow → parallel = gout).

IMAGING STUDIES

Weight-bearing knee films are the initial diagnostic tests of choice for nontraumatic knee disorders (RA or OA) because weight bearing allows a more realistic evaluation of the joint space. If necessary, MRI can visualize all the components, except for normal synovium (too thin).

GENETIC COLLAGEN DISORDERS

The inherited disorders of collagen encompass several different diseases, many of which cause hypermobility—e.g., Marfan syndrome, Ehlers-Danlos syndrome (EDS), and homocystinuria. Defects in elastic fiber formation (Marfan syndrome) or in type II collagen (Stickler syndrome) are well defined; different proteins are responsible for these syndromes.

The following are the ones to remember.

Marfan syndrome:

- Long limbs (outstretched arm length > height)
- Pectus excavatum (sternum dips inward), or pectus carinatum (sternum protrudes outward)
- Aortic aneurysm/dissection
- Ectopia lentis (lenses displaced upward)
- Heart valve disease

Ehlers-Danlos syndrome: variable skin hyperelasticity and joint hypermobility. Several classifications:

- Classic type (old Types I and II) = includes most severe form (easily scarred skin and hypermobile joints)
- Hypermobility type (old Type III) = manifestations predominantly joint, not skin
- Vascular type (old Type IV) = manifestations predominantly skin, not joint, and predilection for rupture of large vessels
- Several other rarer types

Osteogenesis imperfecta (OI): Defects in procollagen genes cause the variants, but all have:

- Osteopenia
- Multiple bone fractures
- Varying degrees of blue sclera
- Lucent (brittle) teeth
- Hearing loss

There are 7 types of OI; Type I is autosomal dominant and the mildest.

Pseudoxanthoma elasticum: autosomal recessive and involves skin (easy bruising), blood vessels, and eyes. The main problem is recurrent UGI bleeds as they affect the elastic media of blood vessels. Classic findings include a cobblestone appearance of the skin with yellow papules and plaques that resemble "plucked chicken skin" on the neck/axillae and angioid streaks on funduscopic exam. (But this also occurs in Paget disease!)

RHEUMATOID ARTHRITIS

OVERVIEW

The worldwide prevalence of RA is ~ 0.5–1%. Women outnumber men 3:1. The typical age of onset is 40–50 years. Etiology of RA is multifactorial and basically unknown. There is a low concordant incidence of RA in identical twins, but RA does seem to have some genetic basis (~ 10% of patients have a 1st degree relative with RA; higher concordance in identical twins than in fraternal ones).

It is now recognized that RA is a heterogeneous disease with various HLA polymorphisms resulting in anything from mild joint involvement to severely erosive

6 CONNECTIVE TISSUE AND JOINT DISEASES

Connective Tissue Diseases

Systemic Lupus Erythematosus

A. General characteristics

1. An autoimmune disorder leading to inflammation and tissue damage involving multiple organ systems.
2. Systemic lupus erythematosus (SLE) is an idiopathic chronic inflammatory disease with **genetic**, **environmental**, and **hormonal** factors involved.
3. The pathophysiology involves autoantibody production, deposition of immune complexes, complement activation, and accompanying tissue destruction/vasculitis.
4. Types
   a. Spontaneous SLE.
   b. Discoid lupus (skin lesions without systemic disease)
   c. Drug-induced lupus
   d. ANA-negative lupus—associated findings
      - Arthritis, Raynaud phenomenon, subacute cutaneous lupus
      - Serology: Ro (anti-SS-A) antibody-positive, ANA negative
      - Risk of neonatal lupus in infants of affected women

Quick HIT

Epidemiology of SLE
- **Women** of childbearing age account for 90% of cases.
- **African-American patients** are more frequently affected than Caucasian patients.
- Very mild in elderly patients; more severe in children.
- Usually appears in late childhood or adolescence.

B. Clinical features

1. Constitutional symptoms: Fatigue (often the sign of an impending exacerbation and a prominent finding in most patients), malaise, fever, weight loss
2. Cutaneous: Butterfly rash (erythematous rash over cheeks and bridge of nose—found in one-third of patients) (Figure 6-1), photosensitivity, discoid lesions (erythematous raised patches with keratotic scaling), oral or nasopharyngeal ulcers, alopecia, **Raynaud phenomenon** (vasospasm of small vessels when exposed to cold, usually in fingers—found in about 20% of cases)
3. Musculoskeletal: Joint pain (may be the first symptom of the disease—found in 90% of patients), arthritis (inflammatory and symmetric, not erosive as in rheumatoid arthritis [RA]), arthralgias, myalgia with or without myositis
4. Cardiac: Pericarditis, endocarditis (**Libman–Sacks endocarditis** is a serious complication), myocarditis
5. Pulmonary: Pleuritis (most common pulmonary finding), pleural effusion, pneumonitis (may lead to fibrosis), pulmonary HTN (rare)
6. Hematologic: Hemolytic anemia with anemia or reticulocytosis of chronic disease, leukopenia, lymphopenia, thrombocytopenia
7. Renal: Proteinuria >0.5 g/day (may have nephrotic syndrome), cellular casts, glomerulonephritis (may have hematuria), azotemia, pyuria, uremia, HTN
8. Immunologic: Impaired immune response due to many factors, including autoantibodies to lymphocytes, abnormal T-cell function, and immunosuppressive medications; often associated with antiphospholipid syndrome

Quick HIT

Clinical findings associated with ***neonatal lupus***
- Skin lesions
- Cardiac abnormalities (AV block, transposition of the great vessels)
- Valvular and septal defects

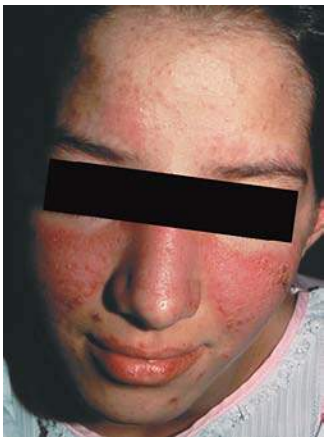


FIGURE 6-1 **SLE butterfly rash.**
(From Goodheart HP. *Goodheart's Photoguide of Common Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2003, Figure 25.24.)

9. GI: Nausea/vomiting, dyspepsia, dysphagia, peptic ulcer disease
10. CNS: Seizures, psychosis (may be subtle), depression, headaches, TIA, cerebrovascular accident
11. Other findings include conjunctivitis and an increased incidence of Raynaud phenomenon and Sjögren syndrome

C. Diagnosis

1. **Positive ANA screening test:** Sensitive but not specific; almost all patients with SLE have elevated serum ANA levels (see Clinical Pearl 6-1, Figure 6-2, and Table 6-1)
2. Anti-ds DNA (in 40%) and anti-Sm Ab (in 30%): The presence of either of these is diagnostic of SLE—very specific (but obviously not sensitive) (see Table 6-2)
3. Anti-ss DNA (in 70%)
4. **Antihistone Abs** (in 70%) are present in 100% of cases of **drug-induced lupus** (see Clinical Pearl 6-2). If negative, drug-induced lupus can be excluded.
5. **Ro (SS-A)** and **La (SS-B)** are found in 15% to 35%. Associated with:
   a. Sjögren syndrome
   b. Subacute cutaneous SLE
   c. Neonatal lupus (with congenital heart block)
   d. Complement deficiency (C2 and C4)
   e. ANA-negative lupus

CLINICAL PEARL 6-1

Useful Criteria for Diagnosing SLE

A patient has SLE if four or more of these 11 criteria are present at any time.

1. Mucocutaneous signs (each counts as one)
   - Butterfly rash
   - Photosensitivity
   - Oral or nasopharyngeal ulcers
   - Discoid rash
2. Arthritis
3. Pericarditis, pleuritic
4. Hematologic disease—hemolytic anemia with reticulocytosis, leukopenia, lymphopenia, thrombocytopenia
5. Renal disease: Proteinuria >0.5 g/day, cellular casts
6. CNS—seizures, psychosis
7. Immunologic manifestations—positive LE preparation, false-positive test result for syphilis, anti-ds DNA, anti-Sm Ab
8. ANAs

Quick HIT

Clinical Course of SLE
- A chronic disease characterized by exacerbations and remissions
- Malar rash, joint pain, and fatigue are the most common initial findings. With more advanced disease, renal, pulmonary, cardiovascular, and nervous systems are affected.

Quick HIT

Conditions in which ANAs are Elevated
- SLE
- RA
- Scleroderma
- Sjögren syndrome
- Mixed connective tissue disease
- Polymyositis and dermatomyositis
- Drug-induced lupus

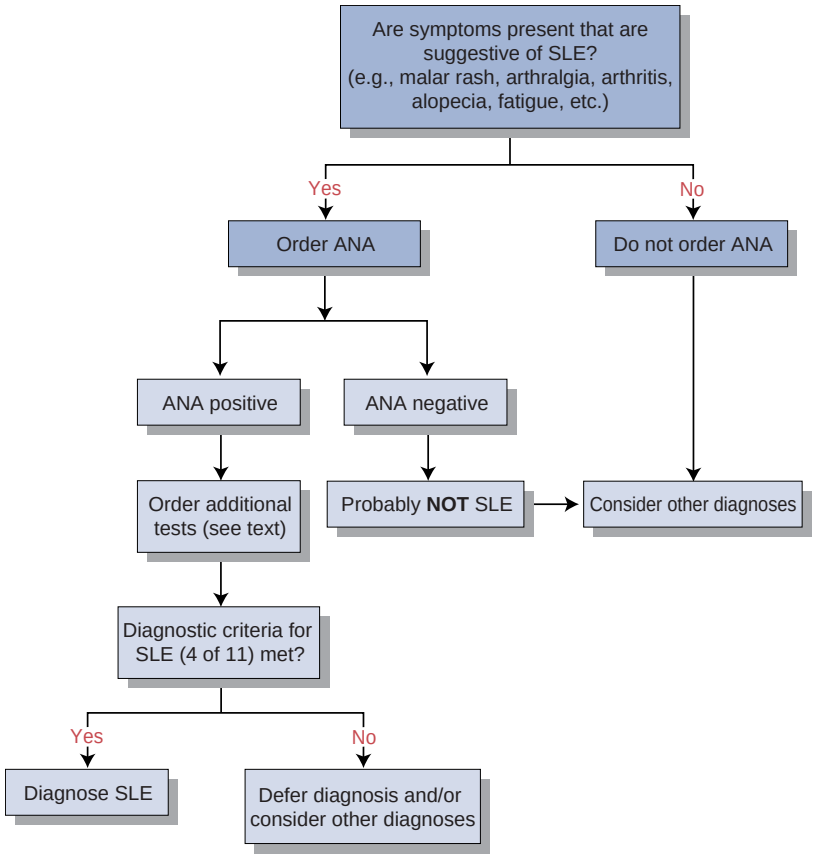


FIGURE 6-2 **Diagnosis of SLE.**

(Adapted from Humes DH, DuPont HL, Gardner LB, et al. *Kelley's Textbook of Internal Medicine.* 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2000:1387, Figure 178-3.)

TABLE 6-1 Common Laboratory Markers in Rheumatologic Diseases

Laboratory Marker	Conditions	Comments
ANAs	• SLE (almost all patients) • Scleroderma • Sjögren syndrome • Polymyositis	Highly sensitive for SLE but not for the others
RF	• RA (70% of patients) • Healthy populations (up to 3%)	Neither sensitive nor specific for RA
C-ANCA	Wegener granulomatosis	Sensitive and specific Can vary with disease activity
P-ANCA	Polyarteritis nodosa	70%–80% sensitive for microscopic PAN Not specific
Lupus anticoagulant	Antiphospholipid syndrome	
ESR	• Infection (acute or chronic) • Malignancy • Rheumatologic diseases • Miscellaneous (tissue necrosis, pregnancy)	• Low sensitivity and specificity • Major uses: Diagnose/rule out inflammatory process and monitor course of inflammatory conditions
C-reactive protein	• Inflammatory states and infection • Miscellaneous conditions (e.g., MI, vasculitis, trauma, malignancy, pancreatitis)	• Primarily used for infection—much more sensitive and specific than ESR • If levels are markedly elevated (>15), bacterial infection is likely present

TABLE 6-2 HLA Associations with Rheumatic Diseases

Disease	Associated HLA
SLE	HLA-DR2 and HLA-DR3
Sjögren syndrome	HLA-DR3
RA	HLA-DR4
Ankylosing spondylitis, Reiter syndrome, psoriatic arthritis	HLA-B27

6. Positive LE preparation: ANAs bind to nuclei of damaged cells, producing LE bodies
7. **False-positive test result for syphilis**
8. Complement levels are usually decreased
9. CBC, renal function tests (BUN, creatinine), urinalysis, serum electrolytes
10. Anticardiolipin and lupus anticoagulant (see Clinical Pearl 6-3)

D. Treatment

1. Avoid sun exposure because it can exacerbate cutaneous rashes
2. NSAIDs—for less severe symptoms
3. Either local or systemic **corticosteroids—for acute exacerbations**
4. Systemic steroids for severe manifestations
5. Best long-term therapy is antimalarial agents such as hydroxychloroquine—for constitutional, cutaneous, and articular manifestations. **Hydroxychloroquine** is continued as a preventative measure even after resolution of symptoms. Annual eye examination is needed because of **retinal toxicity**
6. Cytotoxic agents such as cyclophosphamide—for active glomerulonephritis
7. Monitor the following and treat appropriately:
   a. Renal disease, which produces the most significant morbidity
   b. HTN

Scleroderma (Systemic Sclerosis)

A. General characteristics

1. A chronic connective tissue disorder that can lead to widespread fibrosis.
2. Pathophysiology: Cytokines stimulate fibroblasts, causing an abnormal amount of collagen deposition. It is the high **quantity** of collagen that causes the problems associated with this disease (composition of the collagen is normal).
3. Scleroderma is more common in women. Average age of onset is 35 to 50 years.
4. There are two types of scleroderma: Diffuse (20%) and limited (80%) (see Table 6-3)

CLINICAL PEARL 6-2

Drug-induced Lupus

- Certain drugs may produce a lupus-like syndrome that is similar to SLE except that it **does not affect the CNS or kidneys.**
- If renal or CNS involvement is present, it is **not** drug-induced lupus. In addition, the classic butterfly rash, alopecia, and ulcers are typically not seen in drug-induced lupus.
- Most patients improve after withdrawal of the offending drug. Therefore, the prognosis is obviously more favorable.
- Commonly implicated agents include hydralazine, procainamide, isoniazid, chlorpromazine, methyldopa, and quinidine.
- Laboratory findings in drug-induced lupus: **Antihistone antibodies** are always present; there is an absence of anti-ds DNA and anti-Sm Ab.

Quick HIT

Steroids are the best treatment for SLE patients with acute flare.
Hydroxychloroquine for long-term treatment for SLE can cause retinal toxicity.

Quick HIT

The most common causes of death in SLE are opportunistic infections and renal failure.

Quick HIT

Only **diffuse scleroderma** form has renal, lung, and heart involvement.

CLINICAL PEARL 6-3

Antiphospholipid Antibody Syndrome

- A hypercoagulable state that can be idiopathic or associated with SLE (or other collagen vascular diseases such as scleroderma)
- Typical findings
  - Recurrent venous thrombosis—pulmonary embolism is a risk
  - Recurrent arterial thrombosis
  - Recurrent fetal loss (abortions)
  - Thrombocytopenia
  - Livedo reticularis
- Laboratory findings: Presence of lupus anticoagulant, anticardiolipin antibody, or both. Prolonged PTT or PT is not corrected by adding normal plasma
- Treatment is long-term anticoagulation (INR of 2.5 to 3.5)
- APA antibodies react with cardiolipin, a reagent in VRDL and RPR tests leading to false positives

B. Clinical features

1. **Raynaud phenomenon**
   a. Present in almost all patients; usually appears before other findings
   b. Caused by vasospasm and thickening of vessel walls in the digits
   c. Can lead to digital ischemia, with ulceration and infarction/gangrene
   d. Cold temperature and stress bring about color changes of fingers—blanching first, then cyanotic, and then red from reactive hyperemia
2. Cutaneous fibrosis
   a. Tightening of skin of the face and extremities (**sclerodactyly** refers to a claw-like appearance of the hand)
   b. Can lead to contractures, disability, and disfigurement
3. GI involvement
   a. Occurs in most patients (both diffuse and limited)

TABLE 6-3 Diffuse Versus Limited Scleroderma

Diffuse	Limited
Widespread skin involvement	Skin involvement limited to distal extremities (and face, neck)—sparing of the trunk
Rapid onset of symptoms (skin and other complications occur rapidly after onset of Raynaud phenomenon)	Delayed onset: Skin involvement occurs slowly after the onset of Raynaud phenomenon. Therefore, the patient has a long history or Raynaud phenomenon before other symptoms begin
Significant visceral involvement (i.e., fibrosis of internal organs)—lung, heart, GI tract, kidneys	Visceral involvement occurs late—pulmonary HTN and ischemic vascular disease; minimal constitutional symptoms
Associated with ANAs but absence of anticentromere antibody	Anticentromere antibody is found in most patients
Poorer prognosis—10-yr survival is 40%–65%	Better prognosis than diffuse form. Normal life span is expected in most cases, unless severe pulmonary HTN develops
• Peripheral edema (of hands and legs), polyarthritis, fatigue and weakness (muscle involvement), carpal tunnel syndrome • Renal failure can occur, but now rare • Interstitial lung disease more common	CREST syndrome is a variant **C**alcinosis of the digits **R**aynaud phenomenon **E**sophageal motility dysfunction **S**clerodactyly of the fingers **T**elangiectases (over the digits and under the nails)

b. Findings include dysphagia/reflux from esophageal immobility (up to 90% of patients), delayed gastric emptying, constipation/diarrhea, abdominal distention, and pseudo-obstruction. Prolonged acid reflux may eventually lead to esophageal strictures.

4. Pulmonary involvement
   a. Most common cause of death from scleroderma
   b. Interstitial fibrosis and/or pulmonary HTN may also be present
5. Cardiac involvement: pericardial effusions, myocardial involvement that can lead to CHF, arrhythmias
6. Renal involvement (renal crisis—rapid malignant hypertension) occurs in patients with diffuse disease (rare today)

C. Diagnosis

1. Diagnostic tests are of limited utility. Almost all patients have elevated ANAs (high sensitivity, low specificity).
2. **Anticentromere antibody** is very specific for the limited form.
3. **Antitopoisomerase I** (antiscleroderma-70) Ab is very specific for the diffuse form.
4. Barium swallow (esophageal dysmotility) and pulmonary function test are used to detect complications.

D. Treatment

1. No effective cure, and treatment is symptomatic
2. NSAIDs for musculoskeletal pains
3. H_2 blockers or proton pump inhibitors for esophageal reflux
4. Raynaud phenomenon—avoid cold and smoking, keep hands warm; if severe, use calcium-channel blockers
5. Pulmonary complications—for pulmonary hypertension, treat with bosentan. For pulmonary fibrosis, cyclophosphamide is used
6. ACE inhibitors are used to prevent and treat renal hypertensive crisis

Sjögren Syndrome

A. General characteristics

1. Sjögren's syndrome is an autoimmune disease most common in women. Lymphocytes infiltrate and destroy the lacrimal and salivary glands.
2. A multiorgan disease (can also involve the skin, lungs, thyroid, vessels, and liver)
3. Primary versus secondary Sjögren syndrome
   a. Primary Sjögren syndrome: Dry eyes and dry mouth, along with lymphocytic infiltration of the minor salivary glands (on histology); patients do not have another rheumatologic disease
   b. Secondary Sjögren syndrome: Dry eyes and dry mouth along with a **connective tissue disease** (RA, systemic sclerosis, SLE, polymyositis)
4. Patients have increased risk of non-Hodgkin lymphoma. Malignancy is the most common cause of death.

B. Clinical features

1. Dry eyes—burning, redness, blurred vision, keratoconjunctivitis sicca
2. Dry mouth and tooth decay
3. Arthralgias, arthritis, fatigue
4. Interstitial nephritis and vasculitis

C. Diagnosis

1. ANAs are present in 95% of patients. Rheumatoid factor (RF) is present in 50% to 75% of patients with secondary disease.
2. **Ro (SS-A)** is present in 55% of patients, and **La (SS-B)** Abs is present in 40% of patients.
3. **Schirmer test:** Filter paper inserted in eye to measure lacrimal gland output (degree of wetting in a specified time period)—high sensitivity and specificity.
4. Salivary gland biopsy (lip or parotid) is the most accurate but not needed for diagnosis.

Quick HIT

Differential diagnosis of Raynaud phenomenon
- Primary—no other disorder exists
- Scleroderma
- SLE
- Mixed connective tissue disease
- Vasculitis (e.g., Buerger disease)
- Certain medications (e.g., β-blockers, nicotine, bleomycin)
- Disorders that disrupt blood flow or vessels, such as thromboangiitis obliterans

Quick HIT

The **degree of skin involvement** predicts prognosis: Diffuse scleroderma has a worse prognosis than limited scleroderma.

Quick HIT

- Twenty percent of patients with scleroderma have Sjögren syndrome.
- In patients with Sjögren syndrome, search for **occult lymphoma** (look for lymphadenopathy and hepatosplenomegaly).

Quick HIT

Patients with antibodies to Ro (SS-A) are at increased risk of having a child with neonatal SLE (with congenital heart block).

D. Treatment

1. Pilocarpine or Cevimeline (enhance oral and ocular secretions via acytelcholine)
2. Artificial tears for dry eyes
3. Good oral hygiene
4. NSAIDs, steroids for arthralgias, arthritis
5. Patients with secondary Sjögren syndrome—therapy for connective tissue disease

Mixed Connective Tissue Disease

- Mixed connective tissue disease is an "overlap" syndrome with clinical features similar to those of SLE, RA, systemic sclerosis, and polymyositis. Findings consistent with each of these diseases do not necessarily occur simultaneously. It usually takes some time for a pattern to be identified and a diagnosis of mixed connective tissue disease to be made.
- Clinical findings include pulmonary involvement, esophageal dysfunction, polyarthritis, sclerodactyly, cutaneous manifestations, myopathy, and Raynaud phenomenon.
- The presence of **anti-U1-RNP Abs** is a key laboratory finding. High ANA and RF may be present.
- Treatment varies according to which specific disease predominates.

Quick HIT

RA is Unlikely if:
- Joint distribution is not symmetric OR
- DIP is involved OR
- Constitutional symptoms (especially morning stiffness) are absent

Rheumatoid Arthritis

A. General characteristics

1. RA is a chronic **inflammatory** autoimmune disease involving the **synovium of joints.** The inflamed synovium can cause damage to cartilage and bone.
2. It is a systemic disease that has many extra-articular manifestations (see below).
3. The usual age of onset is 20 to 40 years; it is more common in women than in men (3:1).
4. Etiology is uncertain. It may be caused by an infection or a series of infections (most likely viral), but genetic predisposition is necessary.

Quick HIT

Much of the joint damage that ultimately leads to disability occurs early in the course of the disease, so early treatment with DMARDs is critical.

B. Clinical features

1. Inflammatory polyarthritis (joint swelling is the most common sign)—can involve every joint in the body **except the DIP joints** (Figure 6-3).
   a. Pain on motion of joints/tenderness in joints.
   b. Joints commonly involved include **joints of the hands (PIP, MCP) and wrists,** knees, ankles, elbows, hips, and shoulders.
   c. Characteristic hand deformities.
      - Ulnar deviation of the MCP joints (Figure 6-4A).
      - *Boutonnière deformities* of the PIP joints (PIP flexed, DIP hyperextended) (Figure 6-4C).
      - *Swan-neck contractures* of the fingers (MCP flexed, PIP hyperextended, DIP flexed) (Figure 6-4B).
2. Constitutional symptoms can be prominent (see Table 6-4).
   a. **Morning stiffness** (present in all patients)—improves as the day progresses.
   b. Low-grade fever, weight loss.
   c. Fatigue can be prominent because this is a systemic disease.
3. Cervical spine involvement is common at **C1-C2 (subluxation and instability),** but it is less common in the lower cervical spine.
   a. Instability of the cervical spine is a potentially life-threatening complication of RA. Most patients do not have neurologic involvement, but if they do, it can be progressive and fatal if not treated surgically.
   b. This is seen in 30% to 40% of patients. All patients with RA should have cervical spine **radiographs before undergoing any surgery** (due to risk of neurologic injury during intubation). However, disease-modifying antirheumatic drugs (DMARDs) have dramatically reduced the need for cervical spine surgery in RA patients.
4. Cardiac involvement may include pericarditis, pericardial effusions, conduction abnormalities, and valvular incompetence.

Quick HIT

Poor Prognostic Indicators in RA
- High RF titers
- Subcutaneous nodules
- Erosive arthritis
- Autoantibodies to RF

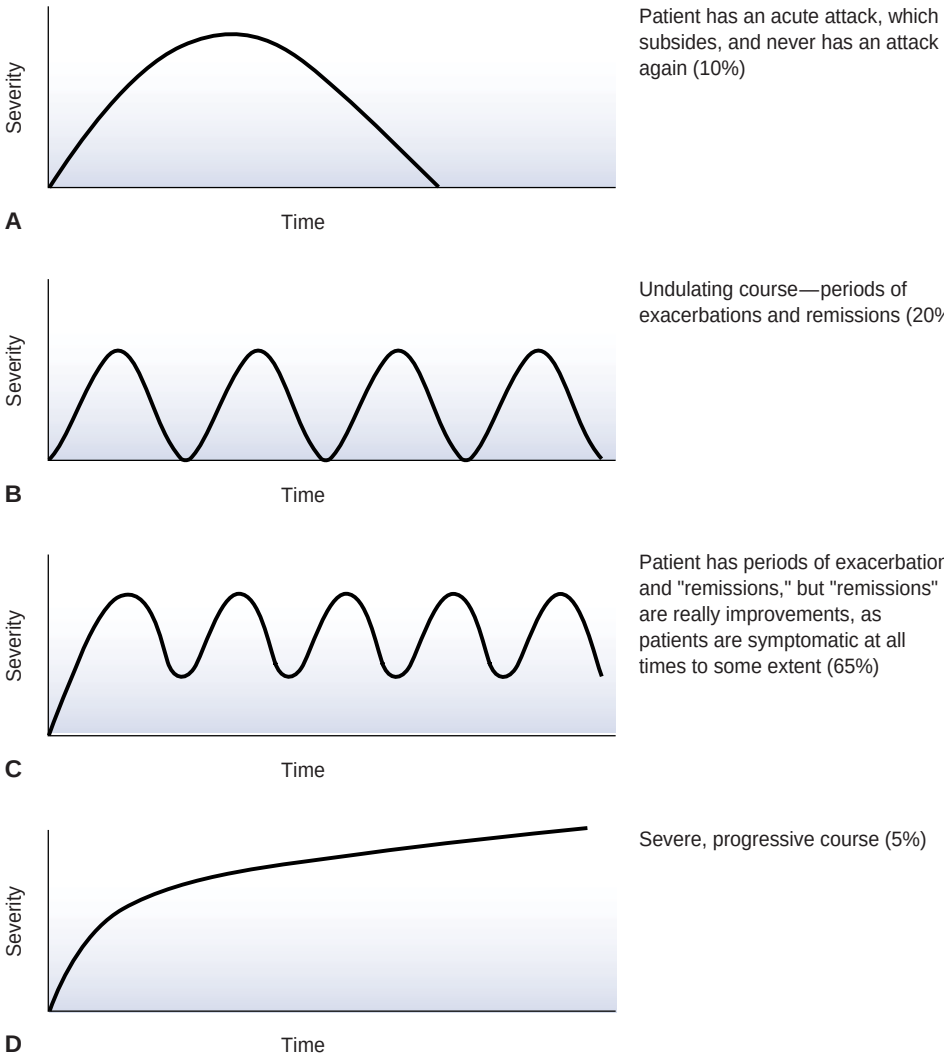


FIGURE 6-3 **The clinical course of RA can be grouped into four classes of patients.**

5. Pulmonary involvement—usually pleural effusions; interstitial fibrosis may occur.
6. Ocular involvement—episcleritis or scleritis.
7. Soft tissue swelling (rather than bony enlargement).
8. Drying of mucous membranes: Sjögren xerostomia.
9. Subcutaneous **rheumatoid nodules** over extensor surfaces may also occur in visceral structures—for example, lungs, pleura, pericardium (Figure 6-5).
   a. Pathognomonic for RA.
   b. Nearly always occurs in seropositive patients (i.e., those with RF).

C. Diagnosis

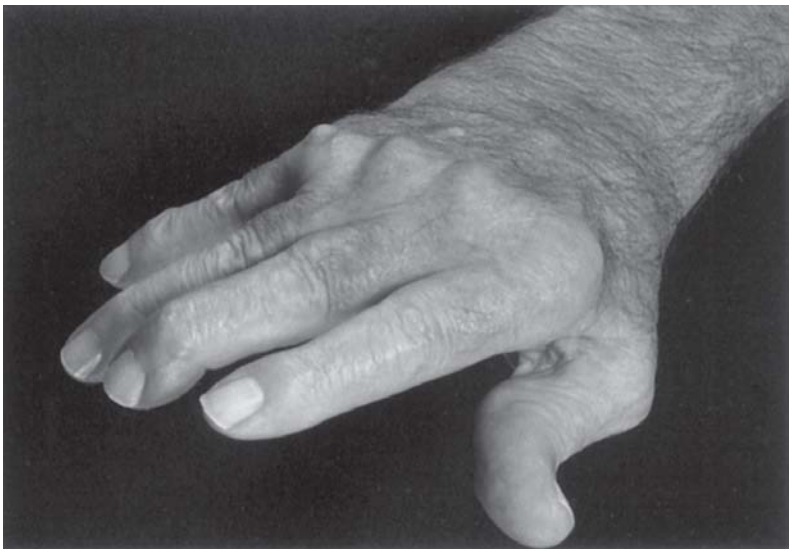
1. Laboratory findings (see Clinical Pearl 6-4)
   a. High titers of RF are associated with more severe disease and are generally nonspecific. RF is eventually present in 80% of patients with RA (may be absent early in the disease), but is also present in up to 3% of the healthy population.
      • RF titers rarely change with disease activity and are not useful for following patients.
      • Helpful in determining prognosis. High titers → more severe disease.
   b. Anticitrullinated peptide/protein antibodies (ACPA)—sensitivity is 50% to 75%, specificity is over 90%.
   c. Elevated ESR, C-reactive protein.
   d. Anemia of chronic disease.

Quick HIT

In RA, changes in joints are usually more extensive than in OA because the entire synovium is involved in RA. Note that osteophytes (characteristic of OA) are not present in RA.

Quick HIT

Patients with diagnosis of RA who have a positive RF, ACPA, or both are at a higher risk of developing erosive joint damage—early treatment with DMARDs is indicated.



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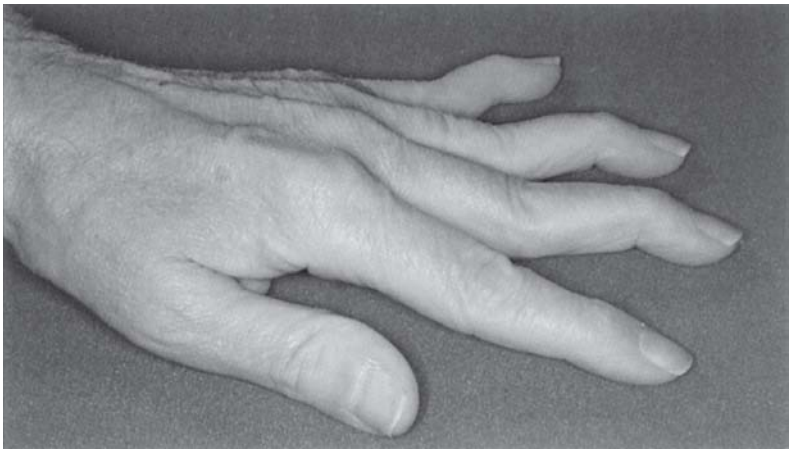

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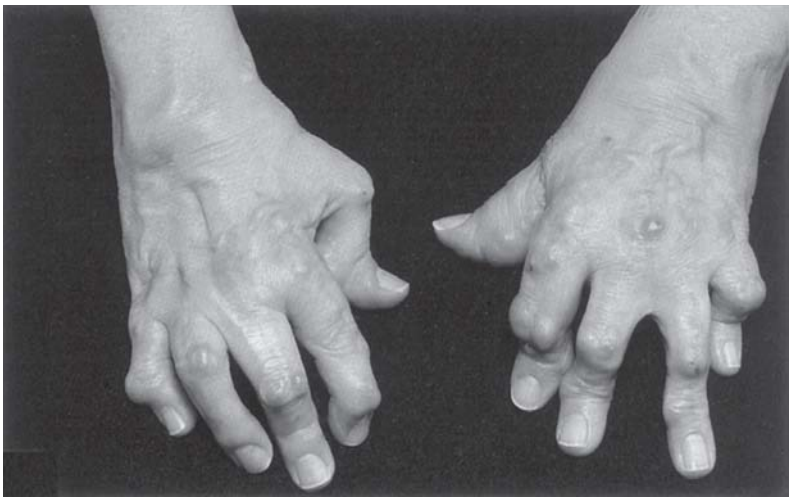


C

FIGURE 6-4 **Rheumatoid arthritis. A: Ulnar deviation at metacarpophalangeal joints. B: Swan-neck deformity. C: Boutonnière deformity.**

(From Hunder GG. *Atlas of Rheumatology.* 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2000:11, Figures 1-27, 1-28, and 1-29A, respectively; and *Curr Med.* 2002:11.)

TABLE 6-4 Extra-articular Manifestations in Rheumatoid Arthritis

Constitutional Symptoms	Malaise, Anorexia, Some Weight Loss, Fever
Cutaneous	• Skin becomes thin and atrophic and bruises easily • Vasculitic changes/ulcerations involving fingers, nail folds • Subcutaneous **rheumatoid nodules** (elbows, sacrum, occiput)—**pathognomonic for RA**
Pulmonary	• Pleural effusions (very common)—**pleural fluid characteristically has very low glucose** and low complement • Pulmonary fibrosis—with a restrictive pattern on pulmonary function tests and a honeycomb pattern on CXR • Pulmonary infiltrates • Rheumatic nodules in lungs (similar to those on skin)—can cavitate or become infected
Cardiac	• Rheumatic nodules in heart—can lead to conduction disturbances (heart block and bundle branch block) • Pericarditis—in 40% of patients with RA • Pericardial effusion
Eyes	• Scleritis • Scleromalacia—softening of the sclera; if not treated may perforate, leading to blindness • Dry eyes (and dry mucous membranes in general); may develop Sjögren syndrome
Nervous System	Mononeuritic multiplex—infarction of nerve trunk Patient cannot move the arm or leg; implies systemic vasculitis, which is a bad sign
Felty Syndrome	• Triad of RA, neutropenia, and splenomegaly • Also anemia, thrombocytopenia, and lymphadenopathy • Associated with high titers of RF and extra-articular disease • Increased susceptibility to infection • Usually occurs fairly late in the disease process
Blood	• Anemia of chronic disease: Mild, normocytic, normochromic anemia • Thrombocytosis
Vasculitis	A microvascular vasculitis—can progress to mesenteric vasculitis, PAN, or other vascular syndromes

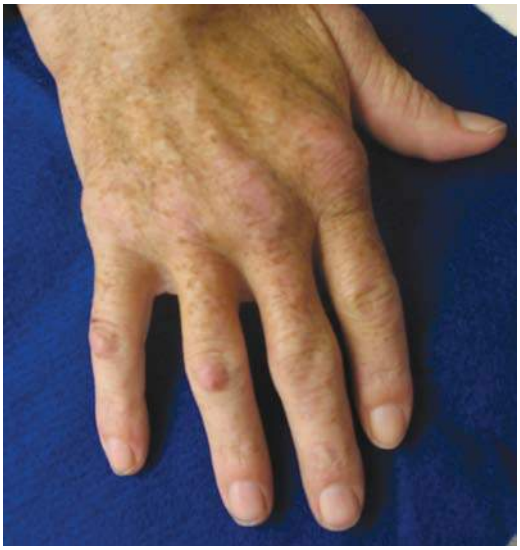


FIGURE 6-5 Rheumatoid nodules of the hand.
(Image provided by Stedman's.)

CLINICAL PEARL 6-4

Diagnosis of RA

1. Inflammatory arthritis of three or more joints—MCP, PIP, wrist, elbow, knee, ankle, MIP joints
2. Symptoms lasting at least 6 weeks
3. Elevated CRP and ESR
4. Positive serum RF or ACPA
5. Radiographic changes consistent with RA (erosions and periarticular decalcification)

Quick HIT

Radiographs have become less important in diagnosis of RA, as joint abnormalities occur very late. DMARDs started well before radiographs indicate abnormality.

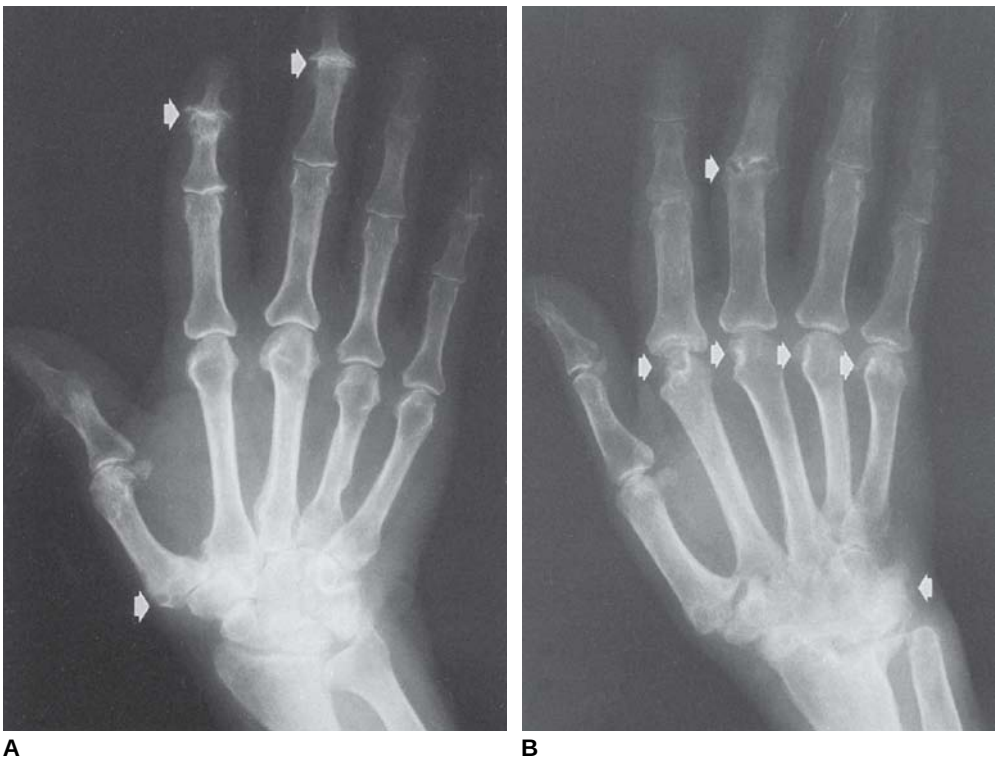
2. Radiographs (Figure 6-6).
   a. Loss of juxta-articular bone mass (periarticular osteoporosis) near the finger joints.
   b. **Narrowing of the joint space** (due to thinning of the articular cartilage) is usually seen late in the disease.
   c. **Bony erosions** at the margins of the joint.
3. Synovial fluid analysis (see Table 6-5) is nonspecific.

D. Treatment

1. Goal is to minimize pain and swelling, prevent disease progression, and help patient remain as functional as possible.
2. Exercise helps to maintain range of motion and muscle strength.
3. Symptomatic treatment.
   a. NSAIDs are the drugs of choice for pain control.
   b. Corticosteroids (low dose)—use these if NSAIDs do not provide adequate relief. Short-term treatment may be appropriate but avoid long-term use.

Quick HIT

NSAIDs and DMARDs are the two main classes of medications used in RA.



A B

FIGURE 6-6 **Posteroanterior radiographs of the hand showing the typical pattern of involvement for (A) osteoarthritis (osteophytes, subchondral sclerosis, joint space narrowing) (*arrows*) and (B) rheumatoid arthritis (periarticular erosions, osteopenia) (*arrows*).**

(**A** and **B** from Humes DH, DuPont HL, Gardner LB, et al. *Kelley's Textbook of Internal Medicine.* 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2000:1463, Figures 190.4A and B.)

TABLE 6-5 Synovial Fluid Analysis

Condition	Appearance of Fluid	WBC/mm^3	PMNs	Other Findings
Normal	Clear	<200	<25%	
Noninflammatory arthritis (OA/trauma)	Clear, yellow: Possibly red if traumatic	<2,000	<25%	RBCs for trauma
Inflammatory arthritis (RA, gout, pseudogout, Reiter syndrome)	Cloudy yellow	>5,000	50%–70%	Positively birefringent crystals with pseudogout; negatively birefringent crystals with gout
Septic arthritis (bacterial, tuberculosis)	Turbid, purulent	Usually >50,000	>70%	Synovial fluid culture positive for most cases of bacterial arthritis except gonococcal (only 25% are positive)

4. DMARDs
   a. General principles
      - Can reduce morbidity and mortality (by nearly 30%)—by limiting complications, slowing progression of disease, and preserving joint function
      - **Should be initiated early** (at the time of diagnosis)
      - They have a slow onset of action (6 weeks or longer for effect to be seen), so begin treating RA while waiting for the disease-modifying therapy to take effect. Gradually taper and discontinue NSAIDs and corticosteroids once effects are evident
   b. First-line agents
      - Methotrexate—best initial DMARD
      - Initial improvement is seen in 4 to 6 weeks.
      - Side effects include GI upset, oral ulcers (stomatitis), mild alopecia, **bone marrow suppression** (coadminister with folinic acid), hepatocellular injury, and idiosyncratic interstitial pneumonitis, which may lead to pulmonary fibrosis. It increases liver enzymes in some patients
      - Closely monitor liver and renal function
      - Supplement with folate.
      - Leflunomide is an alternative to methotrexate or can be used as an adjunct to therapy with a DMARD.
      - Hydroxychloroquine
      - This is an alternative first-line DMARD, but usually not as effective as methotrexate and is typically used in less severe cases
      - It requires eye examinations every 6 months because of the risk of visual loss due to retinopathy
      - Sulfasalazine—alternate first-line agent, but less effective than methotrexate
      - Antitumor necrosis factor (anti-TNF) inhibiting agents (etanercept, infliximab, etc.)—used if methotrexate does not fully control the disease
      - Requires PPD screening because of risk of reactivation of TB
5. Surgery (in severe cases)
   a. Synovectomy (arthroscopic) decreases joint pain and swelling but does not prevent x-ray progression and does not improve joint range of motion
   b. Joint replacement surgery for severe pain unresponsive to conservative measures

Quick HIT

Variants of RA
- **Felty syndrome:** anemia, neutropenia, splenomegaly, and RA.
- **Juvenile RA:** begins before 18 years of age. Extra-articular manifestations may predominate (***Still disease***) or arthritis may predominate.
- **Caplan syndrome:** RA associated with pneumoconiosis.

Quick HIT

Combination therapy with first-line drugs (methotrexate, hydroxychloroquine, and sulfasalazine) produces higher remission rates.

Quick HIT

Methotrexate is the mainstay of therapy in RA.

Crystal-induced Arthritides

Gout

A. General characteristics

1. Gout is an inflammatory monoarticular arthritis caused by the crystallization of monosodium urate in joints (Figure 6-7) (see Table 6-6). Hyperuricemia is a hallmark of the disease, but it does not by itself indicate gout.
2. Ninety percent of patients are men over 30 years of age. Women are not affected until after menopause.
3. Pathogenesis
   a. Increased production of uric acid.
      - Hypoxanthine-guanine phosphoribosyltransferase deficiency—for example, in Lesch–Nyhan syndrome
      - **Phosphoribosyl pyrophosphate synthetase** overactivity
      - **Increased cell turnover** associated with a number of conditions, including cancer chemotherapy, chronic hemolysis, and hematologic malignancies

   b. Decreased excretion of uric acid (accounts for 90% of cases)
      - Renal disease
      - NSAIDs, diuretics
      - Acidosis
4. Pathophysiology of inflammation
   a. PMNs play a key role in the acute inflammation of gout
   b. It develops when uric acid crystals collect in the synovial fluid as the extracellular fluid becomes saturated with uric acid
   c. IgGs coat monosodium urate crystals, which are phagocytized by PMNs, leading to the release of inflammatory mediators and proteolytic enzymes from the PMNs, which then result in inflammation.

Quick HIT

Precipitants of an Acute Gouty Attack
- Decrease in temperature
- Dehydration
- Stress (emotional or physical)
- Excessive alcohol intake
- Starvation

B. Clinical features (four stages)

1. Asymptomatic hyperuricemia.
   a. Increased serum uric acid level in the absence of clinical findings of gout, may be present without symptoms for 10 to 20 years or longer.
   b. Should not be treated because over 95% of patients remain asymptomatic.
2. Acute gouty arthritis.
   a. Peak age of onset is 40 to 60 years of age for men.
   b. Initial attack usually involves sudden onset of exquisite pain. Pain often wakes the patient from sleep.

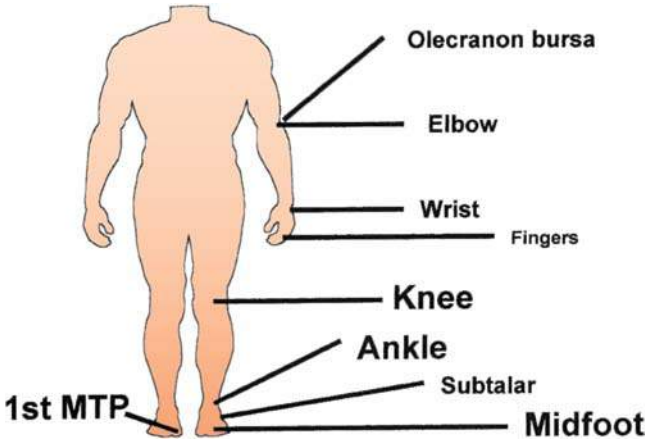


FIGURE 6-7 **Gout: common sites of involvement. MTP, metatarsophalangeal joint.**
(From Stoller JK, Ahmad M, Longworth DL. *The Cleveland Clinic Intensive Review of Internal Medicine.* 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2002:374, Figure 30.6.)

TABLE 6-6 Major Arthritides

	Osteoarthritis	Rheumatoid Arthritis	Gouty Arthritis
Onset	Insidious	Insidious	Sudden
Common locations	Weight-bearing joints (knees, hips, lumbar/cervical spine), hands	Hands (PIP, MCP), wrists, ankles, knees	Great toe, ankles, knees, elbows
Presence of inflammation	No	Yes	Yes
Radiographic changes	Narrowed joint space, osteophytes, subchondral sclerosis, subchondral cysts	Narrowed joint space, bony erosions	Punched-out erosions with overhanging rim of cortical bone
Laboratory findings	None	Elevated ESR, RF, anemia	Crystals
Other features	• No systemic findings • Bouchard nodes and Heberden nodes in hands	• Systemic findings—extra-articular manifestations common • Ulnar deviation, swan-neck, and boutonnière deformity	• Tophi • Nephrolithiasis

- Most often affects the big toe—the first metatarsophalangeal joint (**podagra**). Other common joints affected are ankles and knees.

c. Pain and cellulitic changes—erythema, swelling, tenderness, and warmth.
d. Fever may or may not be present.
e. As it resolves, the patient may have desquamation of overlying skin.

3. Intercritical gout.
   a. An asymptomatic period after the initial attack. The patient may not have another attack for years.
   b. Sixty percent of patients have a recurrence within 1 year. Some patients (fewer than 10%) never have another attack of gout.
   c. There is a 75% likelihood of a second attack within the first 2 years.
   d. Attacks tend to become polyarticular with increased severity over time.
4. Chronic tophaceous gout.
   a. Occurs in people who have had poorly controlled gout for more than 10 to 20 years.
   b. Tophi
      - Aggregations of urate crystals surrounded by giant cells in an inflammatory reaction.
      - Tophi cause deformity and destruction of hard and soft tissues. In joints, they lead to destruction of cartilage and bone, triggering secondary degeneration and development of arthritis. They may be extra-articular.
   c. Common locations of tophi: Extensor surface of forearms, elbows, knees, Achilles tendons, and pinna of external ear.

C. Diagnosis

1. Joint aspiration and synovial fluid analysis (under a polarizing microscope) is the only way to make a definitive diagnosis—**needle-shaped and negatively birefringent urate crystals** appear in synovial fluid.
2. Serum uric acid is **not** helpful in diagnosis because it can be normal even during an acute gouty attack.
3. Radiographs reveal punched-out erosions with an overhanging rim of cortical bone in advanced disease.

Quick HIT

Do a Gram stain and culture of the synovial fluid to **rule out septic arthritis,** which is the most worrisome diagnosis on the differential list.

Quick HIT

Complications of Gout
- Nephrolithiasis—risk is small (less than 1% per year)
- Degenerative arthritis occurs in less than 15% of patients.

D. Treatment

1. In all stages, avoid secondary causes of hyperuricemia.
   a. Medications that increase uric acid levels (thiazide and loop diuretics).
   b. Obesity
   c. Reduce alcohol intake.
   d. Reduce dietary purine intake. Limit intake of seafood/red meat.
2. Acute gout.
   a. Bed rest is important. Early ambulation may precipitate a recurrence.
   b. NSAIDs
      - Treatment of choice in acute gout (indomethacin is traditionally used, but other NSAIDs are effective).
   c. Colchicine
      - An alternative for patients who cannot take NSAIDs or did not respond to NSAIDs.
      - Effective but less favored because 80% of treated patients develop significant nausea/vomiting, abdominal cramps, and severe diarrhea. Compliance tends to be low due to these side effects.
      - It is contraindicated in renal insufficiency and can cause cytopenia.
   d. Corticosteroids
      - Oral prednisone (7- to 10-day course) if patient does not respond to or cannot tolerate NSAIDs and colchicine.
      - Intra-articular corticosteroid injections (if only one joint is involved)—dramatic relief of symptoms.
3. Prophylactic therapy.
   a. Wait until patient has had at least two acute gouty attacks (or perhaps three) before initiating prophylactic therapy. This is because the second attack may take years to occur (if at all), and so the risk-to-benefit ratio for prophylactic medication (allopurinol or uricosuric agents) is not favorable after one gouty attack.
   b. When giving prophylaxis, add either colchicine or an NSAID for 3 to 6 months to prevent an acute attack. The colchicine or NSAID can then be discontinued, and the patient can remain on the uricosuric agent or allopurinol indefinitely.
   c. The choice of whether to use uricosuric drugs or allopurinol depends on how much uric acid is excreted in the urine in a 24-hour period.
      - Uricosuric drugs (probenecid, sulfinpyrazone)—if the 24-hour urine uric acid is **<800 mg/day**, this indicates undersecretion of urate. These drugs **increase renal excretion** of uric acid; use them only in patients with normal renal function. They are contraindicated if the patient has a history of renal stones.
      - Allopurinol, a xanthine oxidase inhibitor, **decreases uric acid synthesis**—if the 24-hour urine uric acid is **>800 mg/day**, this indicates overproduction. Never give this for acute gout; it makes it worse. Use once-daily dosing. It is well tolerated. Watch for rash or Stevens–Johnson syndrome. Unlike NSAIDS and uricosuric drugs, allopurinol is not contraindicated in kidney dysfunction.

Quick HIT

In acute gout, avoid aspirin (can aggravate the problem) and acetaminophen (has no anti-inflammatory properties).

Pseudogout (Calcium Pyrophosphate Deposition Disease)

A. General characteristics

1. Calcium pyrophosphate crystals deposit in joints, leading to inflammation.
2. Risk factors.
   a. Deposition increases with age and with OA of the joints. Therefore, pseudogout is common in **elderly patients with degenerative joint disease.**
   b. Other conditions that may increase crystal deposition include **hemochromatosis**, **hyperparathyroidism**, hypothyroidism, and Bartter syndrome.

Quick HIT

Presentation of pseudogout is similar to gout, but typically occurs in larger joints (knee).

B. Clinical features

1. The most common joints affected are knees and wrists.
2. It is classically monoarticular, but can be polyarticular as well.

C. Diagnosis

1. Joint aspirate is required for definitive diagnosis—**weakly positively birefringent, rod-shaped and rhomboidal crystals** in synovial fluid (calcium pyrophosphate crystals) (Figure 6-8)
2. Radiographs—chondrocalcinosis (cartilage calcification)

D. Treatment

1. Treat the underlying disorder (if identified)
2. Symptomatic management is similar to that for gout
   - First-line therapy includes NSAIDS
   - Colchicine is useful for prophylaxis
   - Intra-articular steroid injections, particularly with triamcinolone
3. Total joint replacement is appropriate if symptoms are debilitating

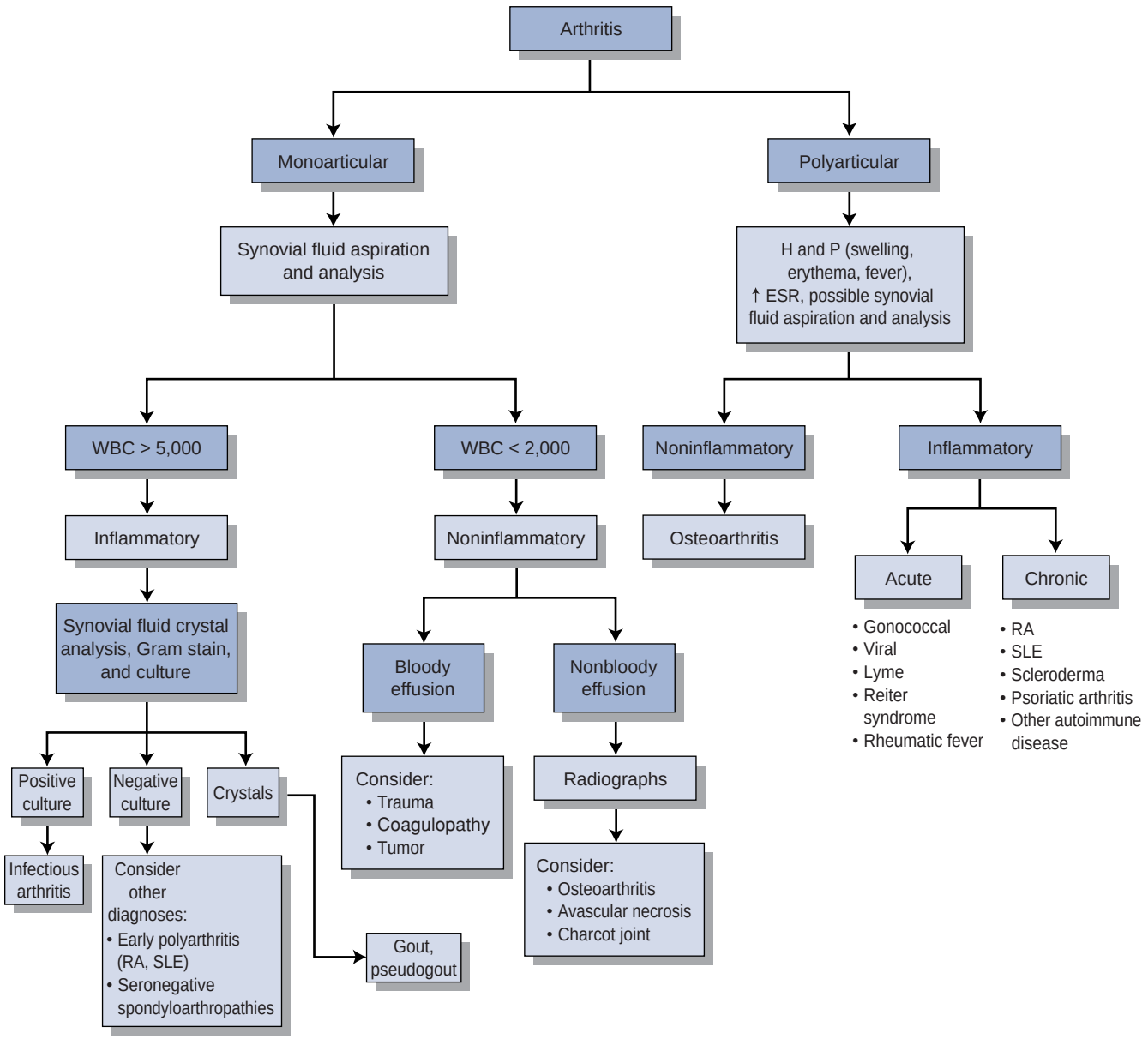


FIGURE 6-8 **Evaluation of joint pain.**

Myopathies and Pain Syndromes

Idiopathic Inflammatory Myopathies

A. General characteristics

1. Classification
   a. **Polymyositis** (does not involve skin)
   b. **Dermatomyositis** (associated with characteristic skin rash)

B. Causes

1. Hypothesis: A genetically susceptible individual plus an environmental trigger leads to immune activation, which results in chronic inflammation.
2. Pathologic changes in muscle
   a. Dermatomyositis—**humoral** immune mechanisms
   b. Polymyositis and inclusion body myositis—**cell-mediated** process

C. Clinical features

1. Features common to both polymyositis and dermatomyositis (see Clinical Pearl 6-5)
   a. **Symmetrical proximal muscle weakness** that develops subacutely over weeks or several months
      • The earliest and most severely affected muscle groups are the neck flexors, shoulder girdle, and pelvic girdle muscles
      • Distal extremity weakness is less frequent and typically less severe
   b. Myalgia in 33% of patients
   c. Dysphagia in up to 30% of patients (involvement of striated muscle in the upper GI tract)
   d. More common in female patients
   e. Associated finding include CHF conduction defects, arthralgias, and interstitial lung disease
2. Features unique to dermatomyositis
   a. *Heliotrope rash* (butterfly)—around eyes, bridge of nose, cheeks
   b. *Gottron papules*—papular, erythematous, scaly lesions over the knuckles (MCP, PIP, DIP)
   c. *V sign*—rash on the face, neck, and anterior chest
   d. *Shawl sign*—rash on shoulders and upper back, elbows, and knees
   e. Periungual erythema with telangiectases
   f. Subcutaneous calcifications in children—can be extremely painful
   g. Associated with vasculitis of the GI tract, kidneys, lungs, and eyes (more common in children)
   h. There is an **increased incidence of malignancy** in older adults (lung, breast, ovary, GI tract, and myeloproliferative disorders). Once dermatomyositis is diagnosed, make an effort to uncover an occult malignancy. Dermatomyositis associated with malignancy often remits once the tumor is removed

CLINICAL PEARL 6-5

Diagnostic Criteria for Polymyositis

If two of first four → possible polymyositis
If three of first four → probable polymyositis
If all four → definite polymyositis

- Symmetric proximal muscle weakness
- Elevation in serum creatine phosphokinase
- EMG findings of a myopathy
- Biopsy evidence of myositis
- Characteristic rash of dermatomyositis

D. Diagnosis

1. Laboratory
   a. CK level is significantly elevated. CK levels correspond to the **degree of muscle necrosis**, so one can monitor the disease severity
   b. LDH, aldolase, AST, ALT elevated
   c. ANA in over 50%
   d. Antisynthetase antibodies **(anti-Jo-1 antibodies)**—abrupt onset of fever, cracked hands, Raynaud phenomenon, interstitial lung disease and fibrosis, arthritis; does not respond well to therapy
   e. Antisignal recognition particle
      • Cardiac manifestations (common)
      • Worst prognosis of all subsets
   f. Anti-Mi-2 antibodies—better prognosis
2. EMG—abnormal in 90% of patients
3. Muscle biopsy
   a. Shows inflammation and muscle fiber fibrosis in *all three*
   b. Dermatomyositis—**perivascular and perimysial**
   c. Polymyositis and inclusion body myositis—**endomysial**

E. Treatment

1. Corticosteroids are the initial treatment
2. Immunosuppressive agents (for patients who do not respond to steroids)—methotrexate, cyclophosphamide, chlorambucil
3. Physical therapy

Inclusion Body Myositis

A. General characteristics

- More common in men (elderly)
- Insidious onset of slowly progressive proximal **and** distal weakness, often leads to delay in diagnosis
- There is early weakness and atrophy of quadriceps, forearm flexors, and tibialis anterior muscles. Involvement is asymmetrical. Facial weakness occurs in one-third of patients, and dysphagia in one-half of patients
- Patients can also have loss of deep tendon reflexes (nerves are not involved in polymyositis and dermatomyositis)
- Extramuscular manifestations are rare
- Diagnosis—slight elevation of CK levels (relatively low)
- Poor response to therapy
- Not associated with autoantibodies

Quick HIT

Inclusion body myositis is the "oddball of Inflammatory myopathies" for the following reasons: Affects male patients more than female patients, absence of autoantibodies, distal muscle involvement, and relatively low creatine kinase (CK); prognosis is poor.

Polymyalgia Rheumatica

A. General characteristics

1. Usually occurs in **elderly patients** (rare before the age of 50). The mean age of onset is 70, and it is more common in women.
2. The cause is unknown, but an autoimmune process may be responsible. There is a possible genetic link (association with HLA-DR4 allele).
3. Self-limited disease (duration of 1 to 2 years).

B. Clinical features

1. Hip and shoulder muscle pain (bilateral)
   a. Often begins abruptly (but may be gradual)
   b. Stiffness in shoulder and hip regions after a period of inactivity is the most prominent symptom
   c. Pain occurs on movement; muscle strength is normal
   d. Profound morning stiffness is common

Quick HIT

About 10% of people with polymyalgia rheumatica develop **temporal arteritis;** whereas up to 40% to 50% of people with temporal arteritis have coexisting polymyalgia rheumatica.

2. Constitutional symptoms are usually present: Malaise, fever, depression, weight loss, and fatigue
3. Joint swelling
   a. Up to 20% of patients have synovitis in knees, wrists, or hand joints (can be confused with RA)
   b. Synovitis and tenosynovitis around the shoulder may lead to rotator cuff tendonitis or adhesive capsulitis
4. Signs and symptoms of temporal arteritis (if present)

C. Diagnosis

1. Essentially a clinical diagnosis
2. **ESR is usually elevated** and aids in diagnosis
   a. Almost always >50, frequently >100
   b. Correlates with disease activity

D. Treatment: corticosteroids

1. Response usually occurs within 1 to 7 days. Corticosteroids are not curative, but are effective in suppressing inflammation until the disease resolves itself.
2. After 4 to 6 weeks, begin to taper slowly.
3. Most patients (60% to 70%) can stop corticosteroids within 2 years. A few patients have symptoms for up to 10 years.

Fibromyalgia

A. General characteristics

1. Adult women account for 80% to 90% of cases.
2. Chronic nonprogressive course with waxing and waning in severity; many patients improve with time.
3. **Key to diagnosis: multiple trigger points** (points that are tender to palpation)
   a. Symmetrical.
   b. Eighteen characteristic locations have been identified, including occiput, neck, shoulder, ribs, elbows, buttocks, and knees.
4. Etiology is unknown—somatization is not a proven cause.

B. Clinical features

1. **Stiffness,** body aches (musculoskeletal), fatigue.
   a. Pain is constant and aching, and is aggravated by weather changes, stress, sleep deprivation, and cold temperature. It is worse in the morning.
   b. Rest, warmth, and mild exercise improve the pain.
2. Sleep patterns are disrupted, and sleep is unrefreshing.
3. Anxiety and depression are common.

C. Diagnosis

1. Diagnostic criteria
   a. Widespread pain including axial pain for at least 3 months
   b. Pain in at least 11 of the 18 possible tender point sites
2. There are no specific confirmatory tests for fibromyalgia, therefore, it is important to rule out/consider the following conditions: Myofascial syndromes, rheumatoid disease, polymyalgia rheumatica, ankylosing spondylitis, spondyloarthropathy, chronic fatigue syndrome, Lyme disease, hypothyroidism, polymyositis, depression and somatization disorder, and hypertrophic osteoarthropathy.

D. Treatment and management

1. Advise the patient to stay active and engage in low intensity exercise
2. First-line treatment for fibromyalgia is amitriptyline
3. Local anesthetic at trigger points is used acutely
4. Milnacipran (SNRI) and pregabalin are also used
5. Cognitive behavioral therapy; consider psychiatric evaluation

Seronegative Spondyloarthropathies

Ankylosing Spondylitis

A. General characteristics

1. Strong association with **HLA-B27** (90% of patients) (see Table 6-2), however, presence of HLA-B27 should not be considered diagnostic (see Clinical Pearl 6-6).
2. Three times more common in male than in female patients.
3. **Bilateral sacroiliitis** is a prerequisite for making the diagnosis.
4. Onset is in adolescence or young adulthood.
5. It is characterized by "fusion" of the spine in an ascending manner (from lumbar to cervical spine).
6. Course.
   a. There is a slow progression, but the course is highly variable; acute exacerbations are common.
   b. Life expectancy is usually normal.
   c. The first 10 years of the disease can give an indication of long-term severity.

B. Clinical features

1. Low back pain and stiffness (secondary to sacroiliitis)—limited motion in lumbar spine
2. Neck pain and limited motion in cervical spine—occurs later in course of disease
3. **Enthesitis**—inflammation at tendinous insertions into bone (Achilles tendon and supraspinatus tendon)
4. With extensive spinal involvement, the spine becomes brittle and is prone to fractures with minimal trauma. Severe spinal cord injury can occur with such trauma
5. Chest pain and diminished chest expansion—due to thoracic spine involvement
6. Shoulder and hip pain—most commonly the peripheral joints are affected
7. Constitutional symptoms—fatigue, low-grade fever, weight loss
8. Extra-articular manifestations
   a. Eye involvement (most common)—acute **anterior uveitis** or iridocyclitis
   b. Other extra-articular features are rare, but may involve the following systems: Cardiac (**AV heart block and aortic insufficiency**), renal, pulmonary, and nervous systems
9. Loss of lumbar lordosis can occur as disease advances, leading to inability to stand upright. When severe and symptomatic, this may require spine reconstruction

Quick HIT

In ankylosing spondylitis, low back pain and stiffness are characteristically worse in the morning and better as the day progresses. They **improve with activity** and a hot shower and worsen with rest or inactivity.

CLINICAL PEARL 6-6

Seronegative Spondyloarthropathies

Diseases that belong to seronegative spondyloarthropathies include the following:

- Ankylosing spondylitis
- Reactive arthritis (and Reiter syndrome)
- Psoriatic arthritis
- Arthropathy of IBD
- Undifferentiated spondyloarthropathies

Seronegative spondyloarthropathies have the following **in common:**

- Negative RF
- Strong association with HLA-B27 antigen
- Oligoarthritis (asymmetrical)
- Enthesitis (inflammation at sites of insertion of fascia, ligament, or tendon to bone)
- Inflammatory arthritis (axial and sacroiliac joints)
- Extra-articular features (eyes, skin, genitourinary tract)
- Familial predisposition

Quick HIT

Complications of Ankylosing Spondylitis
- Restrictive lung disease
- Cauda equina syndrome
- Spine fracture with spinal cord injury
- Osteoporosis
- Spondylodiscitis

C. Diagnosis

1. Imaging studies of lumbar spine and pelvis (plain film, MRI, or CT) reveal sacroiliitis—sclerotic changes in the sacroiliac area. Eventually, the vertebral columns fuse, producing "**bamboo spine**."
2. Elevated ESR in up to 75% of patients (due to inflammation)—nonspecific
3. HLA-B27 is not necessary for diagnosis. Present in 8% of general population

D. Treatment

1. NSAIDs (indomethacin) for symptomatic relief
2. Anti-TNF medications (etanercept, infliximab)
3. Physical therapy (maintaining good posture, extension exercises)
4. Surgery may be necessary in some patients with severe spinal deformity
5. Patients with ankylosing spondylitis who sustain even minor trauma and who complain of neck or back pain should be strictly immobilized to prevent spinal cord injury until thorough imaging studies are obtained

Reactive Arthritis/Reiter Syndrome

Quick HIT

Reactive arthritis is a clinical diagnosis. If any patient has acute asymmetric arthritis that progresses sequentially from one joint to another, reactive arthritis should be in the differential diagnosis.

A. General characteristics

1. Reactive arthritis is asymmetric inflammatory oligoarthritis of lower extremities (upper extremities less common) (see Table 6-7). The arthritis is preceded by an infectious process that is remote from the site of arthritis (1 to 4 weeks prior), usually after enteric or urogenital infections.
2. It occurs mostly in HLA-B27–positive individuals.
3. **Reiter syndrome** is an example of reactive arthritis, but most patients do not have the classic findings of Reiter syndrome (arthritis, uveitis, and urethritis), so the term reactive arthritis is now used.
4. The organisms usually associated with reactive arthritis include *Salmonella, Shigella, Campylobacter, Chlamydia, Yersinia.*

Quick HIT

The term **undifferentiated spondyloarthropathy** is used when a patient has features of reactive arthritis but there is no evidence of previous infection (in the GI or genitourinary tract) and the classic findings of Reiter syndrome are absent.

B. Clinical features

1. Look for evidence of infection (GI or genitourinary) 1 to 4 weeks before the onset of symptoms.
2. Asymmetric arthritis—new joints may be involved sequentially over days. Joints are painful, with effusions and lack of mobility.
3. Fatigue, malaise, weight loss, and fever are common.
4. Joint pain may persist or recur over a long-term period.

C. Diagnosis: Send synovial fluid for analysis (to rule out infection or crystals). There is no test specific to reactive arthritis.

TABLE 6-7 Causes of Joint Pain

Polyarticular Joint Pain	Monoarticular Joint Pain
RA	Osteoarthritis
SLE	Gout
Viral arthritis	Pseudogout
Reiter syndrome	Trauma
Rheumatic fever	Septic arthritis
Lyme disease	Hemarthrosis
Gonococcal arthritis	
Drug-induced arthritis	

D. Treatment

1. NSAIDs are first-line therapy.
2. If there is no response, then try sulfasalazine and immunosuppressive agents such as azathioprine.
3. Antibiotic use is controversial—usually not given.

Psoriatic Arthritis

- Develops in fewer than 10% of patients with psoriasis.
- It is typically gradual in onset. Patients usually have skin disease for months to years before arthritis develops.
- Usually asymmetric and polyarticular. Characteristic "**sausage digits**" and **nail pitting** may also be present.
- Upper extremities most often involved; smaller joints more common than large joints
- Initial treatment is NSAIDs, but persistent arthritis may require methotrexate or anti-TNF agents. Steroids are typically not used.

Vasculitis

Temporal/Giant Cell Arteritis

A. General characteristics

1. Vasculitis of unknown cause; typical patient is >50 years of age; twice as common in women as men (see Clinical Pearl 6-7).
2. The temporal arteries are most frequently affected, but it may involve other arteries, such as the aorta or carotids. Carotid bruits, decreased pulses in the arms, and aortic regurgitation may also be observed.
3. Associated with increased risk of aortic aneurysm and aortic dissection.

B. Clinical features

1. Constitutional symptoms of malaise, fatigue, weight loss, and low-grade fever
2. Headaches—may be severe
3. Visual impairment (in only 25% to 50%)
   a. Caused by involvement of ophthalmic artery
   b. Optic neuritis; amaurosis fugax; may lead to **blindness** in up to 50% if not treated early and aggressively
4. Jaw pain with chewing—intermittent **claudication of jaw/tongue** when chewing
5. Tenderness over temporal artery; absent temporal pulse
6. Palpable nodules
7. **Forty percent of patients also have polymyalgia rheumatica**

C. Diagnosis

1. **ESR elevated** (but normal ESR does not exclude the diagnosis)

CLINICAL PEARL 6-7

Vasculitis

- In all of the vasculitic syndromes, blood vessels are inflamed and vascular necrosis can result. Findings depend on the size of the vessel involved and the location of involvement (target organ ischemia).
- If any patient has a systemic illness that has not been explained by another process (or has ischemia involving one or more systems), entertain the diagnosis of vasculitis.
- Classified according to size of vessel
  - **Large vessel:** Takayasu arteritis, temporal arteritis
  - **Medium vessel:** PAN, Kawasaki disease (a pediatric disease), Wegener granulomatosis, Churg–Strauss syndrome, microscopic polyangiitis
  - **Small vessel:** Henoch–Schönlein purpura, hypersensitivity vasculitis, Behçet syndrome

Quick HIT

Keys to Diagnosing Temporal Arteritis
- Age >50 years
- New headache
- Tender/palpable temporal artery
- High ESR
- Jaw claudication

Quick HIT

If temporal arteritis is suspected, begin prednisone and order a temporal artery biopsy.

Quick HIT

Suspect Takayasu arteritis in a young woman with:
- Decreased/absent peripheral pulses
- Discrepancies of BP (arm vs. leg)
- Arterial bruits

2. Biopsy of the temporal artery has a sensitivity of 90%. A single negative biopsy does not exclude the diagnosis

D. Treatment

1. Use high-dose steroids (prednisone) early to prevent blindness.
   a. Start treatment **immediately,** even if temporal arteritis is only suspected. **Do not wait for biopsy results.** If visual loss is present, admit the patient to the hospital for IV steroids; otherwise, start oral prednisone.
   b. If the diagnosis is confirmed, continue treatment for at least 4 weeks, then taper gradually, but maintain steroid therapy for up to 2 to 3 years. Relapse is likely to occur if steroids are stopped prematurely.
2. Follow up on ESR levels to monitor effectiveness of treatment.
3. Visual loss in one eye may be temporary or permanent. Prompt and aggressive steroid treatment is primarily given to prevent involvement of the other eye, but it may improve the visual outcome in the affected eye as well.
4. Even if untreated, the disease is usually eventually self-limiting in most patients, although vision loss may be permanent.

Takayasu Arteritis

A. General characteristics

1. Most common in young Asian women
2. Granulomatous vasculitis of aortic arch and its major branches—leading to fibrosis and potentially causing to stenosis or narrowing of vessels
3. Diagnosed via arteriogram

B. Clinical features

1. Constitutional symptoms—fever, night sweats, malaise, arthralgias, fatigue
2. Pain and tenderness over involved vessels
3. Absent pulses in carotid, radial, or ulnar arteries; aortic regurgitation may be present
4. Signs and symptoms of ischemia eventually develop in areas supplied by involved vessels
5. Severe complications include limb ischemia, aortic aneurysms, aortic regurgitation, stroke, and secondary HTN due to renal artery stenosis. The main prognostic predictor is the presence or absence of these complications.
6. Causes visual disturbances due to ocular involvement and hemorrhage of retinal arteries.

C. Treatment

1. Steroids such as prednisone may relieve the symptoms.
2. Treat HTN.
3. Surgery or angioplasty may be required to recannulate stenosed vessels. Bypass grafting is sometimes necessary.

Churg–Strauss Syndrome

- Vasculitis involving many organ systems (respiratory, cardiac, GI, skin, renal, neurologic)
- Clinical features include constitutional findings (fever, fatigue, weight loss), prominent respiratory tract findings (**asthma**, dyspnea), skin lesions (subcutaneous nodules, palpable purpura), as well as **eosinophilia.**
- Diagnosis is made by biopsy of lung or skin tissue (prominence of eosinophils). **It is associated with p-ANCA.**
- The prognosis is poor with a 5-year survival of 25% (death is usually due to cardiac or pulmonary complications). With treatment (steroids), the 5-year prognosis improves to 50%.

Wegener Granulomatosis

A. General characteristics: Vasculitis predominantly involving the kidneys and upper and lower respiratory tract (sometimes other organs as well)

B. Clinical features

1. Upper respiratory symptoms (e.g., **sinusitis**); purulent or bloody nasal discharge
2. Oral ulcers (may be painful)
3. Pulmonary symptoms (cough, hemoptysis, dyspnea)
4. Renal involvement (glomerulonephritis—may have rapidly progressive renal failure)
5. Eye disease (conjunctivitis, scleritis)
6. Musculoskeletal (arthralgias, myalgias)
7. Tracheal stenosis
8. Constitutional findings (e.g., fever, weight loss)

C. Diagnosis

1. Chest radiograph is abnormal (nodules or infiltrates).
2. Laboratory findings: Markedly elevated ESR, anemia (normochromic normocytic), hematuria, **positive c-ANCA in 90%** *of patients*—sensitive and specific; thrombocytopenia may be present.
3. Open lung biopsy confirms diagnosis.

D. Prognosis and treatment

1. Prognosis is poor—most patients die within 1 year after the diagnosis.
2. A combination of **cyclophosphamide and corticosteroids** can induce remissions in many patients, but a relapse may occur at any time.
3. Consider renal transplantation if the patient has end-stage renal disease (ESRD).

Quick HIT

Most patients with Wegener granulomatosis also have sinus disease, pulmonary disease, and glomerulonephritis. Renal disease accounts for the majority of deaths.

Polyarteritis Nodosa

A. General characteristics

1. Vasculitis of medium-sized vessels involving the nervous system and GI tract
2. Can be associated with **hepatitis B**, HIV, and drug reactions
3. Pathophysiology: PMN invasion of all layers and fibrinoid necrosis plus resulting intimal proliferation lead to reduced luminal area, which results in ischemia, infarction, and aneurysms
4. Necrosis is segmented leading to "rosary sign" as a result of aneurisms

B. Clinical findings

1. Early symptoms are fever, weakness, weight loss, myalgias and arthralgias, and abdominal pain (bowel angina).
2. Other findings are HTN, mononeuritic multiplex, and livedo reticularis.

C. Diagnosis

1. Diagnosis is made by biopsy of involved tissue or mesenteric angiography.
2. ESR is usually elevated, and p-ANCA may be present.
3. Test for fecal occult blood.

D. Prognosis and treatment: The prognosis is poor, but is improved to a limited extent with treatment. Start with corticosteroids. If polyarteritis nodosa (PAN) is se vere, add cyclophosphamide.

Quick HIT

There is **no pulmonary involvement** in PAN (which distinguishes it from Wegener granulomatosis).

Behçet Syndrome

- An autoimmune, multisystem vasculitic disease; cause is unknown.
- Clinical features: painful, sterile oral and genital ulcerations (**pathergy**), arthritis (knees and ankles most common), **eye involvement** (uveitis, optic neuritis, iritis, conjunctivitis), CNS involvement (meningoencephalitis, intracranial HTN), fever, and weight loss.

- Diagnosis is made by biopsy of involved tissue (laboratory tests are not helpful).
- Treatment is steroids, which are helpful.
- Often presents in Middle Easterners.

Buerger Disease (Thromboangiitis Obliterans)

- Occurs mostly in young men who **smoke cigarettes**
- Acute, **segmental inflammation** of small- and medium-sized arteries and veins, affecting arms and legs
- inflammation in veins leads to superficial nodular phlebitis
- May lead to gangrene and **autoamputation**
- Clinical features include ischemic claudication; cold, cyanotic, painful distal extremities; paresthesias of distal extremities; and ulceration of digits. Raynaud phenomena may also be observed
- Smoking cessation is mandatory to reduce progression

Hypersensitivity Vasculitis

- Small-vessel vasculitis that is a hypersensitivity reaction in response to a drug (penicillin, sulfa drugs), infection, or other stimulus.
- Skin is predominantly involved—palpable purpura, macules, or vesicles (common on lower extremities) can occur. Lesions can be painful.
- Constitutional symptoms (fever, weight loss, fatigue) may be present.
- Diagnosis is made by biopsy of tissue.
- Prognosis is very good—spontaneous remissions are common.
- Withdrawal of the offending agent and steroids are the treatments of choice.

1. Empiric therapy requires antibiotics with high bone penetration including cephalosporins (cefazolin, ceftriaxone, cefuroxime), fluroquinolones (levofloxacin, ciprofloxacin, moxifloxacin), vancomycin, linezolid, daptomycin, and clindamycin. Rifampin can also be added as adjunct to help with biofilm penetration.
2. Add an aminoglycoside and possibly a β-lactam antibiotic if there is a possibility of infection with a gram-negative organism.
3. Surgical debridement of infected necrotic bone is an important aspect of treatment.

Quick HIT

Chronic osteomyelitis refers to bone necrosis and soft tissue compromise or to a relapse of previously treated osteomyelitis. It is very challenging to treat and almost impossible to completely eradicate.

Acute Infectious Arthritis

A. General characteristics

1. Acute infectious arthritis occurs when microorganisms (usually bacteria) invade the joint space (not the bone itself), where they release endotoxins and trigger cytokine release and neutrophil infiltration. These inflammatory reactions ultimately lead to erosion and destruction of the joint.
2. Pathogenesis—microorganisms penetrate the joint via the following mechanisms:
   a. Hematogenous spread—most common route.
   b. Contiguous spread from another locus of infection (e.g., osteomyelitis, abscess, or cellulitis).
   c. Traumatic injury to joint.
   d. Iatrogenic (e.g., from arthrocentesis, arthroscopy).
3. Microbiology
   a. The most common offender is bacteria.
   b. Acute bacterial arthritis can be caused by any of the following:
      - ***S. aureus* is the most common agent overall in adults and children.** Various streptococcal species are also frequently involved.
      - An important gram-negative agent is *N. gonorrhoeae*. **Gonococcal arthritis is the most common cause of acute infectious arthritis in young, sexually active adults (see also Clinical Pearl 10-6).**
      - Consider gram-negative organisms such as *Pseudomonas aeruginosa* or *Salmonella* spp. if there is a history of sickle cell disease, immunodeficiency, or IV drug abuse.
4. Other risk factors for acute infectious arthritis.
   a. Prior joint damage (e.g., rheumatoid arthritis).
   b. Joint prosthesis
   c. Diabetes mellitus

Quick HIT

If patient has a painless range of motion of involved joint, septic arthritis is very unlikely, even in the presence of erythema. Micromotion of joint causes severe pain in septic arthritis.

B. Clinical features

1. The joint is swollen, warm, and painful.
   a. **The range of motion (active or passive) is very limited.**
   b. An effusion can be palpated.
2. Constitutional symptoms such as fever, chills, and malaise are common.

Quick HIT

Septic Arthritis

- **The most common joint affected is the knee.** The hip, wrist, shoulder, and ankle may also be involved.
- Patients with immunosuppression or connective tissue diseases may have polyarticular arthritis (and a worse prognosis).

CLINICAL PEARL 10-6

Gonococcal Arthritis

- This presents with acute monoarthritis or oligoarthritis, and often progresses within days in a migratory or additive pattern.
- Knees, wrists, hands, and ankles are the most commonly involved.
- Tenosynovitis is often present in the hands and feet.
- Fever, chills, and rash (macules, papules, and/or pustules) are signs of disseminated gonococcal infection. If the patient has disseminated gonococcal infection, admit to the hospital.
- After the joint is initially aspirated, repeated aspiration is unnecessary (unlike in other causes of septic arthritis), and antibiotics alone usually lead to improvement. Treat presumptively for chlamydial infection (e.g., with doxycycline).
- Consider testing for HIV and syphilis. Educate the patient about the risks of sexual practices.

C. Diagnosis

1. **Perform a joint aspiration ("tap") and analysis of synovial fluid in all patients suspected of having a septic joint.** Order the following studies on aspirated synovial fluid.
   a. WBC count with differential—usually >50,000 WBCs/mm^3 with >80% PMNs—the most helpful test.
   b. Gram stain of fluid—positive in approximately 75% of gram-positive cases, but only 30% to 50% of gram-negative cases.
   c. Culture—aerobic and anaerobic.
   d. Crystal analysis—keep in mind that acute gout may present like septic arthritis.
   e. PCR of synovial fluid—this may be useful if gonococcal arthritis is suspected but Gram stain and cultures are negative.
2. Blood cultures are positive in >50% of all cases (frequently negative in gonococcal arthritis).
3. Other laboratory abnormalities.
   a. Leukocytosis—present in about half of patients with a septic joint.
   b. Elevated ESR—elevated in up to 90% of patients with septic joint.
   c. Elevated CRP—useful in monitoring clinical improvement.
4. Imaging studies.
   a. Plain radiographs—generally not useful unless joint damage is severe.
   b. CT or MRI—helpful if the sacroiliac or facet joints are involved.
5. Obtain cultures from appropriate mucosal surfaces (e.g., genitourinary tract) if gonococcal arthritis is suspected.

D. Treatment

1. Prompt antibiotic treatment.
   a. Do not delay in initiating antimicrobial therapy when acute infectious arthritis is suspected.
   b. If the Gram stain result is negative but acute bacterial arthritis is still suspected, treat empirically based on the clinical scenario (see Table 10-10) until culture and sensitivity results are available.
2. Drainage
   a. Daily aspiration of affected joint as long as effusion persists is one treatment option. However, surgical drainage is recommended to prevent further damage to the articular cartilage that occurs with persistent infectious process. Certain joints are amenable to arthroscopic drainage (shoulder, knee) whereas others are not (hip, wrist, elbow, ankle) and should be opened.

Quick HIT

Complications of Septic Arthritis
- Destruction of joint and surrounding structures (e.g., ligaments, tendons), leading to stiffness, pain, and loss of function
- Avascular necrosis (if hip is involved)
- Sepsis

TABLE 10-10 Medical Treatment of Acute Bacterial Arthritis

Adult (Relatively Healthy): Treat for *S. aureus*	Patient Is Immunocompromised or Has Significant Risk Factors for Gram-negative Arthritis	Young Adult With History and Presentation Consistent with Gonococcal Arthritis
Parenteral, β-lactamase–resistant penicillin (e.g., oxacillin) or first-generation cephalosporin × 4 wks	Parenteral, broad-spectrum antibiotics (with gram-negative coverage) (e.g., a third-generation cephalosporin or aminoglycoside) for 3–4 wks	Parenteral, third-generation cephalosporin (e.g., ceftriaxone) until there is improvement
Treat with vancomycin if MRSA is suspected	For pseudomonal infection, use aminoglycoside + extended-spectrum penicillin	Switch to an oral agent with gram-negative coverage (e.g., ciprofloxacin 3–10 days) once there is clinical improvement

b. Treatment is NSAIDs and activity modification. If symptoms persist, local cortisone injections into the bursa are very effective in providing relief.

Carpal Tunnel Syndrome

Quick HIT

A negative Phalen test or Tinel sign does not exclude carpal tunnel syndrome.

A. General characteristics

1. Caused by **median nerve compression** within the tight confines of the carpal tunnel, causing numbness and pain in median nerve distribution. If long standing and severe, atrophy of thenar muscles may be seen.
2. Associated conditions include hypothyroidism, diabetes, repetitive use of hands in certain activities, pregnancy, recent trauma, or fracture of the wrist.

B. Clinical features

1. Numbness, pain, or tingling in the **median nerve distribution**—usually worse at night; sometimes patient has pain/numbness along the entire arm (as far as the shoulder).
2. Muscle weakness and thenar atrophy may develop later.

C. Diagnosis

1. Physical examination
   a. **Tinel sign**—tap over median nerve at wrist crease; causes paresthesias in median nerve distribution
   b. **Phalen test**—palmar flexion of the wrist for 1 minute; causes paresthesias in median nerve distribution
2. Electromyography (EMG) and nerve conduction velocity (NCV) study
   a. For definitive diagnosis
   b. Indicated if diagnosis is not clear from clinical findings or if patient develops weakness or persistent symptoms

D. Treatment

1. Wrist splints (volar carpal splint) should be worn at night during sleep. The purpose is to prevent wrist flexion during sleep (which compresses the nerve).
2. Anti-inflammatory medications (NSAIDs).
3. Local corticosteroid injection—relief can be long term in some patients.
4. Surgical release is very effective. Consider this option for patients who have persistent symptoms or if the symptoms are limiting the patient's activities or quality of life.

Osteoarthritis

A. General characteristics

1. Osteoarthritis is characterized by **degeneration of cartilage** (due to wear and tear) and by hypertrophy of bone at the articular margins.
2. By age 65, more than 75% of the population has radiographic evidence of osteoarthritis in weight-bearing joints (hips, knees, lumbar spine).
3. Any joint can be affected, but weight-bearing joints are most commonly involved (hips, knees, cervical, and lumbar spine).

B. Risk factors

1. Age
2. Obesity
3. Excessive joint loading (manual labor, athletes, etc.)
4. Trauma
   a. Repeated microtrauma—in many cases, a patient's occupation or athletic activities require repetitive motions (such as repeated knee bending) that predispose the patient to degenerative joint disease in later years
   b. Macrotrauma (fractures, ligament injuries)—fractures that are intra-articular can cause OA
5. Genetic predisposition

6. Altered joint anatomy or instability (developmental hip dysplasia, dislocation due to trauma, rheumatoid arthritis, gout, pseudogout)
7. Deposition diseases cause chondrocyte injury, or make the cartilage more stiff (hemochromatosis, ochronosis, alkaptonuria, Wilson disease, Gaucher disease, gout, CPPD)
8. Hemophilia (hemarthroses)

C. Clinical features

1. Joint pain (often monoarticular)
   a. This is caused by movement of one joint surface against another (bone on bone) because of cartilage loss. There are no pain fibers in cartilage, so its insidious destruction over time goes unnoticed. Once it is completely worn out, the bones (which do have pain fibers) start rubbing against each other, producing the pain of osteoarthritis
   b. Deep, dull ache that is relieved with rest and worsened with activity
   c. Insidious onset, with gradual progression over many years
2. Stiffness in the morning or after a period of inactivity (Note: morning stiffness lasting >30 minutes may suggest an inflammatory arthritis such as rheumatoid arthritis)
3. Limited range of motion (late stages) due to bony enlargement of joints (osteophytes); bony crepitus may be present
4. No systemic symptoms; no erythema or warmth. Swelling may be present and suggests inflammation

D. Diagnosis

1. Plain radiographs are the initial tests and should be obtained in all patients suspected of having osteoarthritis (Figure 12-4). Ideally, radiographs should be obtained in the standing position (for lower extremities). Findings include:
   a. **Joint space narrowing** (due to loss of cartilage)—key finding on radiographs
   b. **Osteophytes**
   c. **Sclerosis** of subchondral bony end-plates adjacent to diseased cartilage—most severe at points of maximum pressure
   d. **Subchondral cysts**—occur as a result of increased transmission of intra-articular pressure to the subchondral bone
2. All blood tests are normal
3. MRI of the spine if indicated (neurologic findings, before surgery)

E. Treatment

1. Nonpharmacologic treatment.
   a. Avoid activities that involve excessive use of the joint.
   b. Weight loss is very important.
   c. Physical therapy can be beneficial. Goals are to maintain range of motion and muscle strength. Swimming is an ideal exercise (involves minimal involvement of weight-bearing joints); avoid excessive walking.
   d. Use canes or crutches to reduce weight on the joint.
2. Pharmacologic treatment.
   a. Acetaminophen is the first-line agent.
   b. NSAIDs are just as effective as acetaminophen (but GI bleeding is a concern with long-term use). Of selective COX-2 inhibitors, only celecoxib remains on the market but is rarely used. All the others have been removed from the market due to increased risk of cardiovascular events. Main benefit of selective COX-2 inhibitors is a decrease in gastric/duodenal ulcers and a decrease in GI symptoms, with the same (not superior) analgesic and anti-inflammatory effects of the nonselective NSAIDs.
   c. Intra-articular injections of corticosteroids are very helpful, but more than three to four injections per year is not recommended. Patients may have up to 3 months of pain relief with each injection. In elderly patients with severe OA who are not good surgical candidates for joint replacement, more frequent injections are justified if it provides good pain control.

Quick HIT

The following can contribute to or exacerbate forces to the cartilage:
- Compromised pain sensation or proprioception
- Ligamental laxity
- Falls of very short distances (because they do not provide ample opportunity for compensatory movements to decrease the impact load)

Quick HIT

If the spine is involved, nerve roots may become compressed and lead to radicular pain.

Quick HIT

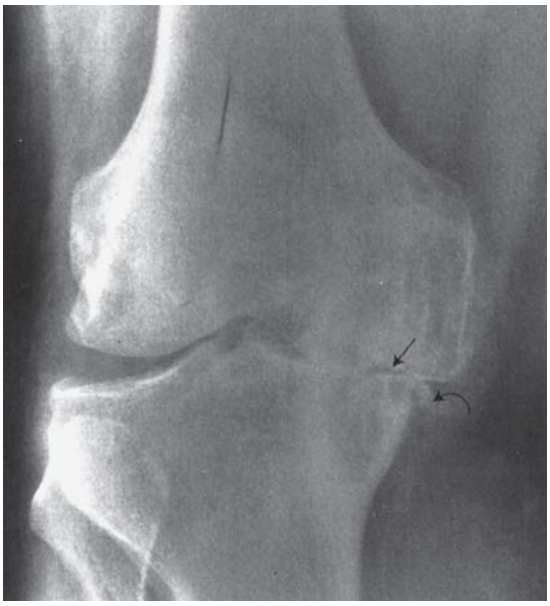
Hip osteoarthritis causes pain in the groin (not lateral hip or buttock). If patient is tender over the lateral aspect of hip, suspect greater trochanteric bursitis.

Quick HIT

Radiographic findings in osteoarthritis: joint space narrowing, osteophytes, subchondral sclerosis, subchondral cysts.

Quick HIT

Common (but Useless) "pimp" Information
- *Bouchard nodes:* Bony overgrowth and significant osteoarthritic changes (i.e., osteophytes) at the PIP joints
- *Heberden nodes:* Bony overgrowth and significant osteoarthritic changes (i.e., osteophytes) at the DIP joints



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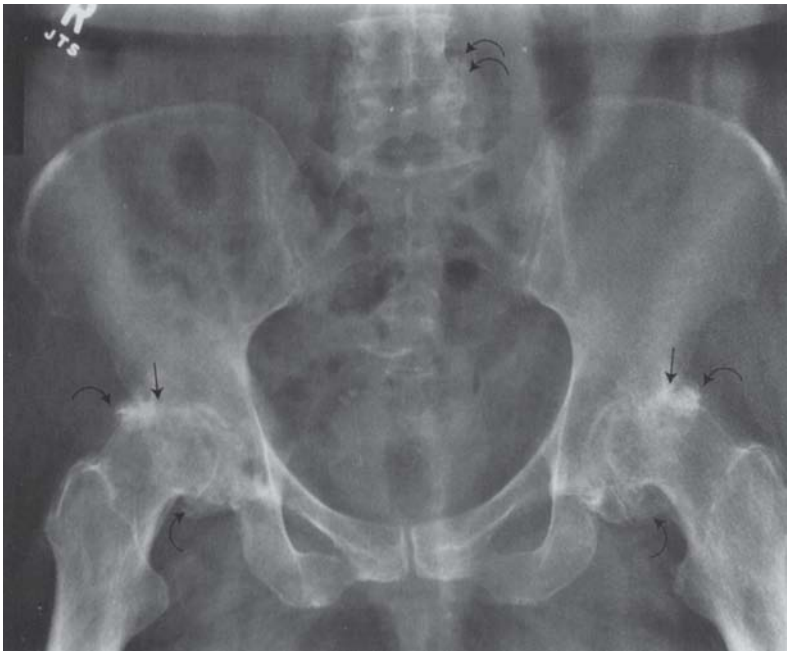

B

FIGURE 12-4 **A: Right knee AP radiograph showing osteoarthritis. Note medial joint space narrowing, osteophyte formation (*curved arrow*), and irregular articular surfaces (*straight arrow*). B: Pelvic AP radiograph. Bilateral osteoarthritis of the hip. Note narrowing of hip joint spaces, osteophytes (*curved arrows*), and osteophytes in the lumbar spine (*double curved arrows*). Also note subchondral cysts and sclerosis of the femoral heads.**

(**A** from Erkonen WE, Smith WL. *Radiology 101: The Basics and Fundamentals of Imaging*. Philadelphia, PA: Lippincott Williams & Wilkins, 1998:287, Figure 11-72.) (**B** from Erkonen WE, Smith WL. *Radiology 101: The Basics and Fundamentals of Imaging*. Philadelphia, PA: Lippincott Williams & Wilkins, 1998:288, Figure 11-73A.)

Quick HIT

With osteoarthritis of the hips, the pain is in the **groin region** and sometimes radiates to the anterior thigh.

Quick HIT

For **left** knee or hip pain, the cane should be held in the **right** hand.

d. Viscosupplementation—recent studies show good pain relief, but results are variable. Hyaluronic acid is injected into the knee joint and augments the viscoelastic properties of normal synovial fluid.

3. Surgery for serious disability.
   a. Total joint replacement may be performed if conservative therapy fails to control pain. It should be delayed as long as possible because a revision may be

needed 15 to 20 years after surgery. Total hip and knee replacements are among the most successful procedures in orthopedics with reliable pain relief.

4. Nutritional products—glucosamine and chondroitin sulfate.
   a. Over-the-counter products that many patients claim to improve arthritis symptoms, although high-quality randomized trials have not shown any meaningful benefit.

Osteoporosis

A. General characteristics

1. Decreased bone mass/quality causes increased bone fragility and fracture risk. In osteoporosis, the bone mineral density is at least 2.5 standard deviations below that of young, normal individuals.
2. Mechanism: failure to attain optimal (peak) bone mass before age 30, or rate of bone resorption exceeds rate of bone formation after peak bone mass is attained
3. Most osteoporotic patients are postmenopausal women and elderly men
4. Classification
   a. Primary osteoporosis (two types that are impractical clinically)
      - Type I (most often in postmenopausal women 51 to 75 years of age)—excess loss of trabecular bone; vertebral compression fractures and Colles fractures are common
      - Type II (most often in men and women over 70 years of age)—equal loss of both cortical and trabecular bone; fractures of femoral neck, proximal humerus, and pelvis most common
   b. Secondary osteoporosis—An obvious cause is present, such as excess steroid therapy/Cushing syndrome, immobilization, hyperthyroidism, long-term heparin, hypogonadism in men, and vitamin D deficiency

B. Risk factors

1. Estrogen depletion
   a. Postmenopausal state—all women are estrogen deficient after menopause; however, osteoporosis does not develop in all women
   b. History of athletic amenorrhea, eating disorders, oligomenorrhea
   c. Early menopause
2. Female gender—women have a lower peak bone mass and smaller vertebral end plates
3. Calcium deficiency/vitamin D deficiency
4. Decreased peak bone mass
5. Heritable risk factors—family history, European or Asian ancestry, thinness/slight build
6. Decreased physical activity (prolonged immobility)
7. Endocrine—hypogonadism in men (with low testosterone), hyperthyroidism, vitamin D deficiency (see Clinical Pearl 12-9)

CLINICAL PEARL 12-9

Osteoporotic Fracture Risk Assessment

Validated risk factors for osteoporotic fracture risk that are independent of bone mineral density are:

- Advanced age
- Previous osteoporotic fracture
- Long-term steroid therapy
- Cigarette smoking
- Low body weight (<58 kg)
- Family history of hip fracture
- Excess alcohol intake
- Rheumatoid arthritis
- Secondary osteoporosis

Quick HIT

Although x-rays are diagnostic of OA, not all patients with x-ray findings of OA have symptoms. There is no consistent correlation between symptoms and severity of x-ray findings.

Quick HIT

It is often difficult to differentiate between primary and secondary osteoporosis, and the two may coexist. It is best to attempt to identify any predisposing conditions and eliminate them if possible.

Quick HIT

Some elderly patients have progressive kyphosis (hunchback deformity) because they have multiple vertebral compression fractures.

Quick HIT

Osteoporosis is a "silent" disease. It is asymptomatic until a fracture occurs.

Quick HIT

An exercise program with calcium and vitamin D supplements is the mainstay of the therapy for prevention or treatment of osteoporosis.

Quick HIT

The **PROOF trial** showed the following regarding **calcitonin:**
- No effect at hip
- Shown to decrease risk of vertebral fractures by as much as 40%
- Slight increase in bone density at lumbar vertebrae

Quick HIT

Recommend the following to all patients with osteoporosis:
- Daily calcium
- Daily vitamin D
- Weight-bearing exercise
- Smoking cessation

Quick HIT

Of all fragility fractures, hip fractures have highest morbidity and mortality.

Quick HIT

If DEXA scan is normal and no risk factors, repeat DEXA in 3 to 5 years.

Quick HIT

Unfortunately, most patients with fragility fractures do not subsequently receive osteoporosis therapy, despite data showing a beneficial effect in reducing the risk of a second fracture.

8. Smoking and alcohol abuse
9. Medications—corticosteroids, prolonged heparin use

C. Clinical features

1. Vertebral body compression fractures (of the middle and lower thoracic and upper lumbar spine) are the most common. Very rare in cervical spine
   a. Result in pain and deformity, including kyphosis
   b. Severe back pain after minor trauma
   c. Restricted spinal movement, loss of height
2. Colles fracture (distal radius fracture)—usually due to fall on outstretched hand; more common in postmenopausal women
3. Hip fractures—femoral neck, intertrochanteric fractures
4. Increased incidence of long bone fractures—humerus, femur, tibia

D. Diagnosis

1. DEXA (dual-energy x-ray absorptiometry) scan is the gold standard.
   a. Very precise for measuring bone density.
   b. Indications for bone mineral density measurement:
      - All women 65 and older.
      - Postmenopausal women <65 with one or more risk factors for fracture.
      - Men with risk factors for fracture.
   c. Sites selected are femoral neck and lumbar spine. Compare the density of bone with a standard control, which is the bone density of a healthy 30-year-old person.
   d. Can range from normal to osteopenia to osteoporosis. T-scores are used according to WHO classification (see Table 12-8).
      - WHO classification (T-scores) are used in all postmenopausal and perimenopausal women, and in men over age 50. In all other patients (including premenopausal women), z-scores are used.
2. Rule out secondary causes—check calcium, phosphorus, alkaline phosphatase, TSH, vitamin D, free PTH, creatinine, CBC.

E. Treatment

1. Nonpharmacologic therapy
   a. Diet—adequate calorie intake, avoid malnutrition
      - Supplemental elemental calcium (1,200 mg/day)
      - 800 international units of vitamin D daily
   b. Exercise—weight-bearing exercise for 30 minutes, at least 3 times a week, to stimulate bone formation
   c. Smoking cessation is critical—smoking accelerates bone loss
   d. Eliminate or reduce alcohol intake

TABLE 12-8 Bone Mineral Density T-score Criteria for Osteopenia and Osteoporosis

Diagnosis	T-score
Normal	Greater than or equal to 1.0
Osteopenia	Between –1.0 and –2.5
Osteoporosis	Less than or equal to –2.5
Severe osteoporosis	Less than or equal to –2.5 and fragility fracture

Adapted from World Health Organization: http://www.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf

2. Pharmacologic therapy
   a. Indicated in the following patients:
      • Postmenopausal women with established osteoporosis (T-score 2.5 or less) or fragility fracture (hip or vertebral)
      • High-risk postmenopausal women with T-score between −1.0 and −2.5
   b. Bisphosphonates inhibit bone resorption and are first-line treatment
      • They decrease osteoclastic activity (via binding to hydroxyapatite) and decrease the risk of fractures
      • Oral bisphosphonates (alendronate, risedronate) are preferred in most patients
      • Side effects include reflux, esophageal irritation, and ulceration
      • If patient cannot tolerate oral bisphosphonates, IV bisphosphonates (IV zoledronic acid)
   c. PTH therapy or human recombinant PTH therapy
      • PTH is an effective drug that increases bone mineral density and reduces fracture risk. Due to high cost, subcutaneous administration, and long-term safety concerns, it is not a first-line drug
      • Indicated in patients with severe osteoporosis (T-score less than 2.5) who cannot tolerate bisphosphonates, or who continue to fracture despite being on bisphosphonates for 1 year
      • Maximum duration of treatment is 24 months, because of concern for osteosarcomas, which have been observed in rats. After stopping PTH, can restart bisphosphonates
   d. Calcitonin (can be administered by nasal spray)—long-term benefits are minimal, but it is useful as short-term therapy, especially in elderly female patients with vertebral compression fracture. It is less popular and not commonly used
   e. Estrogen–progestin therapy is no longer a first-line approach for the treatment of osteoporosis in postmenopausal women because of increased risk of breast cancer, stroke, venous thromboembolism, and perhaps CAD

Diseases of the Eye

Age-related Macular Degeneration

- Most common cause of vision loss in people over 65 years of age in developed countries.
- Age-related macular degeneration (ARMD) is characterized by loss of central vision (because the macula is affected). Blurred vision, distortion, and scotoma are common. Complete loss of vision almost never occurs. Peripheral vision is preserved.
- The main risk factor is advanced age. Other risk factors are female gender, Caucasian race, smoking, HTN, and family history.
- Two categories: exudative ("wet") and nonexudative ("dry") macular degeneration.
- Exudative ARMD causes sudden visual loss due to leakage of serous fluid and blood as a result of abnormal vessel formation (neovascularization) under the retina.
- Nonexudative ARMD is characterized by atrophy and degeneration of the central retina. Yellowish-white deposits called **drusen** form under the pigment epithelium and can be seen with an ophthalmoscope.
- Intraocular injections of medications (anti-VEGF inhibitors) have supplanted laser photocoagulation and other therapies for wet ARMD.
- Over-the-counter formulations of vitamins are recommended for dry and wet ARMD.

Glaucoma

A. General characteristics

1. Glaucoma is **one of the most important causes of blindness worldwide.** It is a complex disease typically characterized by increased IOP, damage to the optic nerve, and irreversible vision loss.
2. The pathogenesis of optic nerve damage in glaucoma is not fully understood. Ischemia may play a major role. Over time there is a loss of ganglion cells, leading to atrophy of the optic disc (and enlargement of the optic cup, called "**cupping**").

Quick HIT

Most common causes of visual impairment/loss in developed countries:
- Diabetic retinopathy (most common cause in adults <65 years)
- ARMD (most common cause in adults >65 years)
- Cataracts
- Glaucoma

Quick HIT

Age-related Macular Degeneration
- The "wet" form of ARMD can develop at any time, so patients with "dry" ARMD must be monitored closely.
- Supplements of certain vitamins containing antioxidants are thought to be beneficial, but a preventative or therapeutic effect has not been proven.
- **Ranibizumab (and several other related drugs), given as repeated intraocular injections,** have been shown to be effective in treating "wet" ARMD.