HARRISON'S PRINCIPLES OF INTERNAL MEDICINE — 22nd Edition

Rheumatoid Arthritis

Chapter 370 | Part 11: Immune-Mediated, Inflammatory, and Rheumatologic Disorders | Part 11 – Rheumatology & Immunology | DETAILED EDITION

KEY CLINICAL POINTS

1. Rheumatoid arthritis (RA) is defined as a chronic inflammatory disease characterized by a symmetric, erosive polyarthritis.
2. Morning joint stiffness lasting >1 h that eases with physical activity is a hallmark presenting symptom.
3. The earliest involved joints are mostly the small joints of the hands and feet (MCP, PIP, wrists).
4. Subcutaneous nodules occur in 30–40% of patients, are firm, nontender, and adherent to periosteum/tendons.
5. Secondary Sjögren's syndrome is defined by keratoconjunctivitis sicca and xerostomia in association with RA.
6. Interstitial lung disease (ILD) prevalence in RA is as high as 12%, with UIP and NSIP as main patterns.
7. Cardiovascular disease is the most common cause of death in RA patients, with incidence higher than general population.
8. HLA-DRB1 shared epitope (SE) alleles increase risk 4-fold (single allele) to 8-fold (two alleles).
9. Smoking confers a 20- to 40-fold increased risk of RA when combined with SE alleles.
10. Felty's syndrome is defined by the clinical triad of neutropenia, splenomegaly, and nodular RA.

FIGURES IN THIS CHAPTER

1. Pathophysiologic mechanisms of inflammation and joint...
2. Extraarticular manifestations of rheumatoid arthritis
3. Global prevalence rates of rheumatoid arthritis...
4. Ultrasound demonstrating an effusion (arrow) within...
5. Metacarpophalangeal joint swelling and subluxation
6. Ultrasound demonstrating an effusion (arrow) within...
7. Figure / Illustration

1. DEFINITION & OVERVIEW

• Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by a symmetric, erosive polyarthritis.

• It is the most common form of chronic inflammatory arthritis.

• Persistently active RA often results in articular cartilage and bone destruction and functional disability.

• RA is a systemic disease that may lead to a variety of extraarticular manifestations, including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities.

• The incidence of RA increases between 25 and 55 years of age, after which it plateaus until the age of 75 and then decreases.

1.1 Clinical Presentation

- Presenting symptoms are typically related to inflammation of the joints, tendons, and bursae.
- Patients often complain of early morning joint stiffness lasting >1 h that eases with physical activity.
- The earliest involved joints are mostly the small joints of the hands and feet.
- The initial pattern of joint involvement may be monoarticular, oligoarticular (≤4 joints), or polyarticular (>5 joints), usually in a symmetric distribution.
- Some patients with inflammatory arthritis will present with too few affected joints to be classified as having RA—so-called undifferentiated inflammatory arthritis.
- Those with an undifferentiated arthritis who are most likely to be diagnosed later with RA have a higher number of tender and swollen joints, test positive for serum rheumatoid factor (RF) or ACPA, and have higher scores for physical disability.

1.2 Extraarticular Manifestations

- Extraarticular manifestations may develop during the clinical course of RA in up to 40% of patients, even prior to the onset of arthritis.
- Patients most likely to develop extraarticular disease have a history of cigarette smoking, have early onset of significant physical disability, and test positive for serum RF or ACPA.
- Recent studies have shown a decrease in the incidence and severity of at least some extraarticular manifestations, particularly Felty's syndrome and vasculitis.

Table 1 Extraarticular Manifestations of RA

System	Manifestation
Ocular	Keratoconjunctivitis sicca, episcleritis, scleritis
Neurologic	Cervical myelopathy
Hematologic	Anemia of chronic disease, neutropenia, splenomegaly, Felty's syndrome, large granular lymphocyte leukemia, lymphoma
Oral	Xerostomia, periodontitis
Pulmonary	Pleural effusions, pulmonary nodules, interstitial lung disease, pulmonary vasculitis, organizing pneumonia
Cardiac	Pericarditis, ischemic heart disease, myocarditis, cardiomyopathy, arrhythmia, mitral regurgitation
Renal	Membranous nephropathy, secondary amyloidosis
GI	Vasculitis
Skeletal	Osteoporosis
Skin	Rheumatoid nodules, purpura, pyoderma gangrenosum
Endocrine	Hypoandrogenism

2. EPIDEMIOLOGY

- RA affects ~0.5–1% of the adult population worldwide, although the majority of epidemiologic studies have been done in Western countries.

• There is evidence that the overall incidence of RA has been decreasing in recent decades, whereas the prevalence has remained the same because individuals with RA are living longer.

• The incidence and prevalence of RA vary based on geographic location, both globally and among certain ethnic groups within a country.

• Like many other autoimmune diseases, RA occurs more commonly in females than in males, with a 2–3:1 ratio.

• Studies of RA from some of the Latin American and African countries show an even greater predominance of disease in females compared to males, with ratios of 6–8:1.

2.1 Genetic Considerations

• It has been recognized for >30 years that genetic factors contribute to the occurrence of RA as well as to its severity.

• The likelihood that a first-degree relative of a patient will share the diagnosis of RA is 2–10 times greater than in the general population.

• Heritability estimates range from 40 to 60%, although this may be higher in ACPA-positive patients compared to those without ACPA.

• The alleles known to confer the greatest risk of RA are located within the major histocompatibility complex (MHC) and, in particular, those encoding the MHC class II molecules.

• Most, but probably not all, of this risk is associated with allelic variation in the HLA-DRB1 gene, which encodes the MHC II β-chain molecule.

• The disease-associated HLA-DRB1 alleles share an amino acid sequence at positions 70–74 in the third hypervariable regions of the HLA-DR β-chain, termed the shared epitope (SE).

• These amino acids are located in the antigen-binding groove within the hypervariable regions of the HLA-DRβ1 molecule.

• Peptides derived from posttranslationally modified proteins (via citrullination, acetylation, or carbamylation, for example) may bind with greater avidity to the SE, providing a potential explanation for increased disease risk at a molecular level.

• The risk of RA is four times higher in persons carrying a single SE allele and eight times higher in those carrying two alleles compared to SE-negative individuals.

• Carriership of the SE alleles is associated with production of ACPAs and worse disease outcomes.

• Some HLA-DRB1 alleles bestow a high risk of disease (*0401), whereas others confer a more moderate risk (*0101, 0404, 1001, and 0901).

• Over 90% of patients with RA express at least one of these variants.

• Interestingly, HLA-DRB1*1301 and to a lesser extent HLA-DRB1*1302 confer protection from ACPA-positive RA.

Table 2 Global Prevalence Rates of Rheumatoid Arthritis (RA) with Genetic Associations

Region/Ethnicity	Prevalence (%)	Major Genetic Alleles
European ancestry	0.4–1.5%	HLA-DRB1: *0401, *0404, *0301, *0101
Asian ancestry	2–3%	HLA-DRB1: *0405, *0901
North American	0.7–1.3%	PTPN22, STAT4, TNFAIP3
Jamaica	1.9–2.2%	HLA-DRB1: *0401
Greece	0.2–0.6%	HLA-DRB1: *0101

Region/Ethnicity	Prevalence (%)	Major Genetic Alleles
Hong Kong	0.1–0.5%	HLA-DRB1: *0401 (East Asian)
Japan	0.2–0.3%	HLA-DRB1: *0901 (Japanese, Malaysian, Korean)
South Africa	1.7–4.5%	HLA-DRB1: *0405
Lesotho	0.1–0.2%	Other

2.2 Environmental Factors

• In addition to genetic predisposition, a host of environmental factors have been implicated in the pathogenesis of RA.

• The most reproducible of these environmental links is cigarette smoking.

• Numerous cohort and case-control studies have demonstrated that smoking confers a relative risk for developing RA of 1.5–3.5 times.

• Smoking-related risk interacts in a synergistic manner with MHC risk alleles.

• The classic SE alleles alone increase the likelihood of developing RA by four- to sixfold; however, this risk increases to 20- to 40-fold when combined with smoking.

• In particular, women who smoke cigarettes have a nearly 2.5 times greater risk of RA, a risk that persists even 15 years after smoking cessation.

• A twin who smokes will have a significantly higher risk for RA than their monozygotic co-twin, theoretically with the same genetic risk, who does not smoke.

• Interestingly, the risk of smoking is almost exclusively related to RF and ACPA-positive disease.

• However, it has not been shown that smoking cessation, while having many health benefits, reduces the severity or extent of joint inflammation.

• Inhalant-related occupations and silica inhalants also may increase RA risk.

• These observations have led to the theory that subclinical lung disease may play a critical early role in the initial development of autoreactive immune cells and account for the occurrence of autoantibodies more than a decade prior to the clinical development of joint disease.

• Researchers began to aggressively seek an infectious etiology for RA after the discovery in 1931 that sera from patients with this disease could agglutinate strains of streptococci.

• Certain viruses such as Epstein-Barr virus (EBV) have garnered the most interest over the past 30 years given their ubiquity, ability to persist for many years in the host, and frequent association with arthritic complaints.

• For example, titers of IgG antibodies against EBV antigens in the peripheral blood and saliva are significantly higher in patients with RA than in the general population.

• EBV DNA has also been found in synovial fluid and synovial cells of RA patients.

• Because the evidence for these links is largely circumstantial, it has not been possible to directly implicate infection as a causative factor in RA.

• An attractive hypothesis raised by newer studies is that microbial dysbiosis of the oral or gut microbiome may predispose to the development of RA.

• Recent work suggests that periodontitis in the oral cavity may play a role in disease mechanisms.

• Multiple studies provide evidence for a link between ACPA-positive RA and cigarette smoking, periodontal disease, and the oral microbiome, specifically Porphyromonas gingivalis.

• It has been hypothesized that the immune response to P. gingivalis may trigger the development of RA and the bacterial enzyme peptidyl arginine deiminase (PAD) induces ACPA by catalyzing the citrullination

of arginine residues on the stimulating autoantigens.

• Interestingly, P. gingivalis is the only oral bacterial species known to harbor this enzyme.

• Some studies have shown a relationship between the presence of circulating antibodies to P. gingivalis and RA, as well as with first-degree relatives at risk for this disease.

• However, it remains unproven whether the observed dysbiosis in the oral cavity precedes the development of disease.

• There are also limited data suggesting a role for the gut microbiome in the etiology of RA.

• Some studies have found that the gut microbiome is different in patients with early RA compared with controls.

• In particular, Prevotella copri was reported to be enriched in early untreated RA as well as in an “at-risk” population.

• On the other hand, a common dysbiotic signature does not seem to predominate in patients with RA, and evidence is lacking for a direct immune-modulating effect.

• Epigenetics is the study of heritable traits that affect gene expression but do not modify DNA sequence.

• Epigenetic mechanisms are theoretically involved in three important aspects of RA: contribution to disease etiology, perpetuation of chronic inflammatory responses, and disease severity.

• The best-studied epigenetic mechanisms are those regulating posttranslational histone modifications and DNA methylation.

• DNA methylation patterns have been shown to differ between RA patients and healthy controls, including monozygotic twins, as well as RA from patients with osteoarthritis.

• Epigenetics may also offer a mechanistic explanation for how cigarette smoking confers an increased risk for ACPA-positive RA (see below) as those patients with the SE have higher levels of DNA methylation compared to nonsmokers.

• MicroRNAs, which are noncoding RNAs that function as posttranscriptional regulators of gene expression, represent an additional epigenetic mechanism that may potentially influence cellular responses.

3. ETIOLOGY & PATHOPHYSIOLOGY

• The pathogenic mechanisms of synovial inflammation are likely the result of a complex interplay of genetic, environmental, and immunologic factors that cause immune system dysregulation and a breakdown in self-tolerance.

• Precisely what triggers these initiating events and what genetic and environmental factors disrupt the immune system remains a mystery.

• However, a detailed molecular picture is emerging of the mechanisms underlying the chronic inflammatory response and the resulting destruction of the articular cartilage and bone.

• The pathologic hallmarks of RA are synovial inflammation and proliferation, focal bone erosions, and thinning of articular cartilage.

• Chronic inflammation leads to synovial lining hyperplasia and the formation of pannus, a thickened cellular membrane consisting of multiple layers of fibroblast-like synoviocytes and granulation-reactive fibrovascular tissue that has a propensity for invading underlying cartilage and bone.

• The inflammatory infiltrate is made up of no less than six cell types: T cells, B cells, plasma cells, dendritic cells, mast cells, and, to a lesser extent, granulocytes.

• The T cells compose 30–50% of the infiltrate, with the other cells accounting for the remainder.

• The topographical organization of these cells is complex and may vary among individuals with RA.

• Most often, the lymphocytes are diffusely organized among the tissue resident cells; however, in some cases, the B cells, T cells, and dendritic cells may form higher levels of organization, such as lymphoid

follicles and germinal center–like structures.

• Growth factors secreted by synovial fibroblasts and macrophages promote the formation of new blood vessels in the synovial sublining that supply the increasing demands for oxygenation and nutrition required by the infiltrating leukocytes and expanding synovial tissue.

• The structural damage to the mineralized cartilage and subchondral bone is mediated by the osteoclast.

• Osteoclasts are multinucleated giant cells that appear at the pannus-bone interface where they eventually form resorption lacunae.

• These lesions typically localize where the synovial membrane inserts into the periosteal surface at the edges of bone close to the rim of articular cartilage and at the attachment sites of ligaments and tendon sheaths.

• This process most likely explains why bone erosions usually develop at the radial sites of the MCP joints juxtaposed to the insertion sites of the tendons, collateral ligaments, and synovial membrane.

• Periarticular osteopenia, another form of bone loss, occurs in joints with active inflammation.

• It is associated with substantial thinning of the bony trabeculae along the metaphyses of bones from inflammation of the bone marrow cavity.

• These lesions can be visualized on MRI scans, where they appear as signal alterations in the bone marrow adjacent to inflamed joints.

• Their signal characteristics show they are water-rich with a low-fat content and are consistent with highly vascularized inflammatory tissue.

• These bone marrow lesions are often the forerunner of bone erosions.

• The cortical bone layer that separates the bone marrow from the invading pannus is relatively thin and susceptible to penetration by the inflamed synovium.

• The bone marrow lesions visualized on MRI scans are associated with an endosteal bone response characterized by the accumulation of osteoblasts and deposition of osteoid.

• Finally, generalized osteoporosis, which results in the thinning of trabecular bone throughout the body, is a third form of bone loss found in patients with RA and can lead to fragility fractures.

• Articular cartilage is an avascular tissue comprised of a specialized matrix of collagens, proteoglycans, and other proteins.

• It is organized in four distinct regions (superficial, middle, deep, and calcified cartilage zones)—chondrocytes constitute the unique cellular component in these layers.

• Originally, cartilage was considered to be an inert tissue, but it is now known to be a highly responsive tissue that reacts to inflammatory mediators and mechanical factors, which, in turn, alter the balance between cartilage anabolism and catabolism.

• In RA, the initial areas of cartilage degradation are juxtaposed to the synovial pannus.

• The cartilage matrix is characterized by a generalized loss of proteoglycan, most evident in the superficial zones adjacent to the synovial fluid.

• Degradation of cartilage may also take place in the perichondrocytic zone and in regions adjacent to the subchondral bone.

• The preclinical stage appears to be characterized by a breakdown in self-tolerance.

• This idea is supported by the finding that autoantibodies, such as RF and ACPA, may be found in sera from patients many years before onset of clinical disease.

• However, the antigenic targets of ACPA and RF are not restricted to the joint.

• ACPAs are directed against deaminated peptides, which result from posttranslational modification by the enzyme PADI4.

• They recognize citrulline-containing regions of several different matrix proteins, including filaggrin, keratin, fibrinogen, and vimentin, and are present at higher levels in the joint fluid compared to the

serum.

• Antibodies binding to carbamylated peptides and mutant citrullinated vimentin, as well as the 14-3-3 family of proteins, have also been detected in a minority of RA patients.

• In theory, environmental triggers may synergize with other factors to bring about inflammation in RA.

• People who smoke display higher citrullination of proteins in bronchoalveolar fluid than those who do not smoke.

• Thus, it has been speculated that long-term exposure to tobacco smoke might induce citrullination of cellular proteins via increased PADI expression in the lung and generate a neoepitope capable of inducing self-reactivity, which in turns, leads to formation of immune complexes that trigger joint inflammation and joint damage.

• Microbiota may also be involved in the initiating events of RA.

• The immune system is alerted to the presence of microbial infections when pathogen-associated molecular patterns (PAMPs) on their surface bind to Toll-like receptors (TLRs) on host cells.

• There are 10 TLRs in humans that recognize a variety of microbial products, including bacterial cell-surface lipopolysaccharides and heat-shock proteins (TLR4), lipoproteins (TLR2), double-strand RNA viruses (TLR3), and unmethylated CpG DNA from bacteria (TLR9).

• TLR2, 3, and 4 are abundantly expressed by synovial fibroblasts in early RA and, when bound by their ligands, upregulate the cell's production of proinflammatory cytokines.

• Although TLR ligands may theoretically amplify inflammatory pathways in RA, their specific role in disease pathogenesis remains uncertain.

• The pathogenesis of RA is built upon the concept that self-reactive T cells drive the chronic inflammatory response.

• In theory, self-reactive T cells might arise in RA from abnormal central (thymic) selection or intrinsic defects lowering the threshold in the periphery for T-cell activation.

• Either mechanism might result in abnormal expansion of a self-reactive T-cell repertoire and a breakdown in T-cell tolerance.

• The support for these ideas comes mainly from studies of arthritis in mouse models.

• It has not been shown that patients with RA have abnormal thymic selection of T cells or defective apoptotic pathways regulating cell death.

• At least some antigen stimulation inside the joint seems likely, owing to the fact that T cells in the synovium express a cell-surface phenotype indicating prior antigen exposure and show evidence of clonal expansion.

• There is substantial evidence of a role for CD4+ T cells in the pathogenesis of RA.

• First, the co-receptor CD4 on the surface of T cells binds to invariant sites on MHC class II molecules, stabilizing the MHC-peptide–T-cell receptor complex during T-cell activation.

• Because the SE on MHC class II molecules is a risk factor for RA, it follows that CD4+ T-cell activation plays a role in the pathogenesis of this disease.

• Second, CD4+ memory T cells are enriched in the synovial tissue from patients with RA and therefore are implicated through "guilt by association."

• Third, CD4+ T cells have been shown to be important in the initiation of arthritis in animal models.

• Fourth, some, but not all, T cell–directed therapies have shown clinical efficacy in this disease.

• Taken together, these lines of evidence suggest that CD4+ T cells play an important role in orchestrating the chronic inflammatory response in RA.

• However, other cell types, such as CD8+ T cells, natural killer (NK) cells, and B cells are present in synovial tissue and may also influence pathogenic responses.

3.1 Synovial Membrane Anatomy

• The synovial membrane, which covers most articular surfaces, tendon sheaths, and bursae, normally is a thin layer of connective tissue.

• In joints, it faces the bone and cartilage, bridging the opposing bony surfaces and inserting at periosteal regions close to the articular cartilage.

• It consists primarily of two cell types—type A synoviocytes (macrophage-derived) and type B synoviocytes (fibroblast-derived).

• The synovial fibroblasts are the most abundant and produce the structural components of joints, including collagen, fibronectin, and laminin, as well as other extracellular constituents of the synovial matrix.

• The sublining layer consists of blood vessels and a sparse population of mononuclear cells within a loose network of connective tissue.

• Synovial fluid, an ultrafiltrate of blood, diffuses through the subsynovial lining tissue across the synovial membrane and into the joint cavity.

• Its main constituents are hyaluronan and lubricin.

• Hyaluronan is a glycosaminoglycan that contributes to the viscous nature of synovial fluid, which, along with lubricin, lubricates the surface of the articular cartilage.

4. CLINICAL FEATURES

• The presenting symptoms are typically related to inflammation of the joints, tendons, and bursae.

• Patients often complain of early morning joint stiffness lasting >1 h that eases with physical activity.

• The earliest involved joints are mostly the small joints of the hands and feet.

• The initial pattern of joint involvement may be monoarticular, oligoarticular (≤4 joints), or polyarticular (>5 joints), usually in a symmetric distribution.

• Some patients with inflammatory arthritis will present with too few affected joints to be classified as having RA—so-called undifferentiated inflammatory arthritis.

• Those with an undifferentiated arthritis who are most likely to be diagnosed later with RA have a higher number of tender and swollen joints, test positive for serum rheumatoid factor (RF) or ACPA, and have higher scores for physical disability.

• In established RA, the most frequently involved joints are the wrists and metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints.

• Distal interphalangeal (DIP) joint involvement may occur in patients with RA, but it is usually due to coexistent osteoarthritis.

• Flexor tendon tenosynovitis is a frequent hallmark of RA and leads to decreased range of motion, reduced grip strength, and trigger fingers.

• Flexor tendon involvement may also lead to tendon rupture, most commonly the flexor pollicis longus.

• Progressive destruction of the joints and soft tissues may result in chronic, irreversible deformities.

• Ulnar deviation is a common deformity of long-standing RA that is caused by subluxation of the MCP joints, with subluxation, or partial dislocation, of the proximal phalanx to the volar side of the hand.

• Hyperextension of the PIP joint with flexion of the DIP joint (“swan-neck deformity”), flexion of the PIP joint with hyperextension of the DIP joint (“boutonnière deformity”), and subluxation of the first MCP joint with hyperextension of the first interphalangeal (IP) joint (“Z-line deformity”) also may result from damage to the tendons, joint capsule, and other soft tissues.

• Inflammation about the ulnar styloid and tenosynovitis of the extensor carpi ulnaris may cause subluxation of the distal ulna, resulting in a “piano-key movement” of the ulnar styloid.

• Although metatarsophalangeal (MTP) joint involvement is an early feature of disease, chronic inflammation of the ankle and midtarsal regions usually comes later and may lead to pes planovalgus ("flat feet").

• Large joints, including the knees and shoulders, are often affected in established disease and may remain asymptomatic for many years after onset.

• Atlantoaxial involvement of the cervical spine is clinically noteworthy because of its potential to cause compressive myelopathy and neurologic dysfunction.

• Neurologic manifestations are rarely a presenting sign or symptom of atlantoaxial disease, but they may slowly evolve over time with progressive instability of C1 on C2.

• The prevalence of atlantoaxial subluxation has been declining in recent years and occurs now in <10% of patients.

• Unlike the spondyloarthritides, RA rarely affects the thoracic and lumbar spine.

• Extraarticular manifestations may develop during the clinical course of RA in up to 40% of patients, even prior to the onset of arthritis.

4.1 Constitutional Symptoms

• These signs and symptoms include weight loss, fever, fatigue, malaise, depression, and in the most severe cases, cachexia.

• They generally reflect a high degree of inflammation and may even precede the onset of joint symptoms.

• In general, the presence of a fever of >38.3°C (101°F) at any time during the clinical course should raise suspicion of systemic vasculitis or infection.

4.2 Subcutaneous Nodules

• Subcutaneous nodules have been reported to occur in 30–40% of patients and more commonly in those with the highest levels of disease activity, who carry the disease-related shared epitope (SE), who have a positive test for serum RF, and who show radiographic evidence of joint erosions.

• However, more recent cohort studies suggest a declining prevalence of subcutaneous nodules, perhaps related to early and more aggressive disease-modifying therapy.

• When palpated, the nodules are generally firm; nontender; and adherent to periosteum, tendons, or bursae.

• They develop in areas of the skeleton subject to repeated trauma or irritation such as the forearm, sacral prominences, and Achilles tendon.

• They may also occur in the lungs, pleura, pericardium, and peritoneum.

• Nodules are typically benign, although they can be associated with infection, ulceration, and gangrene.

• Accelerated growth of smaller nodules may occur in up to 10% of patients taking long-term methotrexate, although the mechanisms behind this phenomenon are unclear.

4.3 Secondary Sjögren's Syndrome

• Secondary Sjögren's syndrome, or Sjögren's disease, is defined by the presence of either keratoconjunctivitis sicca (dry eyes) and xerostomia (dry mouth) in association with another connective tissue disease, such as RA.

• Approximately 10% of patients with RA have secondary Sjögren's syndrome.

4.4 Pulmonary Manifestations

• Pleuritis, the most common pulmonary manifestation of RA, may result in pleuritic chest pain and dyspnea, as well as a finding of a pleural friction rub and radiographic evidence of a pleural effusion.

• Pleural effusions tend to be exudative with increased numbers of monocytes and neutrophils.

• ILD may also occur in patients with RA and is heralded by symptoms of dry cough and progressive shortness of breath.

• ILD can be associated with cigarette smoking and is generally found in patients with higher disease activity, although it may be diagnosed in up to 3.5% of patients prior to the onset of joint symptoms.

• Recent studies have shown the overall prevalence of ILD in RA to be as high as 12%.

• Diagnosis is readily made by high-resolution chest computed tomography (CT) scan, which shows infiltrative opacification, or ground-glass opacities, in the periphery of both lungs.

• Usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) are the main histologic and radiologic patterns of ILD.

• UIP causes progressive scarring of the lungs that, on chest CT scan, produces honeycomb changes in the periphery and lower portions of the lungs.

• In contrast, the most common radiographic changes in NSIP are relatively symmetric and bilateral ground-glass opacities with associated fine reticulations, volume loss, and traction bronchiectasis.

• In both cases, pulmonary function testing shows a restrictive pattern (e.g., reduced total lung capacity) and a reduced diffusing capacity for carbon monoxide (DLCO).

• The presence of ILD confers a poor prognosis.

• The prognosis of ILD in RA, however, is not quite as poor as that of idiopathic pulmonary fibrosis (e.g., usual interstitial pneumonitis) and responds better to immunosuppressive therapy.

• Pulmonary nodules are also common in patients with RA and may be solitary or multiple.

• Caplan's syndrome is a rare subset of pulmonary nodulosis characterized by the development of nodules and pneumoconiosis following silica exposure.

• Less commonly, RA may be associated with respiratory bronchiolitis and bronchiectasis.

4.5 Cardiac Manifestations

• The most frequent site of cardiac involvement in RA is the pericardium.

• However, clinical manifestations of pericarditis occur in <10% of patients with RA despite pericardial involvement being detectable in nearly one-half of cases by echocardiogram or at autopsy.

• Up to 20% of patients with RA may have asymptomatic pericardial effusions on echocardiography.

• Cardiomyopathy, another clinically important manifestation of RA, may result from necrotizing or granulomatous myocarditis, coronary artery disease, or diastolic dysfunction.

• This involvement, too, may be subclinical and only identified by echocardiography or cardiac magnetic resonance imaging (MRI).

• Rarely, the heart muscle may contain rheumatoid nodules or be infiltrated with amyloid.

• The most common cause of death in patients with RA is cardiovascular disease.

• The incidence of coronary artery disease and carotid atherosclerosis is higher in RA patients than in the general population even when controlling for traditional cardiac risk factors, such as hypertension, obesity, hypercholesterolemia, diabetes, and cigarette smoking.

• Furthermore, congestive heart failure (including both systolic and diastolic dysfunction) occurs at an approximately twofold higher rate in RA than in the general population.

• The presence of elevated serum inflammatory markers appears to confer an increased risk of cardiovascular disease.

4.6 Vasculitis

• Rheumatoid vasculitis typically occurs in patients with long-standing disease, a positive test for serum RF or ACPA, and hypocomplementemia.

• The overall incidence has decreased significantly in the past decade to <1% of patients.

• The cutaneous signs vary and include petechiae, purpura, digital infarcts, gangrene, livedo reticularis, and in severe cases large, painful lower extremity ulcerations.

• Vascular ulcers, which may be difficult to distinguish from those caused by venous insufficiency, may be treated successfully with immunosuppressive agents including cytotoxic treatment and skin grafting in severe cases.

• Sensorimotor polyneuropathies, such as mononeuritis multiplex, may occur in association with systemic rheumatoid vasculitis; they usually present with new onset of numbness, tingling, or focal muscle weakness.

4.7 Lymphoma

• Large cohort studies have shown a two- to fourfold increased risk of lymphoma in RA patients compared with the general population.

• The most common histopathologic type of lymphoma is a diffuse large B-cell lymphoma.

• The risk of developing lymphoma increases if the patient has high levels of disease activity or Felty's syndrome.

4.8 Hematologic Manifestations

• A normochromic, normocytic anemia often develops in patients with RA and is the most common hematologic abnormality.

• The degree of anemia parallels the degree of inflammation, correlating with the levels of serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

• Platelet counts may also be elevated in RA as an acute-phase reactant; immune-mediated thrombocytopenia is rare.

• Felty's syndrome is defined by the clinical triad of neutropenia, splenomegaly, and nodular RA and is seen in <1% of patients, although its incidence appears to be declining in the face of more aggressive treatment of the joint disease.

• It typically occurs in the late stages of severe RA and is more common in whites than other racial groups.

• T-cell large granular lymphocyte leukemia (T-LGL) may have a similar clinical presentation and often occurs in association with RA.

• T-LGL is characterized by a chronic, indolent clonal growth of LGL cells, leading to neutropenia and splenomegaly.

• As opposed to Felty's syndrome, T-LGL may develop early in the course of RA.

• Leukopenia apart from these disorders is uncommon and most often a side effect of drug therapy.

4.9 Osteoporosis

• Osteoporosis is more common in patients with RA than an age- and sex-matched population, with an incidence rate of nearly double that of the healthy population and a prevalence of approximately one-third in postmenopausal women with RA.

• There is also an increased risk of fragility fracture, with a greater risk among women.

• The inflammatory milieu of the joint promotes generalized bone loss by activating osteoclasts.

• Both trabecular and cortical bone are affected by the inflammatory response, with cortical sites more susceptible to bone loss.

• Chronic use of glucocorticoids and disability-related immobility also contribute to osteoporosis.

• Hip fractures are more likely to occur in patients with RA and are significant predictors of increased disability and mortality rate in this disease.

5. DIFFERENTIAL DIAGNOSIS

• Patients with an undifferentiated arthritis who are most likely to be diagnosed later with RA have a higher number of tender and swollen joints, test positive for serum rheumatoid factor (RF) or ACPA, and have higher scores for physical disability.

• Unlike the spondyloarthritides, RA rarely affects the thoracic and lumbar spine.

• RA rarely affects the thoracic and lumbar spine.

• The differential diagnosis includes thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, disseminated intravascular coagulation, and heparin-induced thrombocytopenia in the context of thrombotic microangiopathy (microangiopathic hemolytic anemia and severe thrombocytopenia) which is a typical finding in CAPS.

• Diagnosis of CAPS should be considered in patients with mainly microvascular thrombotic disease involving multiple organs in a short time period.

• A patient is classified as definite CAPS if all four of the following criteria are fulfilled and as probable CAPS when a combination of these criteria is present: (1) thrombosis in three or more organs/systems; (2) development in less than a week; (3) histologic evidence of small-vessel thrombosis in at least one organ; and (4) aPL presence.

5.1 Undifferentiated Inflammatory Arthritis

• Some patients with inflammatory arthritis will present with too few affected joints to be classified as having RA—so-called undifferentiated inflammatory arthritis.

• Those with an undifferentiated arthritis who are most likely to be diagnosed later with RA have a higher number of tender and swollen joints, test positive for serum rheumatoid factor (RF) or ACPA, and have higher scores for physical disability.

6. INVESTIGATIONS & DIAGNOSIS

• Testing for serum antibodies to anti-citrullinated protein antibodies (ACPA) and rheumatoid factor continues to be valuable in the diagnostic evaluation of patients with suspected RA, and these autoantibodies serve as biomarkers of prognostic significance.

• Advances in imaging modalities assist clinical decision-making by improving the detection of joint inflammation and monitoring the progression of damage.

• The presence of elevated serum inflammatory markers appears to confer an increased risk of cardiovascular disease.

• Diagnosis is readily made by high-resolution chest computed tomography (CT) scan, which shows infiltrative opacification, or ground-glass opacities, in the periphery of both lungs for ILD.

6.1 Laboratory Markers

• Rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) are valuable in the diagnostic evaluation of patients with suspected RA.

• These autoantibodies serve as biomarkers of prognostic significance.

• A normochromic, normocytic anemia often develops in patients with RA and is the most common hematologic abnormality.

• The degree of anemia parallels the degree of inflammation, correlating with the levels of serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

• Platelet counts may also be elevated in RA as an acute-phase reactant; immune-mediated thrombocytopenia is rare.

6.2 Imaging

• Advances in imaging modalities assist clinical decision-making by improving the detection of joint inflammation and monitoring the progression of damage.

• Diagnosis of ILD is readily made by high-resolution chest computed tomography (CT) scan, which shows infiltrative opacification, or ground-glass opacities, in the periphery of both lungs.

• Usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) are the main histologic and radiologic patterns of ILD.

• In both cases, pulmonary function testing shows a restrictive pattern (e.g., reduced total lung capacity) and a reduced diffusing capacity for carbon monoxide (DLCO).

7. MANAGEMENT & TREATMENT

• Reaching a clinical state of low disease activity and remission is now an achievable goal for most patients.

• This shift in treatment strategy dictates a new mindset for primary care practitioners—namely, one that demands early referral of patients with inflammatory arthritis to a rheumatologist for confirmation of the diagnosis and initiation of disease-modifying therapy, since delays in starting effective treatment are associated with worse outcomes.

• For asymptomatic individuals or SLE patients with a high-risk aPL profile and no evidence of a previous thrombotic event or pregnancy morbidity, prophylactic treatment with LDA is recommended.

• In nonpregnant women with a history of APS-related obstetric complications, independently of the presence of underlying SLE diagnosis, treatment with LDA seems to reduce the risk of a subsequent thrombotic event.

• Patients with CAPS should be treated with combination therapy including glucocorticoids, heparin, and plasma exchange or intravenous immunoglobulin (IVIG) together with appropriate management of triggering events such as infections.

• For refractory CAPS, B-cell depletion (e.g., with rituximab) or complement inhibition (e.g., with eculizumab) therapies are alternative options.

• Administration of direct oral anticoagulants (DOACs) recently has been shown to increase the risk of arterial events, especially in patients with triple positivity or previous arterial thrombosis.

• A recent meta-analysis of four open-label randomized controlled trials showed that prior thrombosis type (arterial vs venous) did not affect the increased odds of arterial thrombosis associated with DOACs compared to VKAs in APS.

• In pregnant women with a history of obstetric APS, combination treatment with LDA and prophylactic dose of low-molecular-weight heparin (LMWH) is recommended, whereas in cases of thrombotic APS, LDA plus therapeutic LMWH dose should be administered.

• When recurrent obstetric complications occur despite standard treatment, increasing the LMWH dose (from prophylactic to therapeutic) or administering oral hydroxychloroquine 400 mg/d or low-dose prednisolone in the first trimester are alternative options.

• Following the first thrombotic event, APS patients should be placed on vitamin K antagonists (VKAs) for life, aiming to achieve an international normalized ratio (INR) ranging from 2.0 to 3.0 in case of an unprovoked venous thrombosis.

• For patients with arterial thrombosis, the corresponding INR target should be 3.0–4.0 or 2.0–3.0 with or without low-dose aspirin (LDA, 75–100 mg daily), depending on the thrombotic/hemorrhagic patient profile.

7.1 Pharmacologic Therapy

• Testing for serum antibodies to anti-citrullinated protein antibodies (ACPA) and rheumatoid factor continues to be valuable in the diagnostic evaluation of patients with suspected RA, and these autoantibodies serve as biomarkers of prognostic significance.

• Advances in imaging modalities assist clinical decision-making by improving the detection of joint inflammation and monitoring the progression of damage.

• Reaching a clinical state of low disease activity and remission is now an achievable goal for most patients.

• This shift in treatment strategy dictates a new mindset for primary care practitioners—namely, one that demands early referral of patients with inflammatory arthritis to a rheumatologist for confirmation of the diagnosis and initiation of disease-modifying therapy, since delays in starting effective treatment are associated with worse outcomes.

• Administration of direct oral anticoagulants (DOACs) recently has been shown to increase the risk of arterial events, especially in patients with triple positivity or previous arterial thrombosis.

• A recent meta-analysis of four open-label randomized controlled trials showed that prior thrombosis type (arterial vs venous) did not affect the increased odds of arterial thrombosis associated with DOACs compared to VKAs in APS.

• In pregnant women with a history of obstetric APS, combination treatment with LDA and prophylactic dose of low-molecular-weight heparin (LMWH) is recommended, whereas in cases of thrombotic APS, LDA plus therapeutic LMWH dose should be administered.

• When recurrent obstetric complications occur despite standard treatment, increasing the LMWH dose (from prophylactic to therapeutic) or administering oral hydroxychloroquine 400 mg/d or low-dose prednisolone in the first trimester are alternative options.

• Following the first thrombotic event, APS patients should be placed on vitamin K antagonists (VKAs) for life, aiming to achieve an international normalized ratio (INR) ranging from 2.0 to 3.0 in case of an unprovoked venous thrombosis.

• For patients with arterial thrombosis, the corresponding INR target should be 3.0–4.0 or 2.0–3.0 with or without low-dose aspirin (LDA, 75–100 mg daily), depending on the thrombotic/hemorrhagic patient profile.

• For asymptomatic individuals or SLE patients with a high-risk aPL profile and no evidence of a previous thrombotic event or pregnancy morbidity, prophylactic treatment with LDA is recommended.

• In nonpregnant women with a history of APS-related obstetric complications, independently of the presence of underlying SLE diagnosis, treatment with LDA seems to reduce the risk of a subsequent thrombotic event.

• Patients with CAPS should be treated with combination therapy including glucocorticoids, heparin, and plasma exchange or intravenous immunoglobulin (IVIG) together with appropriate management of triggering events such as infections.

• For refractory CAPS, B-cell depletion (e.g., with rituximab) or complement inhibition (e.g., with eculizumab) therapies are alternative options.

Table 3 Anticoagulation Management in Antiphospholipid Syndrome (APS)

Clinical Scenario	Treatment Recommendation	INR Target / Dose
Unprovoked venous thrombosis	Vitamin K antagonists (VKAs) for life	INR 2.0–3.0
Arterial thrombosis	Vitamin K antagonists (VKAs)	INR 3.0–4.0 or 2.0–3.0 with LDA (75–100 mg daily)
Obstetric APS (history of obstetric complications)	LDA + Prophylactic LMWH	LDA + LMWH

Clinical Scenario	Treatment Recommendation	INR Target / Dose
Thrombotic APS	LDA + Therapeutic LMWH	LDA + LMWH
Recurrent obstetric complications despite standard treatment	Increase LMWH dose (prophylactic to therapeutic) or oral hydroxychloroquine 400 mg/d or low-dose prednisolone	LMWH or Hydroxychloroquine 400 mg/d
Asymptomatic individuals or SLE patients with high-risk aPL profile	Prophylactic treatment with LDA	LDA

7.2 Non-Pharmacologic & Surgical

• Reaching a clinical state of low disease activity and remission is now an achievable goal for most patients.

• This shift in treatment strategy dictates a new mindset for primary care practitioners—namely, one that demands early referral of patients with inflammatory arthritis to a rheumatologist for confirmation of the diagnosis and initiation of disease-modifying therapy, since delays in starting effective treatment are associated with worse outcomes.

• Patients with CAPS should be treated with combination therapy including glucocorticoids, heparin, and plasma exchange or intravenous immunoglobulin (IVIG) together with appropriate management of triggering events such as infections.

• For refractory CAPS, B-cell depletion (e.g., with rituximab) or complement inhibition (e.g., with eculizumab) therapies are alternative options.

8. PROGNOSIS & COMPLICATIONS

• The most common cause of death in patients with RA is cardiovascular disease.

• The incidence of coronary artery disease and carotid atherosclerosis is higher in RA patients than in the general population even when controlling for traditional cardiac risk factors, such as hypertension, obesity, hypercholesterolemia, diabetes, and cigarette smoking.

• Furthermore, congestive heart failure (including both systolic and diastolic dysfunction) occurs at an approximately twofold higher rate in RA than in the general population.

• The presence of elevated serum inflammatory markers appears to confer an increased risk of cardiovascular disease.

• Osteoporosis is more common in patients with RA than an age- and sex-matched population, with an incidence rate of nearly double that of the healthy population and a prevalence of approximately one-third in postmenopausal women with RA.

• There is also an increased risk of fragility fracture, with a greater risk among women.

• The inflammatory milieu of the joint promotes generalized bone loss by activating osteoclasts.

• Both trabecular and cortical bone are affected by the inflammatory response, with cortical sites more susceptible to bone loss.

• Chronic use of glucocorticoids and disability-related immobility also contribute to osteoporosis.

• Hip fractures are more likely to occur in patients with RA and are significant predictors of increased disability and mortality rate in this disease.

• Large cohort studies have shown a two- to fourfold increased risk of lymphoma in RA patients compared with the general population.

• The most common histopathologic type of lymphoma is a diffuse large B-cell lymphoma.

• The risk of developing lymphoma increases if the patient has high levels of disease activity or Felty's syndrome.

• Recent studies have shown a decrease in the incidence and severity of at least some extraarticular manifestations, particularly Felty's syndrome and vasculitis.

8.1 Cardiovascular Disease

• The most common cause of death in patients with RA is cardiovascular disease.

• The incidence of coronary artery disease and carotid atherosclerosis is higher in RA patients than in the general population even when controlling for traditional cardiac risk factors, such as hypertension, obesity, hypercholesterolemia, diabetes, and cigarette smoking.

• Furthermore, congestive heart failure (including both systolic and diastolic dysfunction) occurs at an approximately twofold higher rate in RA than in the general population.

• The presence of elevated serum inflammatory markers appears to confer an increased risk of cardiovascular disease.

8.2 Osteoporosis

• Osteoporosis is more common in patients with RA than an age- and sex-matched population, with an incidence rate of nearly double that of the healthy population and a prevalence of approximately one-third in postmenopausal women with RA.

• There is also an increased risk of fragility fracture, with a greater risk among women.

• The inflammatory milieu of the joint promotes generalized bone loss by activating osteoclasts.

• Both trabecular and cortical bone are affected by the inflammatory response, with cortical sites more susceptible to bone loss.

• Chronic use of glucocorticoids and disability-related immobility also contribute to osteoporosis.

• Hip fractures are more likely to occur in patients with RA and are significant predictors of increased disability and mortality rate in this disease.

8.3 Lymphoma

• Large cohort studies have shown a two- to fourfold increased risk of lymphoma in RA patients compared with the general population.

• The most common histopathologic type of lymphoma is a diffuse large B-cell lymphoma.

• The risk of developing lymphoma increases if the patient has high levels of disease activity or Felty's syndrome.

9. SPECIAL CONSIDERATIONS

• For asymptomatic individuals or SLE patients with a high-risk aPL profile and no evidence of a previous thrombotic event or pregnancy morbidity, prophylactic treatment with LDA is recommended.

• In nonpregnant women with a history of APS-related obstetric complications, independently of the presence of underlying SLE diagnosis, treatment with LDA seems to reduce the risk of a subsequent thrombotic event.

• In pregnant women with a history of obstetric APS, combination treatment with LDA and prophylactic dose of low-molecular-weight heparin (LMWH) is recommended, whereas in cases of thrombotic APS, LDA plus therapeutic LMWH dose should be administered.

• When recurrent obstetric complications occur despite standard treatment, increasing the LMWH dose (from prophylactic to therapeutic) or administering oral hydroxychloroquine 400 mg/d or low-dose prednisolone in the first trimester are alternative options.

9.1 Pregnancy

• In pregnant women with a history of obstetric APS, combination treatment with LDA and prophylactic dose of low-molecular-weight heparin (LMWH) is recommended, whereas in cases of thrombotic APS, LDA plus therapeutic LMWH dose should be administered.

• When recurrent obstetric complications occur despite standard treatment, increasing the LMWH dose (from prophylactic to therapeutic) or administering oral hydroxychloroquine 400 mg/d or low-dose prednisolone in the first trimester are alternative options.

10. KEY PEARLS & CLINICAL TRAPS

• The earliest involved joints are mostly the small joints of the hands and feet.

• Morning joint stiffness lasting >1 h that eases with physical activity is a hallmark presenting symptom.

• Subcutaneous nodules occur in 30–40% of patients, are firm, nontender, and adherent to periosteum/tendons.

• Secondary Sjögren's syndrome is defined by keratoconjunctivitis sicca and xerostomia in association with RA.

• Interstitial lung disease (ILD) prevalence in RA is as high as 12%, with UIP and NSIP as main patterns.

• Cardiovascular disease is the most common cause of death in RA patients.

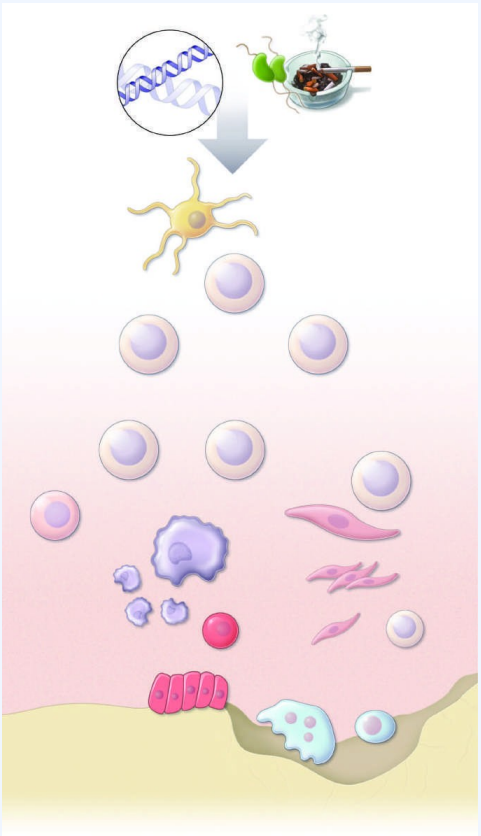
• HLA-DRB1 shared epitope (SE) alleles increase risk 4-fold (single allele) to 8-fold (two alleles).

• Smoking confers a 20- to 40-fold increased risk of RA when combined with SE alleles.

• Felty's syndrome is defined by the clinical triad of neutropenia, splenomegaly, and nodular RA.

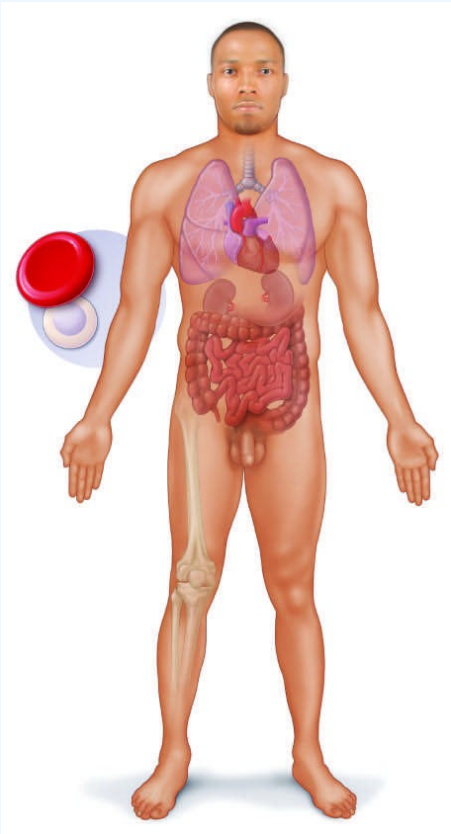
• Unlike the spondyloarthritides, RA rarely affects the thoracic and lumbar spine.

FIGURES & ILLUSTRATIONS — FROM HARRISON'S



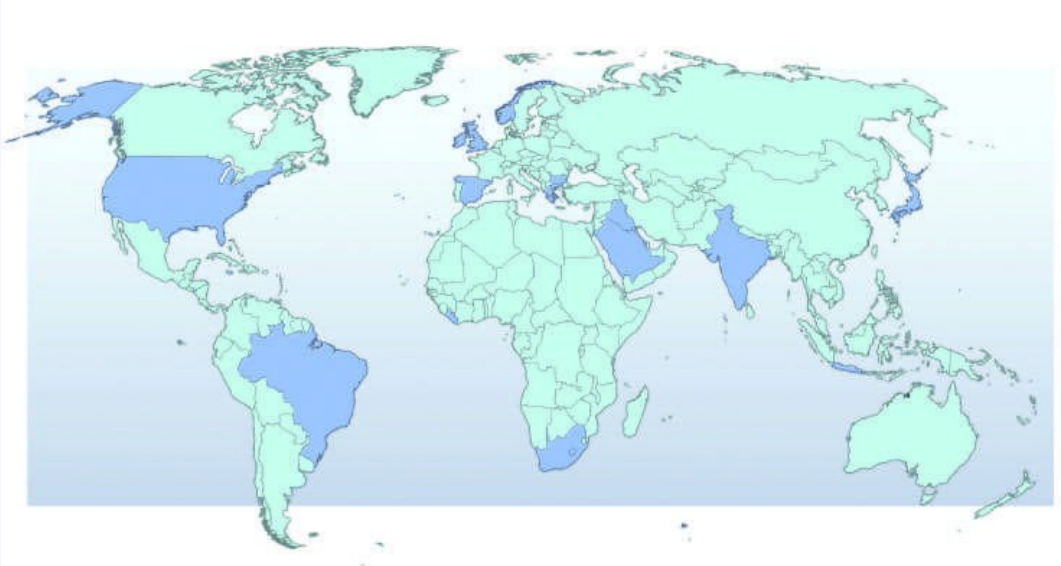
Harrison's 22e · Figure 1

FIGURE 370-4 Pathophysiologic mechanisms of inflammation and joint destruction. of rheumatoid arthritis (RA), with subsequent synovial T-cell activation. CD4+ T cells the T-cell receptor and class II MHC-peptide antigen (signal 1) with co-stimulation ligands binding Toll-like receptors (TLRs) may further stimulate activation of APCs inside distinctive cytokine profile. CD4+ T cells in turn activate B cells, some of which are H possibly comprised of rheumatoid factors (RFs) and anti–cyclic citrullinated peptides amplifying inflammation. T effector cells stimulate synovial macrophages (M) and factor α (TNF-α). TNF-α upregulates adhesion molecules on endothelial cells, promoting mediators, such as interleukin 1 (IL-1), IL-6, and granulocyte-macrophage balance between bone destruction and formation. It upregulates the expression of Wnt is a soluble mediator that promotes osteoblastogenesis and bone formation. In RA, — Overview of Rheumatoid Arthritis clinical presentation and systemic involvement.



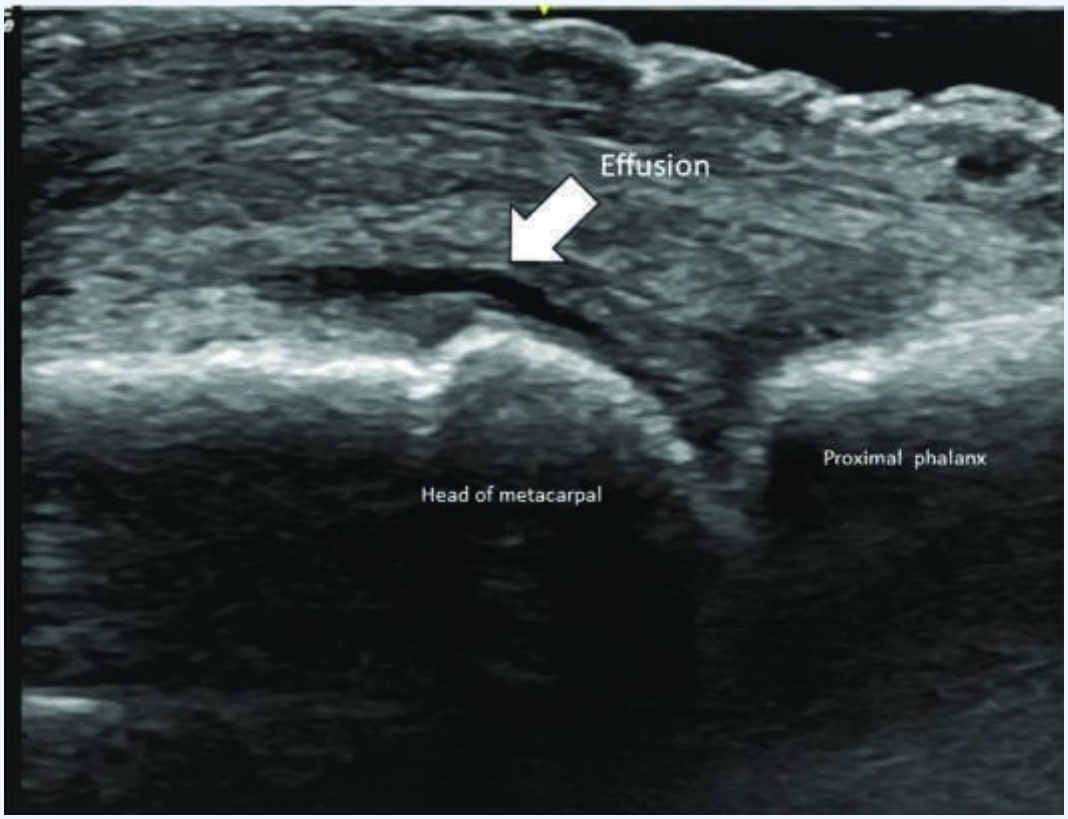
Harrison's 22e · Figure 2

FIGURE 370-2 Extraarticular manifestations of rheumatoid arthritis. — Metacarpophalangeal joint swelling and subluxation showing characteristic deformities.



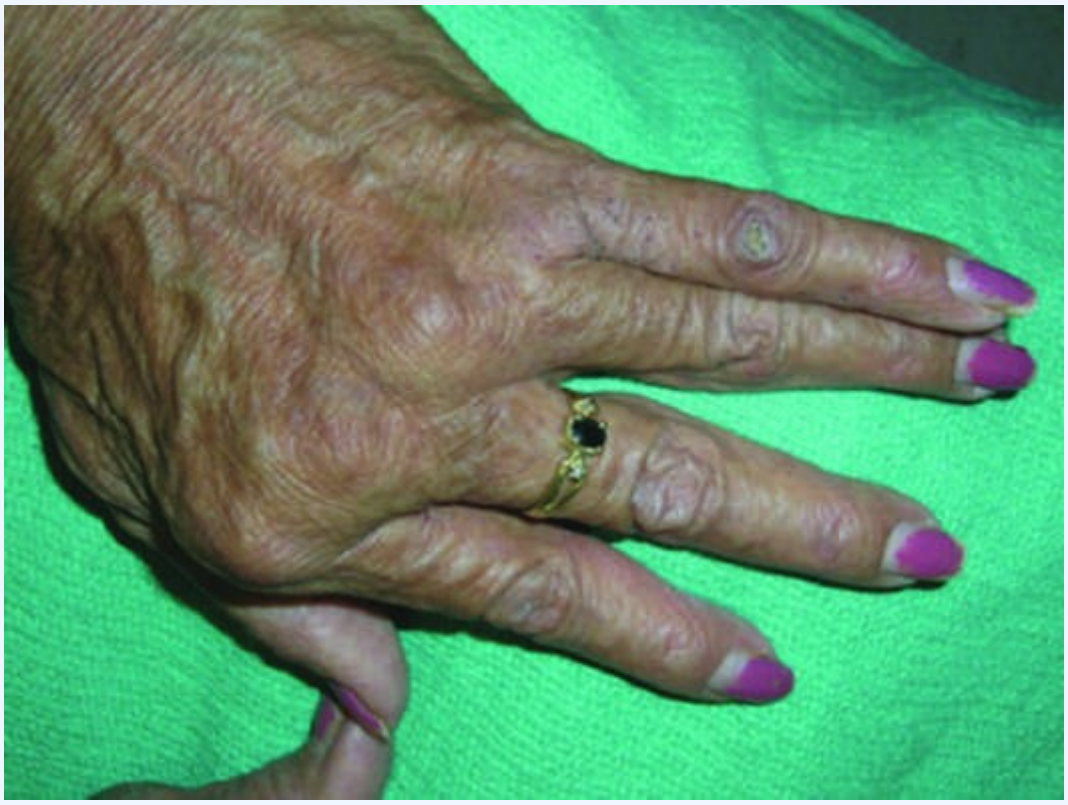
Harrison's 22e · Figure 3

FIGURE 370-3 Global prevalence rates of rheumatoid arthritis (RA) with genetic leukocyte antigen (HLA)-DRB1 mutations are found globally, some alleles have been — Extraarticular manifestations of rheumatoid arthritis including pulmonary, cardiac, and hematologic involvement.



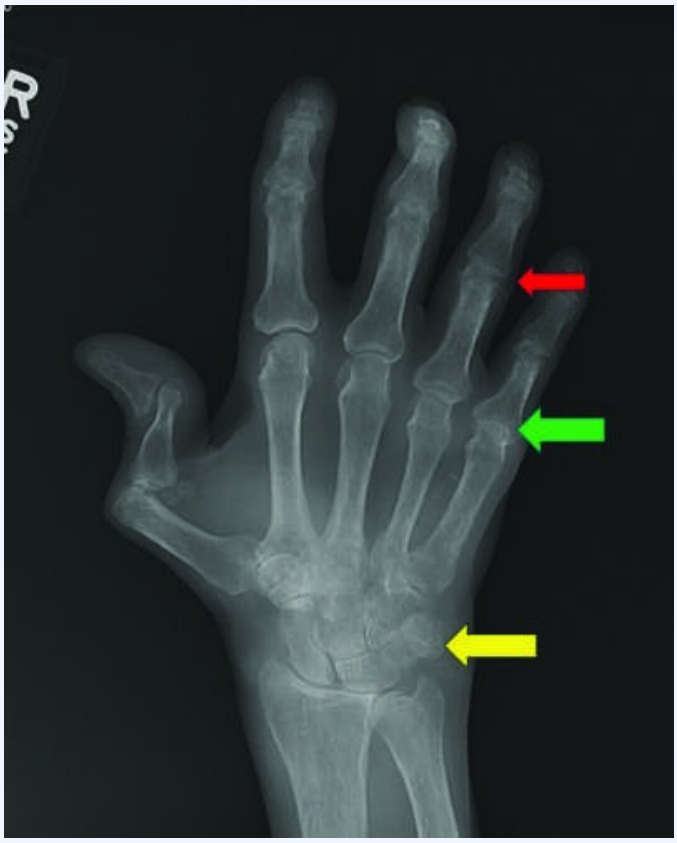
Harrison's 22e · Figure 4

FIGURE 370-6 Ultrasound demonstrating an effusion (arrow) within the metacarpophalangeal joint. (Courtesy of Dr. Ryan Jessee.) — Global prevalence rates of rheumatoid arthritis (RA) with genetic associations and HLA-DRB1 alleles.



Harrison's 22e · Figure 5

FIGURE 370-1 Metacarpophalangeal joint swelling and subluxation. (Reproduced with permission from RP Usatine, MA Smith, EJ Mayeaux: The Color Atlas and Synopsis of Family Medicine, 3rd ed. New York, McGraw Hill, 2019; Fig. 97.5.) — Histologic appearance of synovial membrane showing hyperplasia and pannus formation.



Harrison's 22e · Figure 6

FIGURE 370-6 Ultrasound demonstrating an effusion (arrow) within the metacarpophalangeal joint. (Courtesy of Dr. Ryan Jessee.) — Radiographic progression of joint damage showing erosions and periarticular osteopenia.

Harrison's 22e · Figure 7

Pathophysiologic mechanisms of inflammation and joint destruction involving T-cells, cytokines, and osteoclasts.