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Editorial

Rheumatoid arthritis (RA) is a long-term autoimmune disorder that primarily affects joints. It typically results in warm, swollen, and painful joints. Pain and stiffness often worsen following rest. Most commonly, the wrist and hands are involved, with the same joints typically involved on both sides of the body. The disease may also affect other parts of the body. This may result in a low red blood cell count, inflammation around the lungs, and inflammation around the heart. Fever and low energy may also be present. Often, symptoms come on gradually over weeks to months.

While the cause of rheumatoid arthritis is not clear, it is believed to involve a combination of genetic and environmental factors. The underlying mechanism involves the body's immune system attacking the joints. This results in inflammation and thickening of the joint capsule. It also affects the underlying bone and cartilage. The diagnosis is made mostly on the basis of a person's signs and symptoms. X-rays and laboratory testing may support a diagnosis or exclude other diseases with similar symptoms. Other diseases that may present similarly include systemic lupus erythematosus, psoriatic arthritis, and fibromyalgia among others.

RA affected about 24.5 million people as in 2015. This is between 0.5 and 1% of adults in the developed world with 5 and 50 per 100,000 people newly developing the condition each year. Onset is most frequent during middle age and women are affected 2.5 times as frequently as men. In 2013, it resulted in 38,000 deaths up from 28,000 deaths in 1990. The first recognized description of RA was made in 1800 by Dr. Augustin Jacob Landré-Beauvais (1772–1840) of Paris. The term *rheumatoid arthritis* is based on the Greek for watery and inflamed joints. The **"DISEASE DIAGNOSIS"** segment of this issue highlights all Clinico-diagnostic issues as related to Rheumatoid Arthritis.

"INTERPRETATION" too outlines an early marker of RA Diagnosis namely Anti CCP Antibody.

As all important diagnostic platforms that are made use of in investigating a case of RA are based on ELISA platform, hence, we present to you **"TROUBLE SHOOTING"** various irregularities that are encountered while conducting ELISA based tests.

All work and no PLAY! Well, we don't forget - **"BOUQUET"** is in there!



DISEASE DIAGNOSIS

RHEUMATOID ARTHRITIS

Practice Essentials

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown cause. An external trigger (eg, cigarette smoking, infection, or trauma) that triggers an autoimmune reaction, leading to synovial hypertrophy and chronic joint inflammation along with the potential for extra-articular manifestations, is theorized to occur in genetically susceptible individuals. See the image below.



Rheumatoid changes in the hand.

Background

The hallmark feature of rheumatoid arthritis (RA) is persistent symmetric polyarthritis (synovitis) that affects the hands and feet, though any joint lined by a synovial membrane may be involved. Extra-articular involvement of organs such as the skin, heart, lungs, and eyes can be significant. **No laboratory test results are pathognomonic for RA**, but the presence of anti-cyclic citrullinated protein antibody (ACPA) and rheumatoid factor (RF) is highly specific for this condition. **Optimal care of patients with RA** requires an integrated approach that includes nonpharmacologic therapies and pharmacologic agents such as nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, and corticosteroids. **Early therapy with DMARDs has become the standard of care**; it not only can more efficiently retard disease progression than later treatment but also may induce more remissions. **Many of the newer DMARD therapies**, however, are immunosuppressive in nature, leading to a higher risk for infections. Macrophage activation syndrome is a life-threatening complication of juvenile idiopathic arthritis (JIA) that necessitates immediate treatment with high-dose steroids and cyclosporine.

The following guidelines on treating RA to therapeutic target were issued in 2015 by an international task force of rheumatologists, patient representatives, and a rheumatology nurse:

- The primary target for treatment of RA should be a state of clinical remission. Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity.
- While remission should be a clear target, low-disease activity may be an acceptable alternative therapeutic goal, particularly in long-standing disease.
- The use of validated composite measures of disease activity, which

include joint assessments, is needed in routine clinical practice to guide treatment decisions.

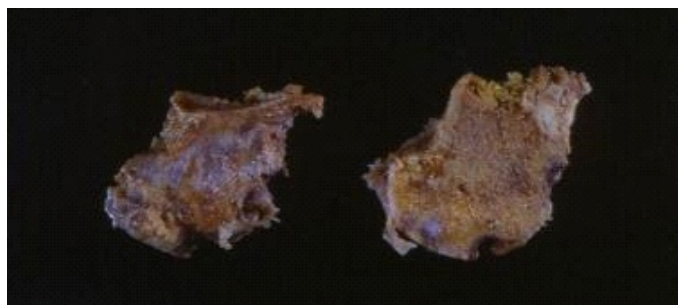
- The choice of the (composite) measure of disease activity and the target value should be influenced by comorbidities, patient factors, and drug-related risks.
- Measures of disease activity must be obtained and documented regularly: as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 6 mo) for patients in sustained low-disease activity or remission.
- Structural changes and functional impairment and comorbidity should be considered when making clinical decisions, in addition to assessing composite measures of disease activity.
- Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 mo.
- The desired treatment target should be maintained throughout the remaining course of the disease.
- The rheumatologist should involve the patient in setting the treatment target and the strategy to reach this target.

Pathophysiology

The pathogenesis of RA is not completely understood. An external trigger (eg, cigarette smoking, infection, or trauma) that sets off an autoimmune reaction, leading to synovial hypertrophy and chronic joint inflammation along with the potential for extra-articular manifestations, is theorized to occur in genetically susceptible individuals. **Synovial cell hyperplasia and endothelial cell activation** are early events in the pathologic process that progresses to uncontrolled inflammation and consequent cartilage and bone destruction. Genetic factors and immune system abnormalities contribute to disease propagation. **CD4 T cells, mononuclear phagocytes, fibroblasts, osteoclasts, and neutrophils** play major cellular roles in the pathophysiology of RA, whereas B cells produce autoantibodies (ie, rheumatoid factors). Abnormal production of numerous cytokines, chemokines, and other inflammatory mediators has been demonstrated in patients with RA, including the following:

- Tumor necrosis factor alpha (TNF- α)
- Interleukin (IL)-1
- IL-6
- IL-8
- Transforming growth factor beta (TGF- β)
- Fibroblast growth factor (FGF)
- Platelet-derived growth factor (PDGF)

Ultimately, inflammation and exuberant proliferation of the synovium (ie, pannus) leads to destruction of various tissues, including cartilage (see the image below), bone, tendons, ligaments, and blood vessels. Although the articular structures are the primary sites involved by RA, other tissues are also affected.



This gross photo shows destruction of the cartilage and erosion of the underlying bone with pannus from a patient with rheumatoid arthritis.

Etiology

The cause of RA is unknown. Genetic, environmental, hormonal, immunologic, and infectious factors may play significant roles. Socioeconomic, psychological, and lifestyle factors (eg, tobacco use, the main environmental risk) may influence disease development and outcome.

Genetic factors

Genetic factors account for 50% of the risk for developing RA. About 60% of RA patients in the United States carry a shared epitope of the human leukocyte antigen (HLA)-DR4 cluster, which constitutes one of the peptide-binding sites of certain HLA-DR molecules associated with RA (eg, HLA-DR beta *0401, 0404, or 0405). HLA-DR1 (HLA-DR beta *0101) also carries this shared epitope and confers risk, particularly in certain southern European areas. Other HLA-DR4 molecules (eg, HLA-DR beta *0402) lack this epitope and do not confer this risk. **Genes other than those of the major histocompatibility complex (MHC)** are also involved. Results from sequencing genes of families with RA suggest the presence of several resistance and susceptibility genes, including *PTPN22* and *TRAF5*. **Juvenile idiopathic arthritis (JIA)**, also known as juvenile rheumatoid arthritis (JRA), is a heterogeneous group of diseases that differs markedly from adult RA. JIA is known to have genetically complex traits in which multiple genes are important for disease onset and manifestations, and it is characterized by arthritis that begins before the age of 16 years, persists for more than 6 weeks, and is of unknown origin. The *IL2RA/CD25* gene has been implicated as a JIA susceptibility locus, as has the *VTCN1* gene. **Some investigators suggest that the future of treatment** and understanding of RA may be based on imprinting and epigenetics. RA is significantly more prevalent in women than in men, which suggests that genomic imprinting from parents participates in its expression. Imprinting is characterized by differential methylation of chromosomes by the parent of origin, resulting in differential expression of maternal over paternal genes. **Epigenetics is the change in DNA expression** that is due to environmentally induced methylation and not to a change in DNA structure. Clearly, the research focus will be on environmental factors in combination with immune genetics.

Infectious agents

For many decades, numerous infectious agents have been suggested as potential causes of RA, including *Mycoplasma* organisms, Epstein-Barr virus (EBV), and rubella virus. This suggestion is indirectly supported by the following evidence:

- Occasional reports of flulike disorders preceding the start of arthritis
- The inducibility of arthritis in experimental animals with different bacteria or bacterial products (eg, streptococcal cell walls)
- The presence of bacterial products, including bacterial RNA, in patients' joints
- The disease-modifying activity of several agents that have antimicrobial effects (eg, gold salts, antimalarial agents, minocycline)

Emerging evidence also points to an association between RA and periodontopathic bacteria. For example, the synovial fluid of RA patients has been found to contain high levels of antibodies to anaerobic bacteria that commonly cause periodontal infection, including *Porphyromonas gingivalis*.

Hormonal factors

Sex hormones may play a role in RA, as evidenced by the disproportionate number of females with this disease, its amelioration during pregnancy, its recurrence in the early postpartum period, and its reduced incidence in women using oral contraceptives.

Hyperprolactinemia may be a risk factor for RA.

Immunologic factors

All of the major immunologic elements play fundamental roles in initiating, propagating, and maintaining the autoimmune process of RA. The exact orchestration of the cellular and cytokine events that lead to pathologic consequences (eg, synovial proliferation and subsequent joint destruction) is complex, involving T and B cells, antigen-presenting cells (eg, B cells, macrophages, and dendritic cells), and various cytokines. Aberrant production and regulation of both proinflammatory and anti-inflammatory cytokines and cytokine pathways are found in RA. **T cells are assumed to play a pivotal role in the initiation of RA**, and the key player in this respect is assumed to be the T helper 1 (Th1) CD4 cells. (Th1 cells produce IL-2 and interferon [IFN] gamma.) These cells may subsequently activate macrophages and other cell populations, including synovial fibroblasts. Macrophages and synovial fibroblasts are the main producers of TNF- α and IL-1. Experimental models suggest that synovial macrophages and fibroblasts may become autonomous and thus lose responsiveness to T-cell activities in the course of RA. **B cells are important in the pathologic process** and may serve as antigen-presenting cells. B cells also produce numerous autoantibodies (eg, RF and ACPA) and secrete cytokines. **The hyperactive and hyperplastic synovial membrane** is ultimately transformed into pannus tissue and invades cartilage and bone, with the latter being degraded by activated osteoclasts. The major difference between RA and other forms of inflammatory arthritis, such as psoriatic arthritis, lies not in their respective cytokine patterns but, rather, in the highly destructive potential of the RA synovial membrane and in the local and systemic autoimmunity. **Whether these 2 events are linked is unclear**; however, the autoimmune response conceivably leads to the formation of immune complexes that activate the inflammatory process to a much higher degree than normal. This theory is supported by the much worse prognosis of RA among patients with positive RF results.

Epidemiology

Worldwide, the annual incidence of RA is approximately 3 cases per 10,000 population, and the prevalence rate is approximately 1%, increasing with age and peaking between the ages of 35 and 50 years. RA affects all populations, though it is much more prevalent in some groups (eg, 5-6% in some Native American groups) and much less prevalent in others (eg, black persons from the Caribbean region). **First-degree relatives of individuals with RA** are at 2- to 3-fold higher risk for the disease. Disease concordance in monozygotic twins is approximately 15-20%, suggesting that nongenetic factors play an important role. Because the worldwide frequency of RA is relatively constant, a ubiquitous infectious agent has been postulated to play an etiologic role. **Women are affected by RA approximately 3 times more often than men are**, but sex differences diminish in older age groups. In investigating whether the higher rate of RA among women could be linked to certain reproductive risk factors, a study from Denmark found that the rate of RA was higher in women who had given birth to just 1 child than in women who had delivered 2 or 3 offspring. However, the rate was not increased in women who were nulliparous or who had a history of lost pregnancies. **Time elapsed since pregnancy is also significant**. In the 1- to 5-year postpartum period, a decreased risk for RA has been recognized, even in those with higher-risk HLA markers. **The Danish study also found a higher risk of RA among women** with a history of preeclampsia, hyperemesis during pregnancy, or gestational hypertension. In the authors' view, this portion of the data suggested that a reduced immune adaptability to pregnancy may exist in women who

are predisposed to the development of RA or that there may be a link between fetal microchimerism (in which fetal cells are present in the maternal circulation) and RA.

Prognosis

Outcome in RA is compromised when diagnosis and treatment are delayed. The clinical course of RA is generally one of exacerbations and remissions. Approximately 40% of patients with this disease become disabled after 10 years, but outcomes are highly variable. Some patients experience a relatively self-limited disease, whereas others have a chronic progressive illness.

Prognostic factors

Intervention with DMARDs in very early RA (symptom duration < 12 weeks at the time of first treatment) provides the best opportunity for achieving disease remission. Better detection of early joint injury has provided a previously unappreciated view of the ubiquity and importance of early joint damage. Nonetheless, predicting the long-term course of an individual case of RA at the outset remains difficult, though the following all correlate with an unfavorable prognosis in terms of joint damage and disability:

- HLA-DRB1*04/04 genotype
- High serum titer of autoantibodies (eg, RF and ACPA)
- Extra-articular manifestations
- Large number of involved joints
- Age younger than 30 years
- Female sex
- Systemic symptoms
- Insidious onset

In a retrospective study that used logistic regression to analyze clinical and laboratory assessments in patients with RA who took only methotrexate, the authors found that measures of C-reactive protein (CRP) and swollen joint count after 12 weeks of methotrexate administration were most associated with radiographic progression at week 52. [The prognosis of RA is generally much worse among patients with positive RF results.](#) For example, the presence of RF in sera has been associated with severe erosive disease. However, the absence of RF does not necessarily portend a good prognosis. [Other laboratory markers of a poor prognosis include](#) early radiologic evidence of bony injury, persistent anemia of chronic disease, elevated levels of the C1q component of complement, and the presence of ACPA (see Workup). In fact, the presence of ACPA and antikeratin antibodies (AKA) in sera has been linked with severe erosive disease, and the combined detection of these autoantibodies can increase the ability to predict erosive disease in RA patients. [RA that remains persistently active for longer than 1 year](#) is likely to lead to joint deformities and disability. Periods of activity lasting only weeks or a few months followed by spontaneous remission portend a better prognosis. [A study by Mollard et al of 8189 women in a US-wide observational cohort](#) who developed RA before menopause found greater functional decline in postmenopausal women than in premenopausal ones; furthermore, the trajectory of functional decline worsened and accelerated after menopause. However, ever-use of hormonal replacement therapy, ever having a pregnancy, and longer length of reproductive life were associated with less functional decline.

Morbidity and mortality

Most data on RA disability rates derive from specialty units caring for referred patients with severe disease. Little information is available on patients cared for in primary care community settings. Estimates suggest that more than 50% of these patients remain fully employed, even after 10-15 years of disease, with one third having only intermittent

low-grade disease and another one third experiencing spontaneous remission. [RA is associated with traditional and nontraditional cardiovascular risk factors.](#) The leading cause of excess mortality in RA is cardiovascular disease, followed by infection, respiratory disease, and malignancies. The effects of concurrent therapy, which is often immunosuppressive, may contribute to mortality in RA. However, studies suggest that control of inflammation may improve mortality. [Nontraditional risk factors appear to play an important role in cardiovascular morbidity and mortality.](#) Myocardial infarction, myocardial dysfunction, and asymptomatic pericardial effusions are common; symptomatic pericarditis and constrictive pericarditis are rare. Myocarditis, coronary vasculitis, valvular disease, and conduction defects are occasionally observed. A large Danish cohort study suggested the presence of an increased risk of atrial fibrillation and stroke in patients with RA. [The overall mortality in patients with RA is reportedly 2.5 times higher](#) than that of the general age-matched population. In the 1980s, mortality among those with severe articular and extra-articular disease approached that among patients with 3-vessel coronary disease or stage IV Hodgkin lymphoma. Much of the excess mortality derives from infection, vasculitis, and poor nutrition. With the exception of lymphoma, mortality from cancer is unchanged.

Patient Education

Patient education and counseling help to reduce pain, disability, and frequency of physician visits. These may represent the most cost-effective intervention for RA.

Informing patient of diagnosis

With a potentially disabling disease such as RA, the act of informing the patient of the diagnosis takes on major importance. The goal is to satisfy the patient's informational needs regarding the diagnosis, prognosis, and treatment in appropriate detail. To understand the patient's perspective, requests, and fears, the physician must employ careful questioning and empathic listening. [Telling patients more than they are intellectually or psychologically prepared](#) to handle (a common practice) risks making the experience so intense as to trigger withdrawal. Conversely, failing to address issues of importance to the patient compromises the development of trust. The patient needs to know that the primary physician understands the situation and is available for support, advice, and therapy as the need arises. Encouraging the patient to ask questions helps to communicate interest and caring.

Discussing prognosis and treatment

Patients and families do best when they know what to expect and can view the illness realistically. Many patients fear crippling consequences and dependency. Accordingly, it is valuable to provide a clear description of the most common disease manifestations. Without encouraging false hopes, the physician can point out that spontaneous remissions can occur and that more than two thirds of patients live independently without major disability. In addition, emphasize that much can be done to minimize discomfort and to preserve function. [A review of available therapies and their efficacy helps patients](#) to overcome feelings of depression stemming from an erroneous expectation of inevitable disability. (See Treatment). Even in those with severe disease, guarded optimism is now appropriate, given the host of effective and well-tolerated disease-modifying treatments that are emerging.

Dealing with misconceptions

Several common misconceptions regarding RA deserve attention. Explaining that no known controllable precipitants exist helps to eliminate much unnecessary guilt and self-recrimination. Dealing in an informative, evidence-based fashion with a patient who expresses

interest in alternative and complementary forms of therapy can help limit expenditures on ineffective treatments. [Another misconception is that a medication must be expensive to be helpful.](#) Generic NSAIDs, low-dose prednisone, and the first-line DMARDs are quite inexpensive yet remarkably effective for relieving symptoms, a point that bears emphasizing. The belief that one must be given the latest TNF inhibitor to be treated effectively can be addressed by a careful review of the overall treatment program and the proper role of such agents in the patient's plan of care. [Active participation of the patient and family](#) in the design and implementation of the therapeutic program helps boost morale and to ensure compliance, as does explaining the rationale for the therapies used. [The family also plays an important part in striking the proper balance](#) between dependence and independence. Household members should avoid overprotecting the patient (eg, the spouse refraining from intercourse out of fear of hurting the patient) and should work to sustain the patient's pride and ability to contribute to the family. Allowing the patient with RA to struggle with a task is sometimes constructive.

Supporting patient with debilitating disease

Abandonment is a major fear in these individuals. Patients are relieved to know that they will be closely observed by the primary physician and healthcare team, working in conjunction with a consulting rheumatologist and physical/occupational therapist, all of whom are committed to maximizing the patient's comfort and independence and to preserving joint function. With occupational therapy, the treatment effort is geared toward helping the patient maintain a meaningful work role within the limitations of the illness. [Persons with long-standing severe disease who have already sustained much irreversible joint destruction](#) benefit from an emphasis on comfort measures, supportive counseling, and attention to minimizing further debility. Such patients need help in grieving for their disfigurement and loss of function. [An accepting, unhurried, empathic manner allows the patient to express feelings.](#) The seemingly insignificant act of touching does much to restore a sense of self-acceptance. Attending to pain with increased social support, medication, and a refocusing of attention to function is useful. A trusting and strong patient-doctor relationship can do much to sustain a patient through times of discomfort and disability. [For more information,](#) see the Arthritis Center and Pain Management Center, as well as Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, Rheumatoid Arthritis Medications, Chronic Fatigue Syndrome, and Chronic Pain.

Clinical Presentation

History

The hallmark feature of rheumatoid arthritis (RA) is persistent symmetric polyarthritis (synovitis) that affects the hands and feet, although any joint lined by a synovial membrane may be involved. The severity of RA may fluctuate over time, but chronic RA most commonly results in the progressive development of various degrees of joint destruction, deformity, and a significant decline in functional status. Extra-articular involvement of organs such as the skin, heart, lungs, and eyes can also be significant. [Juvenile idiopathic arthritis \(JIA\), sometimes referred to as juvenile rheumatoid arthritis \(JRA\),](#) is the most common form of childhood arthritis. In most patients, the immunogenic associations, clinical pattern, and functional outcome of JIA are different from those of adult-onset RA. [Patients with RA may report difficulty performing activities of daily living \(ADLs\),](#) such as dressing, standing, walking, personal hygiene, or use of their hands. In addition to articular deterioration, constitutional symptoms (eg, fatigue, malaise, morning stiffness, weight loss, and low-grade fever) may be present. [In most patients, RA has an insidious onset.](#) It may begin with systemic features

(eg, fever, malaise, arthralgias, and weakness) before the appearance of overt joint inflammation and swelling. A small percentage (approximately 10%) of patients with this disease have an abrupt onset with the acute development of synovitis and extra-articular manifestations. Spontaneous remission is uncommon, especially after the first 3-6 months.

Physical Examination

During the physical examination, it is important to assess the following:

- Stiffness
- Tenderness
- Pain on motion
- Swelling
- Deformity
- Limitation of motion
- Extra-articular manifestations
- Rheumatoid nodules

Joint involvement is the characteristic feature of RA. In general, the small joints of the hands and feet are affected in a relatively symmetric distribution. In decreasing frequency, the metacarpophalangeal (MCP), wrist, proximal interphalangeal (PIP), knee, metatarsophalangeal (MTP), shoulder, ankle, cervical spine, hip, elbow, and temporomandibular joints are most commonly affected. [Affected joints show inflammation](#) with swelling, tenderness, warmth, and decreased range of motion (ROM). Atrophy of the interosseous muscles of the hands is a typical early finding. Joint and tendon destruction may lead to deformities such as ulnar deviation, [boutonniere and swan-neck deformities, hammer toes,](#) and, occasionally, joint ankylosis.

Other commonly observed musculoskeletal manifestations include the following:

- [Tenosynovitis](#) (defined as inflammation of the tendon and its enveloping tendon sheath) and associated tendon rupture due to tendon and ligament involvement, most commonly involving the fourth and fifth digital extensor tendons at the wrist
- Periarticular [osteoporosis](#) due to localized inflammation
- Generalized [osteoporosis](#) due to systemic chronic inflammation, immobilization-related changes, or corticosteroid therapy
- [Carpal tunnel syndrome](#)

Most patients with RA have muscle atrophy from disuse, which is often secondary to joint inflammation.

Examination of upper extremities

Fingers

The boutonniere deformity (see the image below) describes nonreducible flexion at the PIP joint along with hyperextension of the distal interphalangeal (DIP) joint of the finger.



Boutonniere deformity.

This deformity occurs as a result of synovitis stretching or rupturing the PIP joint through the central extensor tendon, with concomitant volar displacement of the lateral bands. When the lateral bands have

subluxed far enough to pass the transverse axis of the joint, they become flexors of the PIP joint. Hyperextension of the DIP joint occurs as the tendons shorten with time. A compensatory and reducible hyperextension may occur at the MCP joint. Consequences of boutonniere deformity are loss of thumb mobility and pincher grasp. **Swan-neck deformity of the finger describes hyperextension** at the PIP joint with flexion of the DIP joint (see the image below).



Rheumatoid changes in the hand

This deformity may be initiated either (a) by disruption of the extensor tendon at the DIP joint, with secondary shortening of the central extensor tendon and hyperextension of the PIP joint, or (b) by volar herniation of the PIP joint capsule due to weakening from chronic synovitis, with subsequent tightening of the lateral bands and central extensor tendon. The lateral bands may become shortened over time and lie dorsally, limiting PIP flexion and ineffectively extending the DIP joint. **Tightness of intrinsic muscles (eg, the interossei and lumbricals) may cause major declines in finger mobility.** This tightness is ascertained on examination when the PIP joint cannot be flexed while the MCP joint is fully extended but can be flexed while the MCP is in flexion (Bunnell test); primary PIP joint pathology is evident with the MCP joint in either position. For accurate assessment, the phalanx must be aligned with the metacarpal; when ulnar deviation at the MCP joint exists, the intrinsic muscles on the ulnar side are slack, allowing more motion. **Flexor tenosynovitis of the fingers is common and suggests a poor prognosis.** "Triggering" of the finger occurs when thickening or nodule formation of the tendon interacts with the concomitant tenosynovial proliferation, trapping the tendon in a flexed position (stenosing tenosynovitis). Tendon rupture may occur as a consequence of infiltrative synovitis in the digit or bony erosion of the tendon at the wrist (especially the flexor pollicis longus). **Arthritis mutilans (sometimes called opera glass hands)** results if destruction is severe and extensive, with dissolution of bone. In the small joints of the hands, the phalanges may shorten, and the joints may become grossly unstable. Pulling on the fingers during examination may lengthen the digit in a manner resembling the opening of opera glasses, or the joint may bend in unusual directions merely under the pull of gravity.

Metacarpophalangeal joints

Two typical deformities that alter the alignment of the palmar skeletal arches and the stability of the fingers may occur at the MCP joints: volar subluxation and ulnar deviation (see the following image).

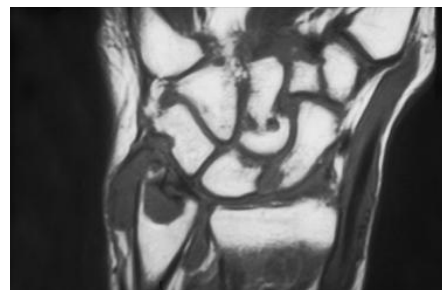


Subluxation in the metacarpophalangeal joints, with ulnar deviation, in a patient with rheumatoid arthritis of the hands.

Most cases of ulnar deviation are accompanied by counterpoised radial deviation of the wrist, roughly proportional to the degree of ulnar deviation of the fingers. The volar plate is firmer and more substantial than other portions of the MCP joint capsule, thus effectively limiting extension and dorsal movement at the joint. The greater strength of the flexor muscles relative to the extensor muscles causes volar migration of the proximal phalanx after synovial-based inflammation has weakened ligament and tendon insertions about the MCP joint capsule. **Ulnar deviation occurs after synovitis** has led to stretching and attenuation of the volar plate and collateral ligaments, allowing dislocation of the flexor tendon volarward and ulnarward. The supporting structures of the extensor tendons also may become attenuated or destroyed by synovial distention and invasion, loosening the tendons so that they no longer ride centrally and dorsally over the metacarpal head but move into the cleft between the MCP joints. **If the extensor tendon subluxation is beyond the transverse axis** of the MCP joint, the tendon becomes a flexor at that joint, further limiting the active extension of the fingers.

Wrists

Multiple deformities may occur in the wrist. Disruption of the radioulnar joint with dorsal subluxation of the ulna (caput ulnae) as well as rotation of the carpus on the distal radius with an ulnarly translocated lunate are common. The combination of an ulnar drift of the fingers and carpal rotation is known as a zigzag deformity. Shortening of the carpal height (noted on radiographs), due in part to cartilage loss, is seen with rotational deformities. **Dorsal subluxation of the ulna often allows the ulnar styloid to be depressed volarly on examination**, much as a piano key is depressed when played. It may lead to rupture of the extensor tendons of the little, ring, and long fingers because the end of the distal ulna is roughened secondary to erosion of bone and may abrade the tendons as they move during normal hand function, much as a rope is frayed when rubbed over a sharp rock (see the image below). This process is especially likely to lead to tendon rupture if tenosynovitis is present.



Coronal, T1-weighted magnetic resonance imaging scan shows characteristic pannus and erosive changes in the wrist in a patient with active rheumatoid arthritis.

Entrapment neuropathy may result from synovitis about the flexor tendons. **Entrapment of the median nerve** as it passes through the carpal tunnel leads to decreased sensation on the palmar aspect of the thumb, index finger, and long finger and on the radial aspect of the ring finger; weakness and atrophy of the muscles in the thenar eminence also occurs. **Entrapment of the ulnar nerve** at the wrist, a less frequent event, causes decreased sensation over the little finger and the ulnar aspect of the ring finger and decreased interosseous muscle strength and mass.

Elbow

Elbow involvement is often detected by palpable synovial proliferation at the radiohumeral joint and is commonly accompanied by a flexion deformity, such as in contractures. Involvement of the olecranon bursa is common, as are rheumatoid nodules in the bursa and along the extensor surface of the ulna (see the image below).



Rheumatoid nodules at the elbow.

Shoulders

RA commonly involves the shoulders and is manifested by tenderness, nocturnal pain, and limited motion. Initially, swelling occurs anteriorly, but it may be difficult to detect and is present on examination in a minority of patients at any point in time. **Rotator cuff degeneration secondary to synovitis may limit abduction and rotation.** Superolateral migration of the humerus occurs with complete tears. Glenohumeral damage results in pain with motion and at rest and typically leads to severely restricted motion or “frozen shoulder syndrome.” Acromioclavicular arthritis is not as frequent or as disabling as the other manifestations of this disease.

Examination of lower extremities

Ankles and feet

The ankle joint itself is rarely involved without midfoot or MTP involvement. Because it is a mortise joint, it does not often deform. Major structural changes occur in the midfoot and foot as a result of the combination of chronic synovitis and weight bearing. Posterior tibialis tendon involvement or rupture may lead to subtalar subluxation, which results in eversion and migration of the talus laterally. Midfoot disease leads to loss of normal arch contour with flattening of the feet. **The MTP joints are inflamed in most patients** and, because of the heavy loads they bear, often become deformed over time. The great toe typically develops hallux valgus (a bunion); subluxation of the phalanx at the MTP joint of the other toes predominantly occurs dorsally. Toes may exhibit compensatory flexion due to a fixed length of the flexor tendons—so-called hammer toes. The second and third metatarsal heads commonly protrude and may become the primary weight-bearing surface at the MTP joints. Calluses and pain upon weight bearing result.

Knees

Affected knees may develop large effusions and abundant accumulation of synovium. Knee effusions and synovial thickening are common in RA and are easily detected during the early course of the disease. Persistent effusions may lead to inhibition of quadriceps function by spinal reflexes, resulting in subsequent atrophy. **Instability may develop after progressive loss of cartilage and weakening of ligaments;** deformity may include genu valgus or varus, as well as flexion deformities. The patient's energy expenditure for standing or walking increases substantially if there are flexion deformities of the knees.

Hips

The hips are commonly involved in RA; however, because of their deep location, their involvement is not always readily apparent early in the course of the disease. Hips are difficult to examine by means of direct inspection or palpation. **Limited motion or pain on motion and weight bearing are the hallmarks of hip involvement.** The Patrick maneuver (flexion, external rotation, and abduction) is abnormal in this situation. A flexion deformity may be demonstrable by conducting a Thomas test, which is performed by flexing one hip (with the patient supine) while restricting pelvic motion by keeping the other hip in the neutral position on the examination table. If the hip cannot be maintained in the neutral position, a contracture is present.

Cervical spine

Cervical spine involvement (see the following image) usually affects C1-C2 and has the potential to cause serious neurologic consequences. Patients who are to undergo intubation or procedures that may involve manipulation of the neck should undergo careful evaluation of the cervical spine.



Ankylosis in the cervical spine at several levels due to long-standing juvenile rheumatoid arthritis (also known as juvenile idiopathic arthritis).

Neck pain on motion and occipital headache are common manifestations of cervical spine involvement. Most patients with cervical spine involvement (see the image below) have had the disease for more than 10 years.



Lateral view of the cervical spine in a patient with rheumatoid arthritis shows erosion of the odontoid process.

Clinical manifestations of early cervical spine disease consist primarily of neck stiffness that is perceived throughout the entire arc of motion. The atlantoaxial joint is a synovial-lined joint and is susceptible to the same proliferative synovitis and subsequent instability seen in the peripheral joints. Patients with severe destruction in the hands (arthritis mutilans) are very likely to have symptomatic cervical spine abnormalities, as are those patients taking significant amounts of corticosteroids for control of RA. **Neurologic involvement in the cervical spine ranges from radicular pain** to a variety of spinal cord lesions that may result in weakness (including quadriparesis), sphincter dysfunction, sensory deficits, and pathologic reflexes. **Transient ischemic attacks (TIAs) and cerebellar signs may reflect** vertebral artery impingement from cervical subluxation or basilar artery impingement from upward migration of the dens. Tenosynovitis of the transverse ligament of C1 may lead to C1-C2 instability. Myelopathy secondary to rupture of the transverse ligament may lead to neurologic deficits. Radiculopathy is most common at the C2 root, though symptomatic subluxations may occur at any level. **Symptoms of cervical myelopathy are gradual in onset** and are often unrelated to either the development or the accentuation of neck pain. When neck pain does occur, it frequently radiates over the occipital region in the distribution of the C1-3 nerve roots. The Lhermitte sign, in which tingling paresthesia that descends through the thoracolumbar spine occurs as the cervical spine is flexed, is typically observed.

Stiffness, Tenderness, and Pain on Motion

On physical examination, stiffness in patients with RA is determined by limitation of motion, which may vary with the time of day. However, stiffness that is due to articular surface derangement or soft tissue contractures about the joint does not vary with the time of day. **Severe stiffness in the hands may improve with heat**, but it is most effectively relieved with active exercise. These modalities reduce stiffness immediately after application, but unfortunately, they do not prevent the return of stiffness. **Direct palpation can elicit joint tenderness**, which can vary significantly among patients and with the method of application of force used. To minimize variation over time, the examiner should try to apply approximately the same pressure for each patient examined. **The enlarged synovial membrane, periarticular ligaments**, and supporting structures are the major pain-sensitive structures. Muscles may also become tender, but rarely is this due to myositis. Muscle tenderness is not specific for RA. Severe muscle tenderness should suggest another differential diagnosis, including fibromyalgia or a regional pain disorder (see DDx). Bony prominences are generally tender; periarticular structures tend to be more vulnerable to palpation at these sites. **Pain on motion is often used as a surrogate for tenderness in joints** that are not readily amenable to direct palpation because of overlying muscle and other tissues. Such areas include the cervical spine, shoulder, and hip. **Pain on motion of the joint may be due to noninflammatory processes** that also interfere with the joint's normal, almost frictionless motion, including damage of cartilage and bone. Additionally, joint instability or subluxation causes pain on motion because of musculotendinous imbalances across the joint. Documenting the positions of motion at which pain occurs can be useful.

Swelling, Deformity, and Limitation of Motion

In RA, enlargement of the synovial membrane is noted on physical examination as thickening of the synovium that may obscure joint margins. This thickening is most evident in the small joints of the hands and feet. In the MCP and MTP joints, the outline of the base of the

proximal phalanx may become indistinct, and in the PIP joints of the fingers, a fusiform swelling is noted that is due to the anatomy of the synovial reflections (see the image below).



Soft-tissue swelling and early erosions in the proximal interphalangeal joints in a patient with rheumatoid arthritis of the hands.

If synovial proliferation is abundant, the resultant soft-tissue mass may have a doughy texture on palpation. Such synovial proliferation is commonly identified in the PIP, MCP, elbow, ankle, MTP, and knee joints, as well as in the flexor tendons of the fingers, the common extensor compartment of the dorsal wrist, and the extensor carpi ulnaris tendon sheath. **Joint effusions may also contribute to swelling by distending the joint**. When the effusion is put under increased pressure with joint flexion, the synovium may be forced between articular structures, with the result that a portion becomes trapped and separated from the rest of the joint, forming a Baker cyst (see the image below). More fluid is forced into the structure with subsequent loading of the distended joint, and a 1-way valve effect may prevent the fluid from returning to the joint.



Anteroposterior radiograph of the knee shows uniform joint-space loss in the medial and lateral knee compartments without osteophytosis. A Baker cyst is seen medially (arrowhead).

Baker cysts may be seen in most peripheral joints and are most commonly recognized in the knee. The larger the effusion, the more likely it is that a painful cyst will develop in the popliteal fossa. Rupture of

a Baker cyst at the knee may resemble acute thrombophlebitis, with distal dissection of inflammatory joint contents along fascial planes as far as the ankle and dorsal foot. **Deformity of the joint may develop over time as articular and supporting structures** are damaged by the inflammatory process. By the time deformity has developed, the diagnosis of RA is in little doubt; however, optimal management of RA requires that the inflammatory aspects of the arthritis be recognized before the development of deformity. **Loss of cartilage from proteolytic and mechanical degradation**, combined with stretching and weakening of the periarticular ligaments and their attachments, allows forces acting across the joints to deform them. The small joints in the hands and feet are most commonly deformed in this manner; more than 10% of patients with RA develop deformity of the small joints of the hands within the first 2 years of the disease, and at least 33% develop such deformities over time. Joint instability is seen if disruption of supporting structures has occurred. **Limitation of motion occurs as a result of articular surface damage**, joint and tendon sheath swelling, or alteration of joint supporting structures. Effusion may limit joint motion through pain or by causing sufficient tightness of the joint capsule to impede joint mobility. Fibrosis involving tendons and muscles may limit normal joint motion and result in flexion contractures. Joint deformities and subluxations invariably limit motion because of mechanical factors.

Extra-articular Manifestations

RA is a systemic disease, and most individuals with this condition experience extra-articular manifestations such as generalized malaise and fatigue. Rarely, a patient presents with extra-articular manifestations before the onset of arthritis. Some of these manifestations are more common in men (eg, pleural involvement, vasculitis, and pericarditis), but overall, the sex distribution of extra-articular manifestations of the disease is similar to that of RA.

Rheumatoid nodules

Rheumatoid nodules occur in approximately 25% of patients with RA, but they occur in fewer than 10% of patients during the first year of the disease. These lesions are most commonly found on extensor surfaces or sites of frequent mechanical irritation. **The olecranon process, the proximal ulna, the back of the heel**, the occiput, and the ischial tuberosities are common periosteal sites for rheumatoid nodule development. Nodules may also form in subcutaneous tissues of the fingers, in toe and heel pads, in tendons, and in viscera. Rheumatoid factor (RF) is almost invariably present in patients with rheumatoid nodules; the absence of RF suggests other diagnoses. **Frequently, there is a discrepancy between the level of articular inflammation** and the progression of nodule formation. Patients with rheumatoid nodulosis have a great number of nodules, usually subcutaneous, and may have little active synovitis. In a similar fashion, patients whose articular inflammation responds well to treatment with methotrexate (MTX) may have a seemingly paradoxical rapid increase in the number of nodules.

Effects on organ systems

RA affects several organ systems, as follows:

- Cutaneous
- Cardiac
- Pulmonary
- Renal
- Gastrointestinal (GI)
- Vascular
- Hematologic

- Neurologic
- Ocular

Subcutaneous nodules (rheumatoid nodules) develop in many RA patients whose RF value is abnormal, often over pressure points (eg, olecranon). Vasculitic lesions of the skin may manifest as palpable purpura or skin ulceration (eg, leg ulceration). Additionally, palmar erythema and pyoderma gangrenosum may be noted. **Cardiovascular morbidity and mortality are increased in patients with RA**. Nontraditional risk factors appear to play an important role. Myocardial infarction, myocardial dysfunction, and asymptomatic pericardial effusions are common; symptomatic pericarditis and constrictive pericarditis are rare. Myocarditis, coronary vasculitis, valvular disease, and conduction defects are occasionally observed. **RA involvement of the lungs may take several forms**, including pleural effusions, interstitial fibrosis, nodules, and bronchiolitis obliterans organizing pneumonia. Methotrexate therapy can induce interstitial fibrosis that may be difficult to distinguish from that which naturally occurs in patients with RA. **The kidneys usually are not directly affected by RA**. Secondary involvement is common, including that due to medications (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], gold, and cyclosporine), inflammation (eg, amyloidosis), and associated diseases (eg, Sjögren syndrome with renal tubular abnormalities). **GI involvement, like renal involvement, is often secondary to associated processes** such as medication effects, inflammation, and other diseases. The liver may be affected in patients with Felty syndrome (ie, RA, splenomegaly, and neutropenia). **Vasculitic lesions can occur in any organ**, but they are most commonly found in the skin. Lesions may present as palpable purpura, skin ulcers, or digital infarcts. **Some patients with active RA have an anemia of chronic disease**. Several hematologic parameters parallel disease activity, including normochromic-normocytic anemia, thrombocytosis, and eosinophilia, though the last of these is uncommon. Leukopenia is a finding in patients with Felty syndrome. **Nerve entrapment is common, as with the median nerve in carpal tunnel syndrome**. Vasculitic lesions, mononeuritis multiplex, and cervical myelopathy may cause serious neurologic consequences. Peripheral myopathy may be noted as well. **Keratoconjunctivitis sicca is common in individuals with RA**, and this condition is often the initial manifestation of secondary Sjögren syndrome. The eye may also have episcleritis, uveitis, and nodular scleritis that may lead to scleromalacia.

Complications

RA itself is not fatal, but complications of the disease may shorten survival by years in some individuals. In general, RA is progressive and cannot be cured, but in some patients, the disease gradually becomes less aggressive, and symptoms may even improve. However, if bone and ligament destruction and any deformities have occurred, the effects are permanent. **Joint disability and pain with daily life are common**. Affected joints can become deformed, and the performance of even ordinary tasks may be very difficult or impossible; these factors can severely affect patients' quality of life. In addition, RA is a systemic disease that can affect other parts of the body in addition to joints. These effects include the following:

- Anemia
- Infections – Patients with RA are at greater risk for infections; immunosuppressive drugs further increase that risk
- GI problems – Patients with RA may experience stomach and intestinal distress; however, lower rates of stomach and colorectal cancers have been reported in RA patients

- Osteoporosis – This condition is more common than average in postmenopausal women with RA; the hip is particularly affected; the risk of osteoporosis appears to be higher than average in men with RA who are older than 60 years
- Lung disease – A small study found a high prevalence of pulmonary inflammation and fibrosis in patients with newly diagnosed RA, but this finding may be associated with smoking
- Heart disease – RA can affect blood vessels and increase the risk of coronary ischemic heart disease
- Sjögren syndrome – Keratoconjunctivitis sicca is a common complication of RA; oral sicca and salivary gland enlargement are less common
- Felty syndrome – This condition is characterized by splenomegaly, leukopenia, and recurrent bacterial infections; it may respond to disease-modifying antirheumatic drugs (DMARDs)
- Lymphoma and other cancers – RA-associated immune system alterations may play a role; aggressive treatments for RA may help prevent such cancers.

Differential Diagnoses

Diagnostic Considerations

Differentiation of rheumatoid arthritis (RA) from other diseases of connective tissue can be difficult; however, certain clinical features are helpful. [Rheumatic fever is characterized by the migratory nature of the arthritis](#), an elevated anti-streptolysin O titer, and a more dramatic and prompt response to aspirin. Carditis and erythema marginatus may occur in adults, but chorea and subcutaneous nodules virtually never do. Systemic lupus erythematosus (SLE) is suggested by the presence of the following:

- Butterfly rash
- Discoid lupus erythematosus
- Photosensitivity
- Alopecia
- High anti-DNA titer
- Renal disease
- Central nervous system (CNS) abnormalities

Degenerative joint disease (DJD) is not associated with constitutional manifestations; in contrast to the morning stiffness of RA, the joint pain from DJD is characteristically relieved by rest. Signs of articular inflammation prominent in RA are usually minimal in DJD, and in contrast to RA, osteoarthritis spares the wrist and the MCP joints. [During the early years of disease, gouty arthritis is almost always intermittent and monoarticular](#); in later years, it can become a chronic polyarticular process that mimics RA. Gouty tophi can at times resemble rheumatoid nodules. The early history of intermittent monoarthritis and the presence of synovial urate crystals are distinctive features of gout. [Pyogenic arthritis can be distinguished by chills and fever](#), demonstration of the causative organism in joint fluid, and the frequent presence of a primary focus elsewhere (eg, gonococcal arthritis). Chronic Lyme disease typically involves only 1 joint, most commonly the knee, and is associated with positive serologic tests. Human parvovirus B19 infection in adults can occasionally mimic RA. [Polymyalgia rheumatica occasionally causes polyarthritis](#) in patients older than 50 years, but these patients have chiefly proximal muscle pain and stiffness and remain negative for rheumatoid factor (RF). [A variety of cancers produce paraneoplastic syndromes](#), including polyarthritis. One form is hypertrophic pulmonary osteoarthropathy, which is most often produced

by lung and gastrointestinal carcinomas. Hypertrophic pulmonary osteoarthropathy is characterized by a rheumatoidlike arthritis associated with clubbing, periosteal new bone formation, and a negative RF test. Diffuse swelling of the hands with palmar fasciitis has also been reported with a variety of cancers, especially ovarian carcinoma.

Differential Diagnoses

- Fibromyalgia
- Lyme Disease
- Myelodysplastic Syndrome
- Osteoarthritis
- Paraneoplastic Syndromes
- Relapsing Polychondritis
- Polymyalgia Rheumatica
- Psoriatic Arthritis
- Sarcoidosis
- Sjogren Syndrome
- Systemic Lupus Erythematosus (SLE)

Workup

Approach Considerations

No test results are pathognomonic for rheumatoid arthritis (RA); instead, the diagnosis is made by using a combination of clinical, laboratory, and imaging features. For clinical and radiologic criteria used in determining disease progression, see 2012 ACR Disease Activity Measures. Bone scanning findings may help distinguish inflammatory from noninflammatory changes in patients with minimal swelling, and densitometry findings are useful for helping diagnose changes in bone mineral density that are indicative of osteoporosis.

Laboratory Studies

Routine viral screening by serologic testing does not significantly facilitate the diagnosis of RA in patients with early RA, nor is it helpful as a potential identifier of disease progression. Potentially useful laboratory studies in suspected RA fall into 3 categories—markers of inflammation, hematologic parameters, and immunologic parameters—and include the following:

- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP) level
- Complete blood count (CBC)
- Rheumatoid factor (RF) assay
- Antinuclear antibody (ANA) assay
- Anti-cyclic citrullinated peptide (anti-CCP) and anti-mutated citrullinated vimentin (anti-MCV) assays (currently used in the 2010 American College of Rheumatology [ACR]/European League Against Rheumatism [EULAR] classification criteria)

Markers of inflammation

The ESR and the CRP level are associated with disease activity. The CRP value over time correlates with radiographic progression.

Hematologic parameters

The CBC commonly demonstrates anemia of chronic disease and correlates with disease activity; it improves with successful therapy. Hypochromic anemia suggests blood loss, commonly from the gastrointestinal (GI) tract (associated with the use of nonsteroidal anti-inflammatory drugs [NSAIDs]). Anemia may also be related to disease-modifying antirheumatic drug (DMARD) therapy. [Thrombocytosis is common and is also associated with disease activity](#). Thrombocytopenia may be a rare adverse event of therapy and may occur in patients with

Felty syndrome. Leukocytosis may occur but is usually mild. Leukopenia may be a consequence of therapy or a component of Felty syndrome, which may then respond to DMARD therapy.

Immunologic parameters

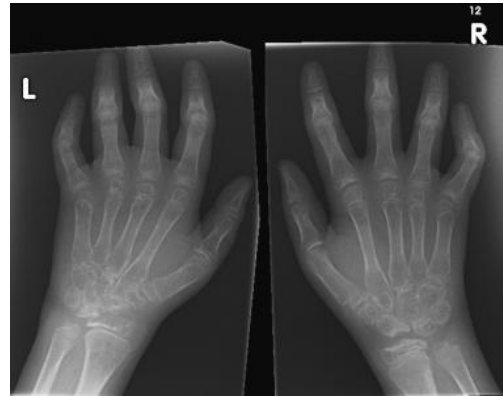
Immunologic parameters include autoantibodies (eg, RF, anti-CCP antibodies, and ANAs). RF is an immunoglobulin (Ig) M antibody directed against the Fc fragment of IgG that is present in approximately 60-80% of patients with RA over the course of their disease (but in fewer than 40% of patients with early RA). RF values fluctuate somewhat with disease activity, though titers of RF generally remain high even in patients with drug-induced remissions. RF is not specific for RA but is also present in other connective tissue diseases, infections, and autoimmune disorders, as well as in 1-5% of healthy people. The presence of RF predicts radiographic progression of bone erosions, independent of disease activity. Although ANAs are present in approximately 40% of patients with RA, test results for antibodies to most nuclear antigen subsets are negative. Assays for anti-citrullinated protein antibody (ACPA; often tested as anti-CCP) are now being used clinically for diagnosing RA. ACPA-positive and ACPA-negative RA may be 2 distinct disease subsets, with different underlying pathogenesis and risks for developing RA. ACPA-positive patients may have a more erosive RA disease course than ACPA-negative patients. However, a 2011 study suggests that reassessment of ACPA or IgM RF during the first year after onset of arthritis does not provide significant additional information. The sensitivity of anti-MCV assays has been reported to be comparable to that of ACPA; however, other studies have found the specificity of anti-MCV to be slightly lower than that of ACPA. Anti-MCV and anti-CCP levels may correlate with disease activity. Studies of anti-CCP antibodies suggest a sensitivity and specificity equal to or better than those of RF, with an increased frequency of positive results in early RA; the presence of both anti-CCP antibodies and RF is highly specific for RA. Additionally, the presence of anti-CCP antibodies, like that of RF, indicates a worse prognosis. A trial that tested for 4 novel RA biomarkers improved the diagnosis of early RA in patients who tested negative on conventional tests. In the study comprising 293 RA patients, 97 healthy control subjects, and 87 rheumatic control patients with other arthritides, the panel of 4 biomarkers—UH-RA.1, UH-RA.9, UH-RA.14 and UH-RA.21—had 83% specificity for RA. These markers were found in 37% of patients with early RA and 26% of those who were seronegative for rheumatoid factor and anticitrullinated protein antibody. The investigators suggested that in addition to an improved diagnosis in early RA, use of these biomarkers may also have prognostic potential.

Pregnancy

RA often goes into remission during pregnancy. The presence of RF neither helps predict nor correlates with the outcome of arthritis during pregnancy. The ESR cannot be used to assess RA disease activity during pregnancy, because pregnancy alters the normal values. The volume expansion that occurs during pregnancy can result in lower hematocrit values.

Radiography

Radiography remains the first choice for imaging in RA; it is inexpensive, readily available, and easily reproducible, and it allows easy serial comparison for assessment of disease progression. Views of the hands, wrists, knees, feet, elbows, shoulders, hips, cervical spine, and other joints should be assessed with radiography when indicated (see the images below). Erosions may be present in the feet, even in the absence of pain and in the absence of erosions in the hands.



Widespread osteopenia, carpal crowding (due to cartilage loss), and several erosions affecting the carpal bones and metacarpal heads in particular in a child with advanced juvenile rheumatoid arthritis (also known as juvenile idiopathic arthritis).



Lateral view of the cervical spine in a patient with rheumatoid arthritis shows erosion of the odontoid process.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) provides a more accurate assessment and earlier detection of lesions than radiography does ; however, the cost of the examination and the small size of the joints involved militate against its widespread use. MRI is used primarily in patients with abnormalities of the cervical spine (see the images below); early recognition of erosions on the basis of MRI images has been sufficiently validated.



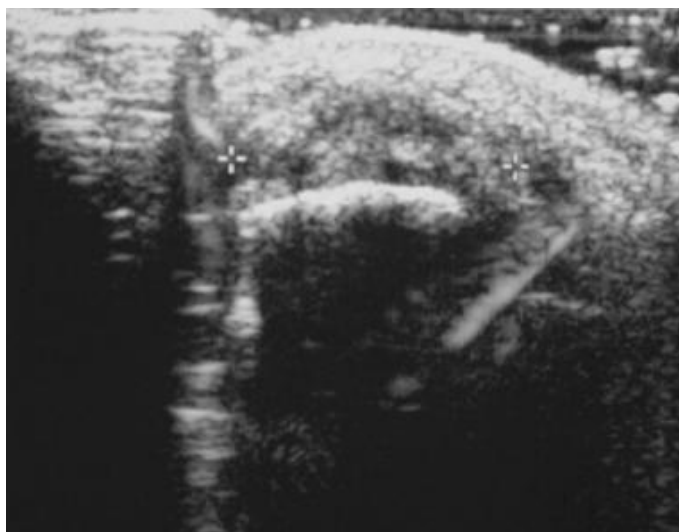
T1-weighted sagittal magnetic resonance image of the cervical spine shows basilar invagination with cranial migration of an eroded odontoid peg. There is minimal pannus. The tip of the peg indents the medulla, and there is narrowing of the foramen magnum due to the presence of the peg. Inflammatory fusion of several cervical vertebral bodies is shown.



Sagittal T2-weighted magnetic resonance image of cervical spine in same patient as in previous image. Compromised foramen magnum is easily appreciated, and there is increased signal intensity within upper cord; this is consistent with compressive myelomalacia. Further narrowing of canal is seen at multiple levels.

Ultrasonography

Ultrasonography of joints (see the image below) is gaining increased widespread acceptance in clinical practice; however, its use in RA is not yet the standard of care. Ultrasonography allows recognition of effusions in joints that are not easily accessible (eg, the hip and, in obese patients, the shoulder) and of cysts (Baker cysts). In addition, high-resolution sonograms allow visualization of tendon sheaths, changes and degree of vascularization of the synovial membrane, and even erosions. Ultrasonography can often be done in the office.



Ultrasonography-guided synovial biopsy of the second metacarpophalangeal joint of the right hand in a patient with rheumatoid arthritis of the hands. The biopsy needle is seen as a straight echogenic line on the left side of the image in an oblique orientation.

Imaging of Specific Structures

Hand

Hand imaging in RA can include radiography, MRI, ultrasonography, and computed tomography (CT), though the last of these plays only a minimal role. Radiography is the mainstay of imaging RA in the hands: It is inexpensive and easily reproducible, and it allows easy serial comparison for assessment of disease progression. Its main disadvantage is the absence of specific radiographic findings in early disease; erosions may only be visualized later. **MRI is sensitive than radiography to early changes in RA**, and in the appropriate clinical setting, it is more accurate than plain radiography in the diagnosis of the disease. However, a systematic literature review concluded that widespread use of MRI for the diagnosis of early RA and for helping determine the prognosis of early RA is not currently recommended, though MRI bone edema may be predictive of progression in certain RA populations. **Ultrasonography has been applied to the assessment of RA** with the goal of improving on the current standard of conventional radiography. Like MRI, ultrasonography serves as an early diagnostic tool and can help in evaluating the cause of joint swelling in a patient with RA. However, the results of one study suggested that NSAID use may mask the ultrasonographic gray scale and power Doppler signal in the assessment of synovitis in RA, resulting in lower scoring despite continuing disease activity. [See Rheumatoid Arthritis Hand Imaging](#) for complete information on this topic.

Spine

Spinal imaging in RA involves radiography, MRI, and CT. As with hand imaging in RA, the mainstay of imaging remains plain radiography. Only about 50% of patients with radiographic evidence of atlantoaxial subluxation are actually symptomatic. **The role of plain radiography is to establish whether the patient has risk factors for cord compression.** The major role for CT and MRI is in preoperative assessment of the 2 main indications for surgical intervention—namely, neurologic deficit and severe pain. Although CT scanning can document bone damage and alignment abnormalities, especially with more detailed multiplanar reconstruction, MRI has become the preferred modality for evaluation of the spinal cord and neural elements.

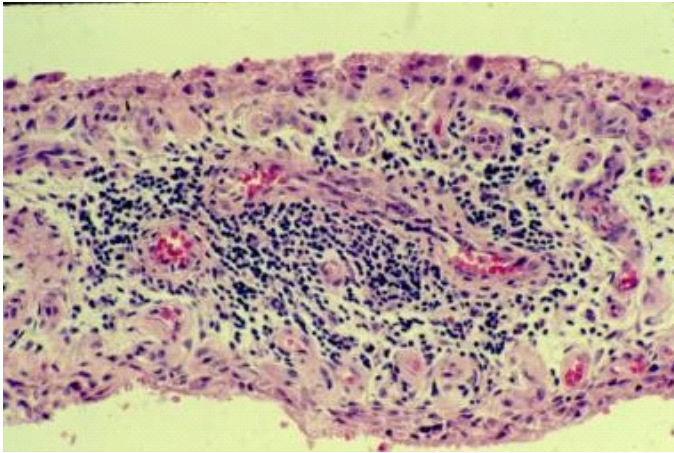
Joint Aspiration

Consider joint aspiration when making the definitive diagnosis of RA or when ruling out coexistent infection or crystal arthritis in an acutely swollen joint. New-onset monoarticular arthritis or an unusual pattern of a joint flare in a patient with RA should encourage strong consideration of joint aspiration and synovial fluid analysis. **Analysis of synovial fluid includes Gram staining, cell count, culture, and assessment of overall appearance.** In patients with RA, analysis typically reveals inflammation (white blood cell [WBC] count $>2000/\mu\text{L}$, generally in the range of 5000–50,000/ μL). Usually, neutrophil predominance (60–80%) is observed in the synovial fluid (in contrast with mononuclear cell predominance in the synovium). Because of a transport defect, glucose levels of synovial fluids (as well as pleural and pericardial fluids) in patients with RA are often low compared with serum glucose levels.

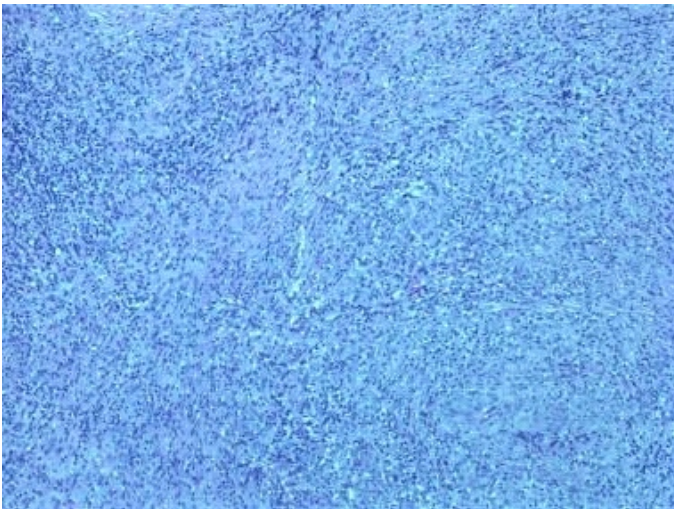
Histologic Findings

Early in the course of the RA disease process, there is an influx of inflammatory cells into the synovial membrane, with subsequent angiogenesis, proliferation of chronic inflammatory (mononuclear) cells and resident synovial cells, and marked histologic changes—a 2-cell-

layer lining membrane changes to a thickened membrane that often has villous projections into the joint space (see the images below).



The hallmark of rheumatoid arthritis is a perivascular mononuclear cell infiltrate in the synovium (pictured here). The early stages are noted to have plasma cells as well, and syphilis needs to be part of the differential diagnosis.



The inflammation involved in rheumatoid arthritis can be intense. It is composed of mononuclear cells and can resemble a pseudosarcoma.

The lymphoplasmacytic infiltration of the synovium with neovascularization seen in RA is similar to that seen in other conditions characterized by inflammatory synovitis. Early rheumatoid nodules are characterized by small-vessel vasculitis and later by granulomatous inflammation.

Treatment & Management

Nonpharmacologic, nonsurgical therapies include the following:

- Heat and cold therapies
- Orthotics and splints
- Therapeutic exercise
- Occupational therapy

- Adaptive equipment
- Joint-protection education
- Energy-conservation education

Guidelines for pharmacologic therapy

- 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis
- 2013 EULAR management guidelines
- 2012 Agency for Healthcare Research and Quality (AHRQ) recommendations

Nonbiologic disease-modifying antirheumatic drugs (DMARDs) include the following:

- Hydroxychloroquine
- Azathioprine
- Sulfasalazine
- Methotrexate
- Leflunomide
- Cyclosporine
- Gold salts
- D-penicillamine
- Minocycline

Biologic tumor necrosis factor (TNF)-inhibiting DMARDs include the following:

- Etanercept
- Infliximab
- Adalimumab
- Certolizumab
- Golimumab

Biologic non-TNF DMARDs include the following:

- Rituximab
- Anakinra
- Abatacept
- Tocilizumab
- Sarilumab
- Tofacitinib
- Baricitinib
- Upadacitinib

Other drugs used therapeutically include the following:

- Corticosteroids
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Analgesics

Surgical treatments include the following:

- Synovectomy
- Tenosynovectomy
- Tendon realignment
- Reconstructive surgery or arthroplasty
- Arthrodesis

INTERPRETATION

Anti-Cyclic Citrullinated Peptide Antibody

Reference Range

Citrullination is a normal physiologic process that occurs in many dying cells. Citrulline is a nonstandard amino acid that is produced by diminution of arginine residue present on certain human proteins by the peptidyl arginine-deiminase (PAD) enzyme. The PAD enzyme has several isoforms, of which PAD2 and PAD4 are expressed in inflammatory leukocytes. The release of PAD from dying cells citrullinates extracellular proteins that contain arginine. Production of anti-citrullinated protein antibody (ACPA) depends on the genetic background of the patient.

- Cut off 10 U/ml
- Negative < 10 U/ml
- Positive ≥ 10 U/ml

Interpretation

Anti-cyclic citrullinated peptide (anti-CCP) antibody levels are characteristically elevated in rheumatoid arthritis, although they can be elevated in other rheumatologic conditions associated with inflammatory arthritis, such as systemic lupus erythematosus. Anti-citrullinated protein antibody (ACPA) level was added to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) diagnostic criteria for rheumatoid arthritis. These criteria, including ACPA levels, identify more patients with rheumatoid arthritis than the previous 1987 criteria. ACPA can be present in the early presentation of rheumatoid arthritis while the rheumatoid factor (RF) is negative. Therefore, if ACPA is identified, the patient likely has rheumatoid arthritis.

The antigen used in most assays is filaggrin, although other antigens are available. ACCP antibodies are a subset of ACPA and are not completely cross-reactive with other citrullinated proteins. The most common test for anti-CCP2 has a sensitivity of 61.6-75.2% for rheumatoid arthritis and specificity of 94-99%. Although multiple assays are available, including antimutated citrullinated vimentin antibody and several generations of anti-CCP, they have all been shown to have comparable diagnostic performance.

Collection and Panels

Serum anti-CCP antibody

Collection details are as follows:

- Specimen - 1 mL of serum
- Container - Plastic screw-cap vial
- Collection method - Routine venipuncture
- Transport temperature - Room temperature
- Reject criteria
 - Gross hemolysis
 - Gross lipemia
 - Plasma
- Methodology – Immunoassay

Background

Citrullination is a normal physiologic process that occurs in many dying cells. Citrulline is a nonstandard amino acid that is produced by diminution of arginine residue present on certain human proteins by the peptidyl arginine-deiminase (PAD) enzyme. The PAD enzyme has several isoforms, of which PAD2 and PAD4 are expressed in inflammatory leukocytes. The release of PAD from dying cells citrullinates extracellular proteins that contain arginine. Production of anti-citrullinated protein antibody (ACPA) depends on the genetic background of the patient.

Citrulline modified proteins are seen in the keratin layer of the epidermis and the brain. Induction of the expression of citrullinated proteins is seen in various inflammatory states and during apoptosis. Joints under normal states do not contain citrullinated proteins, whereas an array of different citrullinated proteins are present during various types of inflammation. ACPA has been identified in the synovial fluid of patients with rheumatoid arthritis.

A study by Mouterde et al found that in patients with early arthritis who were seronegative for rheumatoid factor (RF) and ACPA, the disease was less active at baseline and radiographic progression was less severe at 3-year follow-up than in patients who were seropositive for RF and/or ACPA.

However, a retrospective study by Murata et al indicated that in patients with newly diagnosed rheumatoid arthritis who are positive for anti-cyclic citrullinated peptide (anti-CCP) antibody, there is no association between a family history of rheumatoid arthritis and high disease activity at baseline. Moreover, the investigators reported that such history does not predict poor outcome at 2 years post-onset of the arthritis in these patients.

Anti-CCP antibody and other autoantibody markers can be helpful in determining which patients with rheumatoid arthritis may have benefit from treatments such as anti-tumor necrosis factor- α (TNF α) monoclonal antibodies. Additionally, anti-CCP antibodies have been shown to be predictive of the progression of patients, indicating more erosive disease or increase joint involvement. Anti-CCP was found to be more predictive of erosive arthritis than other measures, such as matrix metalloproteinases-3, erythrocyte sedimentation rate, and C-reactive protein.

A literature review by Kim and Lee found the prevalence of anti-CCP antibody in patients with psoriatic arthritis to be 9.8%, with the antibody being linked to an increased risk of polyarthritis.

TROUBLESHOOTING

ELISA Troubleshooting Tips

ELISA troubleshooting tips guide is designed to help improve and troubleshoot the common problems that Labs have with their ELISA kits when performing assays. Optimising the ELISA and removing common mistakes that are made can dramatically improve the results and the sensitivity of the ELISA assays. This ELISA troubleshooting guide details the common areas where Labs encounter problems with their ELISA.

ELISA Troubleshooting areas

High Signal:

High Signal can occur for numbers reasons including insufficient plate washing, not stopping the reaction and adding too much Conjugate. If you have a high signal this can result in a lot of false positives and incorrect data.

Out of Range:

Sometimes this can happen based on your samples, insufficient washing or incorrect dilutions prepared. This can result in a loss of data

due to negative or no results.

High Variation:

High variation can be due to sample preparation mistakes, pipette errors and inconsistencies, insufficient plate agitation among other problems. Data with high variation can skew the real results and cause inconsistencies in your data.

Background is high

High background may result from inadequate washing steps, cross reactivity of samples or contamination. Again high background may result in false positive/negative data and affect your results.

No Signal

No signal in your ELISA assay may result from numerous sample and assay problems including wash buffer, target below detection of assay or avidin-HRP was not added. No signal may mean no results from precious samples, have a read through the reasons below to avoid these problems.

Poor Standard Curve

A poor standard curve will prove unpublishable results if not prepared correctly. Reasons may included reagents are poorly mixed, the standard has degraded or pipetting errors.

ELISA troubleshooting for High Signal

1.	TMB Substrate Solution was contaminated	<i>Use fresh TMB substrate solution which should be clear and colorless prior to addition to wells. Use a clean V bottom container prior to pipetting substrate solution into wells. Use a clean V bottom container prior to pipetting substrate solution into wells.</i>
2.	Reaction not stopped	<i>Colour will keep developing if the substrate reaction is not stopped.</i>
3.	Plate left too long before reading on the plate reader	<i>Colour will keep developing (though at a slower rate if stop solution has been added)</i>
4.	Contaminants from laboratory glassware	<i>Ensure reagents are fresh and prepared in clean glassware</i>
5.	Substrate incubation carried out in the light	<i>Substrate incubation should be carried out in the dark. Ensure substrate is not exposed to light—store in a dark place. Limit exposure to light while running assay.</i>
6.	Wells are insufficiently washed	<i>Wash wells as per protocol recommendations.</i>
7.	Too much Conjugate added	<i>Ensure the reagent has been diluted and mixed properly.</i>
8.	Precipitate formed in wells upon substrate addition	<i>Increase dilution factor of sample or decrease concentration of substrate.</i>
9.	Dirty plate	<i>Clean the bottom of the plate.</i>
10.	Incorrect standard curve dilutions prepared	<i>Check your pipetting technique. Calibration of pipettes might be required.</i>
11.	Longer incubation times than recommended	<i>Make sure your incubation times are correct and adhere to the protocol provided with the technical manual.</i>
12.	Plate sealers or reagent reservoirs reused, resulting in presence of residual HRP. This will turn the TMB blue non-specifically	<i>Reuse of plate sealers may lead to the presence of residual HRP, leading to non-specific colour change of TMB. To avoid this use fresh plate sealer and reagent reservoir for each step.</i>
13.	Contamination of buffers	<i>Always make fresh buffers.</i>

ELISA Troubleshooting for out of Range

1.	Samples contain no or below detectable levels of analyte	<i>If samples are below detectable levels, it may be possible to use high sample volume. Check with technical support for appropriate protocol modifications.</i>
2.	Samples contain analyte concentrations higher than the highest standard point	<i>Samples may require further dilution</i>
3.	Insufficient washing	<i>Use appropriate washing procedure—see below. At the end of each washing step, invert plate on absorbent tissue and allow to completely drain, tapping forcefully if necessary to remove any residual fluid.</i>
4.	Plate sealers not used or reused	<i>During incubations, cover assay plates with plate sealers. Use a fresh sealer each time the plate is opened. This will prevent wells from contaminating each other.</i>
5.	Incorrect dilutions prepared	<i>Check pipetting technique—see below—and double-check calculations.</i>
6.	Longer incubation times than recommended	<i>Manufactured kits have optimized protocols. Make sure to follow recommended incubation times.</i>
7.	Substrate solution mixed too early and turned blue	<i>Substrate solution should be mixed and used immediately</i>
8.	Too much Conjugate	<i>Check dilution, titrate if necessary</i>
9.	Plate sealers or reagent reservoirs reused, resulting in presence of residual HRP. This will turn the TMB blue non-specifically	<i>Use fresh plate sealer and reagent reservoir for each step</i>
10.	Buffers contaminated	<i>Make fresh buffers</i>

ELISA Troubleshooting for High Variation

1.	Multichannel pipette errors	<i>Calibrate the pipettes</i>
2.	Plate washing was not adequate or uniform	<i>Make sure pipette tips are tightly secured. Confirm all reagents are removed complete in all wash steps</i>
3.	Samples may have high particulate matter	<i>Remove the particulate matter by centrifugation</i>
4.	Insufficient plate agitation	<i>Wherever recommended; plate should be agitated during all incubation steps using an ELISA plate shaker at a speed where solutions in wells are within constant motion without splashing</i>
5.	Cross well contamination	<i>When reusing plate sealers check that no reagent has touched the sealer. Care should be taken when using the same pipette tips used for reagent additions. Ensure that pipette tips do not touch the reagents on the plate.</i>
6.	Plates stacked during the incubations	<i>Stacking of plates does not allow even distribution of temperature across the wells of the plates. Avoid stacking.</i>
7.	Pipette inconsistent	<i>Ensure pipettes are working correctly and are calibrated. Ensure pipette tips are pushed on far enough to create a good seal. Take particular care when diluting down the plate and watch to make sure the pipette tips are all picking up and releasing the correct amount of liquid.</i>
8.	Antibody dilutions/reagents are not well mixed	<i>To ensure a consistent concentration across all wells, ensure all reagents are mixed before pipetting onto the plates.</i>
9.	Well allowed to dry out	<i>Ensure lids are left on the plates at all times when incubating. Place a humidifying water tray (bottled clean/sterile water) in the bottom of the incubator.</i>

10.	Bottom of the plate is dirty	<i>Clean the bottom of the plate carefully before re-reading the plates</i>
11.	Bubbles in wells	<i>Ensure no bubbles are present prior to reading the plate</i>
12.	Edge effects	<i>Ensure the plate and all reagents are at room temperature</i>
13.	Storage	<i>Ensure reagents and samples are stored at correct temperature</i>
14.	Variations in protocols	<i>Adhere to the protocol that comes with your assay</i>
15.	Improper calculations of standard curve	<i>Check calculations, make new standard curve & use internal controls</i>
16.	Buffers contaminated	<i>Use fresh buffers</i>
17.	Well bottom scrapped	<i>Avoid contact with the bottom of the well during pipetting. Aim the pipette tip to the side of the well to avoid disrupting the bottom</i>

ELISA Troubleshooting for Background is high

1.	Background wells were contaminated	<i>Avoid cross-well contamination by using the sealer appropriately. Use multichannel pipettes without touching the reagents on the plate.</i>
2.	Insufficient washes	<i>Refer to wash protocol for number of washes and soaking time between washes prior to addition of substrate solution.</i>
3.	Concentration of conjugate is too high	<i>Perform dilutions as per protocol.</i>
4.	Incorrect assay temperature	<i>Check that the incubation temperature did not exceed 37°C</i>
5.	Inadequate washing	<i>Ensure all wells are filling with wash buffer and are being aspirated completely. Use an automated plate washer if available.</i>
6.	Contaminating enzymes present in sample	<i>Test sample with substrate alone to check for contaminating enzyme activity.</i>
7.	Wells are insufficiently washed	<i>Wash wells as per protocol recommendations.</i>
8.	Contaminated wash buffer	<i>Prepare fresh buffers</i>
9.	Too much detection reagent	<i>Ensure the reagent has been diluted properly.</i>
10.	Waiting too long to read plate after addition of stop solution	<i>Read plate immediately after adding stop solution</i>
11.	Substrate incubation is carried out in light	<i>Substrate incubations should be carried out in the dark or as recommended by manufacturer.</i>
12.	Precipitate formed in wells upon substrate addition	<i>Increase dilution factor of sample.</i>
13.	Dirty plate	<i>Clean the bottom of the plate with a wipe</i>

ELISA Troubleshooting for No Signal

1.	Incorrect concentration or no conjugate was added	<i>Add appropriate detection antibody and continue</i>
2.	Substrate solution was not added	<i>Add substrate solution and continue</i>
3.	Incubation time too short	<i>Follow the protocol for incubation time and temperature.</i>
4.	Analyte present below detection limits of assay	<ul style="list-style-type: none"> · Check sample dilution step · Check calibration · May be sample specific

5.	Incompatible sample type	<i>Detection may be reduced or absent in untested samples types. Use recommended sample type.</i>
6.	Not enough conjugate reagent	<i>Prepare correct concentration of conjugate following manufacturer guidelines</i>
7.	Sample prepared incorrectly	<i>Ensure proper sample preparation/dilution. Sample type used may be incompatible with microtiter plate assay format</i>
8.	Incubation temperature is too low	<i>Ensure the incubations are carried out at the correct temperature. All reagents including plate should be at room temperature or as recommended by the manufacturer before proceeding.</i>
9.	Incorrect wavelength	<i>Verify the wavelength and read the plate again</i>
10.	Plate washing is too vigorous	<i>Check the correct pressure in the automatic plate washer. Pipette wash buffer gently if washes are done manually.</i>
11.	Wells dried out	<i>Do not allow wells to become dry once the assay has started. Cover the plate using sealing film or tape for all incubations.</i>
12.	Slow colour development of enzymatic reactions	<i>Prepare substrate solution immediately before use.</i>
13.	Uneven Colour	<i>Ensure all wells are washed correctly, use a ELISA plate washer where possible</i>
14.	Reagents not at room temperature	<i>All reagents should at room temperature from the start of the assay. Room temperature should be reached following 15–20 minutes on the bench.</i>
15.	Expired Reagents	<i>Ensure all reagents used are within date</i>

ELISA Troubleshooting for Poor standard curve

1.	Standard was incompletely reconstituted or was incorrectly stored	<i>Reconstitute standard according to the protocol provide and follow storage instructions</i>
2.	Reagents were added to the wells at incorrect concentrations	<i>Check for pipetting errors and correct the reagent volume</i>
3.	Incubations done at incorrect temperature	<i>Follow protocol for storage, incubation and agitation</i>
4.	Wells not completely aspirated during washing	<i>Completely aspirate wash buffer between steps, use plate washer where possible</i>
5.	Plates stacked during incubation	<i>Keep plates separated</i>
6.	Poor dilution series	<i>Check dilution steps according to protocol</i>
7.	Reagents poorly mixed	<i>Make sure to mix reagents thoroughly</i>
8.	Standard degraded	<i>Check that standard was stored correctly</i>
9.	Pipetting error	<i>Check pipettes and calibrate</i>
10.	Not enough conjugate	<i>Check dilution.</i>
11.	Incorrect calculation of standard curve dilution	<i>Check your calculations and make a new curve.</i>
12.	Mixing or Substituting reagents from different kits	<i>Avoid this as it can affect the quality of your assay</i>

BOUQUET

Wisdom Whispers

“Don't stop when you're tired. STOP when you are **DONE.**”

Unknown

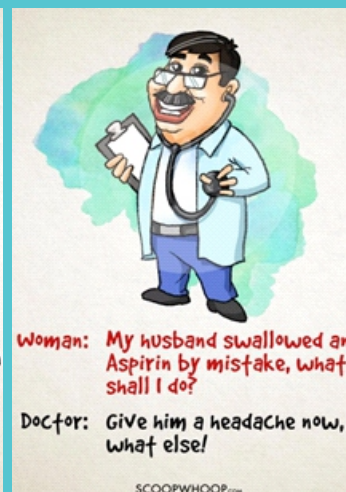
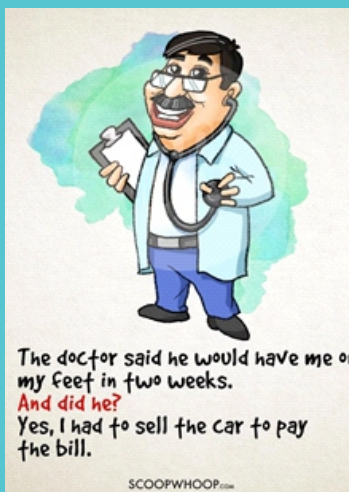
NEVER GIVE UP ON A DREAM JUST BECAUSE OF THE TIME IT WILL TAKE TO ACCOMPLISH IT. THE TIME WILL PASS ANYWAY.

- EARL, NIGHTINGALE

STOP HATING YOURSELF FOR EVERYTHING YOU AREN'T AND START LOVING YOURSELF FOR EVERYTHING YOU ALREADY ARE.

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Brain Teasers

- Rheumatoid factors are usually antibodies of the class.
A. IgG B. IgA C. IgM D. IgE.
- Rheumatoid factors are usually directed against the Fc portion of the class antibodies.
A. IgG B. IgA C. IgM D. IgE.
- What are early signs and symptoms of rheumatoid arthritis (RA)?
A. Joint Pain, Tenderness, redness and swelling.
B. Loss of Joint range of motion
C. Limping
D. All of above
- Rheumatology is the branch of medicine that involves the study of...
A. The Immune System
B. Musculoskeletal (Muscle and Bone) System
C. Rheumatic Diseases
D. All of the above
- In rheumatoid arthritis which of the following antibodies is usually decreased?
A. IgG
B. IgM
C. IgA
D. All are usually increased

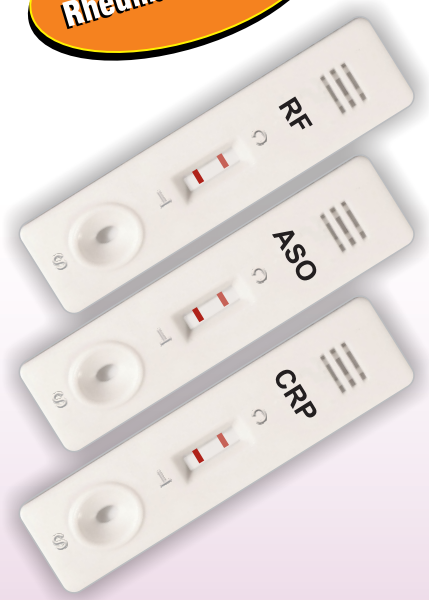
ANSWER: 1. C, 2. A, 3. D, 4. D, 5. D

Insight™ | RF•ASO•CRP

Global First in Rheumatology ICT



Correct classification of sample depends upon accurate CUT OFF that is STABLE during the shelf life of the product



Accurate cut off

- RF: 10IU/ml, CRP: 6 mg/L, ASO: 240 IU/ml
- Correct classification of positives and negatives

Stable cut off

- Eliminates risk of shift in sensitivity
- Facilitates accurate results throughout shelf life

Uniform sample size & sample dilution

- Eliminates complement interference & risk of prozoning
- Single sample dilution can be used for RF, CRP, ASO

→ **Stable** → **Sensitive** → **Rapid**

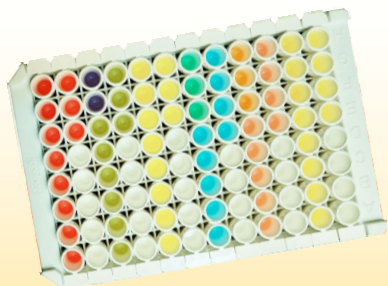
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Anti-Cyclic Citrullinated Peptides



Anti CCP Helps to Identify patients who are likely to have severe disease and irreversible damage

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