# Diagnosis and management of rheumatoid arthritis, Evidence review

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## Abstract:

Early recognition and intervention for rheumatoid arthritis has been shown to improve outcome. In this review, we have summarized the latest evidence regarding managing of RA, side effects of drugs. As well we discuss the diagnosis methods for early detection. We conducted detailed search using the MEDLINE and Cochrane Library databases for all articles concerning Rheumatoid arthritis published up to July, 2018. dynamic course of RA might be minimized or modified by ideal treatment including combination of DMARDs started at earlier duration. Growth of new criteria classify RA patients at very early stage and also allows initiation of therapy for reductions of inflammation as well as lowering illness activity.



## Introduction:

Rheumatoid arthritis (RA) is a chronic, idiopathic, inflammatory joint illness defined by synovitis with extra-articular participation, for instance, serositis, vasculitis, interstitial lung illness and so on. Chronic, long-lasting, uncontrollable arthritis causes joint damage, functioning impairment, low quality of life as well as shortened life expectancy [1]. Early diagnosis as well as aggressive treatment prior to establishing irreversible joint deformity are a principal method to boost

outcomes. Rheumatoid arthritis (RA) is one of the most typical inflammatory arthritis, with a life time prevalence of up to 1 percent worldwide [2]. Beginning could happen at any type of age, yet peaks between 30 as well as 50 years [3].Older age, a family history of the illness, and female sex are related to increased threat of RA, although the sex differential is less famous in older patients [2]. Both current as well as prior smoking boosts the risk of RA [4].

In addition, patients with RA generally suffer gastrointestinal tract troubles especially dyspepsia (bloating, postprandial fullness, nausea or vomiting, early satiation, epigastric pain, and also burning as well as burping), mucosal ulceration, and transformed bowel behaviors (constipation/diarrhea) [5]. A transformed intestinal tract microbiota has therefore been implicated in the etiopathogenesis of RA [6],[7]. Lately, Littman research laboratory recognized Prevotella copri dramatically common in RA patients compared to healthy and balanced controls giving the assistance that the "gut-joint axis" theory is relevant for human rheumatic diseases and also could lead to pathogenesis of RA [8].



Early recognition and intervention for rheumatoid arthritis has been shown to improve outcome. In this review, we have summarized the latest evidence regarding managing of RA, side effects of drugs. As well we discuss the diagnosis methods for early detection.

## Methodology:

We conducted detailed search using the MEDLINE and Cochrane Library databases for all articles concerning Rheumatoid arthritis published up to July, 2018, we searched information using a high-sensitivity strategy as Mesh terms: RA, rheumatoid arthritis, management. Moreover, we have checked the references list of concerned studies for more relevant articles.

## Discussion:

- **DIAGNOSIS**

Diagnosing RA is an extremely individualized procedure led by the rheumatologist. Although no diagnostic requirements exist, classification criteria that include clinical manifestations and serological assays (autoantibody as well as acute-phase reactant levels) inform clinical diagnosis. Algorithms can be used for the analysis work-up of patients who offer with arthritis as well as might bring about a details medical diagnosis or to a diagnosis of undifferentiated arthritis.

**Joint indications.** Soft synovial joint swelling is the vital clinical attribute of RA as well as is typically accompanied by early morning stiffness and tenderness on assessment. Today, such remarkable development of the illness, which severely compromises mobility and could also result in the demand of a mobility device or a bed-ridden state, is seldom seen owing to very early medical diagnosis and also far better therapeutic options. The joints associated with RA are fairly particular as well as distinct from the sorts of involvement in other joint disorders, including the metacarpophalangeal joints and also proximal interphalangeal joint of the hands and feet, as well as the wrist, ankle joint, arm joint, shoulder, knee and also hip joints [9].Although all peripheral joints can be entailed, the absence of RA in the distal interphalangeal joints and in the axial joints is striking. The single crucial exemption to this is the participation of the C1-C2 joint of the spinal column. RA also identifies itself from other kinds of arthritis by its very damaging nature, which results in inflammatory destruction of cartilage material and also damage of articular and periarticular bone. Despite these normal findings, several problems imitate RA, that makes a differential medical diagnosis difficult, specifically in very early illness.

These conditions consist of viral arthritis, Lyme arthritis, connective tissue illness, peripheral spondyloarthritis, psoriatic arthritis, osteo arthritis as well as metabolic diseases.

**Systemic indications.** RA does not exclusively affect the joints. As a systemic illness, RA is associated with a boosted acute-phase response and also can result in a variety of extra-articular indications in the eyes, lungs, heart and also various other organs. Rheumatoid nodules as well as vasculitis might be observed in severe RA, although they are less common nowadays. Nevertheless, heart disease is common in RA, and the incidence of interstitial lung illness has actually also been reported to have actually enhanced gradually, with the incidence estimated at 4 situations each 1,000 people annually in 2010 [10].Although the boost in interstitial lung illness might be attributed to an enhanced awareness as well as some detection bias over time, interstitial lung disease is-beside cardiovascular disease- one of one of the most severe extra-articular symptoms of RA, with an average patient survival of ~ 3 years [11].RA might additionally be accompanied by secondary Sjögren syndrome; the chronic inflammatory procedure could bring about cardiovascular disease, additional amyloidosis and lymphoma. RA could also be accompanied by fibromyalgia. Extra-articular manifestations as well as issues of illness may all be undermined or reduced with efficient treatment [12],[13].

**Classification criteria.** The factors for the absence of diagnostic standards for RA are not just the interindividual and intra-individual heterogeneity of the disease but likewise the prospective consequences of misdiagnosis. When it comes to many other rheumatological problems, only classification criteria are offered [28] (BOX 1). Classification criteria are meant to stratify patients with similar characteristics for scientific research study yet do not intend to record all patients; the high uniqueness but reduced sensitivity differentiates classification criteria from diagnostic criteria. Although they are indicated to recognize patients for clinical studies as well as

tests, they may be utilized to educate diagnostic decision making in clinical practice, where a favorable category could additionally be connected with a negative diagnosis and also vice versa. The difference between analysis standards and category standards has been outlined thoroughly somewhere else [14].The present classification criteria are those by the American College of Rheumatology (ACR) as well as the European League Against Rheumatism (EULAR) developed in 2010 [28], [14] (BOX 1). Significantly, when using classification criteria, the target population must be adhered to, especially when applying them to sustain diagnosis in professional method [15].The ACR/EULAR 2010 standards have actually been established for a target population of individuals presenting with a minimum of one clinically swollen joint that could not be plainly clarified by an additional illness.

**Box 1** .ACR/EULAR 2010 classification criteria for RA[28].

The classification criteria proposed by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR)[28] include clinical and serological variables. The classification criteria should be restricted to individuals with ≥1 swollen joint. A score of ≥6 points is required for classification as definite rheumatoid arthritis (RA).

**Joint involvement and distribution: 0–5 points**
This variable includes any swollen or tender joint (excluding the distal interphalangeal joints of hands and feet, the first metatarsophalangeal joints and the first carpometacarpal joints) on clinical examination; additional evidence from MRI or ultrasonography may be used to identify additional joints.
• 1 large joint (shoulder, elbow, hip, knee or ankle): 0 points
• 2–10 large joints: 1 point
• 1–3 small joints (the metacarpophalangeal joint, the proximal interphalangeal joint, the second to fifth metatarsophalangeal joints, the interphalangeal joint of the thumb and the wrist): 2 points
• 4–10 small joints: 3 points
• >10 joints (of which ≥1 is a small joint[a] ): 5 points

**Symptom duration: 0–1 points**
This variable refers to the patient's self-report on the maximum duration of signs and symptoms of any joint that is clinically involved at the time of assessment.
•< 6weeks: 0 points
• ≥6 weeks: 1 point

**Serology[b] : 0–3 points**
• Negative[c] for RF and negative for ACPA: 0 points
• Low-positive[d] for RF or low-positive for ACPA: 2 points
• High-positive[e] for RF or high-positive for ACPA: 3 points

**Acute-phase reactants[f] : 0–1 points**
• Normal CRP and ESR levels: 0 points
• Abnormal CRP levels or abnormal ESR: 1 point

ACPA, anti-citrullinated protein antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.
[a] Additional small joints include the temporomandibular joint, sternoclavicular joint, acromioclavicular joint and others, as reasonably expected in RA.
[b] If results of RF assays are only qualitatively available, a positive result should be scored as low-positive.
[c] Equal or less than the upper limit of normal (ULN) for the respective laboratory.
[d] >1–3 times ULN.
[e] >3 times ULN.
[f] Determined by local laboratory standards.

- **SCREENING**

Screening for RA involves the identification of disease at a time when patients are still asymptomatic and presents substantial challenges. Although RA is the most common autoimmune inflammatory arthritis, it remains relatively rare. Screening and prevention assume that patients with very early or preclinical RA can be accurately identified and that there are proved prevention strategies; alas, this is not feasible at the present time.



## Identification of individuals with preclinical RA.

Screening for RA includes the identification of disease at once when patients are still asymptomatic as well as offers substantial difficulties. Although RA is the most typical autoimmune inflammatory arthritis, it remains reasonably uncommon. Screening as well as prevention presume that patients with really early or preclinical RA can be accurately recognized which there are proved avoidance methods; alas, this is not possible at the here and now time.

## Recognition of people with preclinical RA

Variables beneficial in screening for preclinical RA include hereditary, serological, environmental as well as way of living aspects (mainly smoking cigarettes and periodontal condition). More than 100 hereditary threat variants for RA have actually been determined so far

[17], however scoring systems based upon genes demonstrate just a small rise in the risk of developing RA [29].Hence, making use of genes to evaluate the threat of establishing RA is restricted. Serological biomarkers, such as autoantibodies, allow the identification of people at enhanced danger of developing RA. Two-thirds of individuals eventually detected with RA were positive for ACPAs 6-10 years before their medical diagnosis [18].Nevertheless, although the visibility of ACPAs identifies a group of individuals at significantly boosted risk of creating RA, the population prevalence (that is, pre-test chance) of RA is low, the positive predictive worth is moderate (~ 70%) as well as regarding 2-5% of the healthy populace have ACPAs. Thus, the chances of developing RA in unselected ACPA-positive people (that is, post-test probability) can be approximated at only 50%. The posttest probability may be boosted with really high titres of ACPAs or by combining RF as well as ACPAs.



**Screening programmes.** Screening programmes [19] have usually targeted primary care doctors or nonphysician care carriers (such as nurses or pharmacists) that could acknowledge patients yet to be diagnosed with RA that may have very early inflammatory arthritis. Screening programmes for very early inflammatory arthritis have targeted different populations as well as made use of different approaches [20] (FIG. 1; TABLE 1).These programmes have lowered times to medical diagnosis and also therapy. Within 1 year, approximately one-third of patients fulfil requirements for RA, with one more 5% fulfilling the standards in the subsequent year [21].Predictors of satisfying classification criteria include the participation of several joints at discussion, female sex, older age, presence of autoantibodies, acute-phase reactants and early morning stiffness [22].

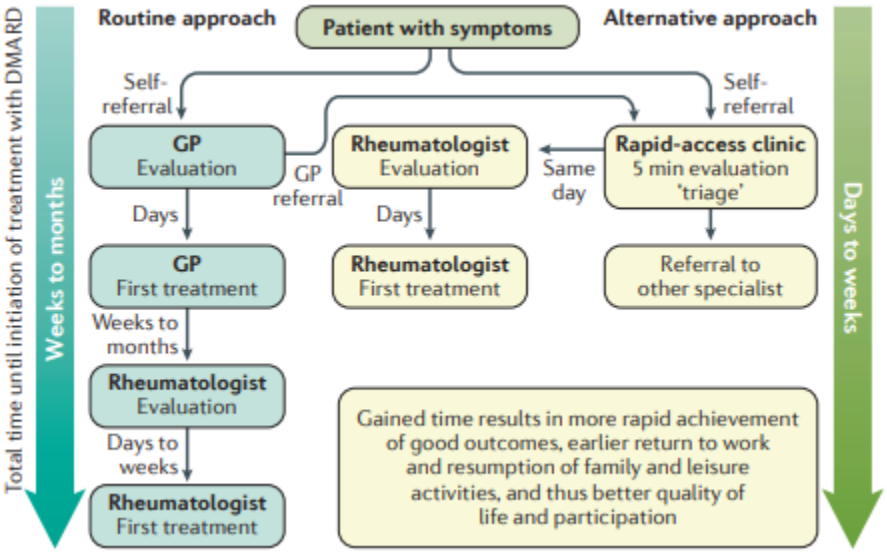


**Figure 1**. Screening for rheumatoid arthritis. Rapid triage of patients very quickly after the onset of symptoms by an experienced rheumatologist enables early recognition and treatment initiation [23],[24]. Abbreviation: DMARD, disease-modifying antirheumatic drug; GP, general practitioner.

**Table 1.** Screening programs in RA

| Target population | Analysis | Outcome | Refs |
|---|---|---|---|
| Recruitment of individuals at health fairs with a first-degree relative with RA, joint pain or general arthritis concerns | Assessment of synovitis and ACPAs | • 1.5% of individuals had diagnosable RA at the time of screening<br>• 2.5% of individuals had early inflammatory arthritis with synovitis and were autoantibody positive | [25] |
| Recruitment of unaffected first-degree relatives of patients with RA | • Full examinations to rule out inflammatory arthritis<br>•Genotyping<br>• Serological testing | •Genetic analysis alone identified that 9% of screened individuals were at very high risk of developing RA<br>• 5% of screened individuals were autoantibody positive<br>• 51% of screened individuals were at higher-than-normal risk (≥5% lifetime risk) of developing RA on the basis of a personalized risk calculator that comprises the factors age, sex, family history and risk-related behaviour (smoking, obesity, fish consumption and oral health) | [26], [27] |
| Self-referral or referral by a clinician (non-rheumatologist) | Establishment of a 'rapid-access clinic' for a very brief (usually 5–10min) first assessment by a senior rheumatologist with | • Reduction of waiting time to see a rheumatologist<br>• Improved patient care by assuring quick assessment and referral<br>• Earlier diagnosis<br>• Earlier treatment | [23], [24] |

| | | | |
|---|---|---|---|
| | same-day referral if needed | | |

ACPA, anti-citrullinated protein antibody; RA, rheumatoid arthritis

- **TREATMENT**

After RA has actually been identified and a preliminary assessment performed, therapy ought to begin. Current guidelines have actually resolved the management of RA, [31], [32] however patient preference likewise plays an important role. There are unique factors to consider for females of childbearing age because lots of medications have deleterious impacts on maternity. Objectives of treatment consist of reducing joint pain as well as swelling, stopping defect (such as ulnar deviation) and also radiographic damages (such as erosions), preserving quality of life (individual and work), and controlling extra-articular indications. Illness customizing antirheumatic drugs (DMARDs) are the pillar of RA therapy.



## DMARDS

DMARDs can be nonbiologic or biologic (Table 2) [33].Biologic agents made of monoclonal antibodies and recombinant receptors to block cytokines that stimulate the inflammation in charge of RA symptoms. Methotrexate is recommended as the firstline therapy in patients with active RA, unless contraindicated or not tolerated [31].Leflunomide (Arava) might be used as a choice to methotrexate, although gastrointestinal damaging impacts are a lot more usual. Hydroxychloroquine (Plaquenil) or Sulfasalazine (Azulfidine) is recommended as monotherapy in patients with reduced illness function or without poor prognostic features (e.g., seronegative, nonerosive RA) [31],[33].Combination treatment with two or even more DMARDs is more reliable compared to monotherapy; nevertheless, adverse effects may likewise be greater [34].If RA is not well managed with a nonbiologic DMARD, a biologic DMARD needs to be launched

[31], [32].TNF inhibitors are the first-line biologic treatment and are one of the most researched of these agents. If TNF preventions are inefficient, additional biologic treatments could be taken into consideration. Simultaneous use of greater than one biologic therapy (e.g., adalimumab [Humira] with abatacept [Orencia] is not recommended due to an undesirable rate of damaging results [31].

**Table 2.** Biologic and Nonbiologic Disease-Modifying Antirheumatic Drugs[33].

| **Drug*** | **Mechanism for rheumatoid arthritis** | **Adverse effects** |
|---|---|---|
| **Nonbiologic (More commonly used)** | | |
| Methotrexate | Inhibits dihydrofolate reductase | Liver effects, teratogenesis, hair loss, oral ulcers |
| Leflunomide (Arava) | Inhibits pyrimidine synthesis | Liver effects, gastrointestinal effects, teratogenesis |
| Hydroxychloroquine (Plaquenil) | Antimalarial, blocks toll-like receptors | Rare ocular toxicity |
| Sulfasalazine (Azulfidine) | Folate depletion, other mechanisms unknown | Anemia in G6PD deficiency, gastrointestinal effects |
| Minocycline (Minocin) | Antimicrobial, other mechanisms unknown | Drug-induced lupus erythematosus, Clostridium difficile colitis |
| **Biologic** | | |
| ***Anti-TNF agents*** | | |
| Adalimumab (Humira) | Anti-TNF-α | TB, opportunistic infection |
| Certolizumab pegol (Cimzia) | Anti-TNF-α, pegylated | TB, opportunistic infection |
| Etanercept (Enbrel) | Anti-TNF-α, receptor | TB, opportunistic infection |
| Golimumab (Simponi) | Anti-TNF-α | TB, opportunistic infection |
| Infliximab (Remicade) | Anti-TNF-α | TB, opportunistic infection, infusion reaction |
| ***Other biologic agents*** | | |
| Abatacept (Orencia) | Costimulator blocker, cytotoxic T lymphocyte antigen 4 | Opportunistic infection |
| Anakinra (Kineret) | Anti-interleukin-1 receptor blocker | Opportunistic infection, injection site pain |
| Rituximab (Rituxan) | Anti-CD20, eliminates B cells | Infusion reaction, opportunistic infection, progressive multifocal leukoencephalopathy |
| Tocilizumab (Actemr a) | Anti-interleukin-6 receptor blocker | Opportunistic infection |

G6PD = glucose-6-phosphate dehydrogenase; TB = tuberculosis; TNF = tumor necrosis factor.
*—Nonbiologic drugs listed in approximate order of priority, biologic drugs listed in alphabetical order.

## NSAIDS and Corticosteroids

Medicine treatment for RA might entail NSAIDs and oral, intramuscular, or intra-articular corticosteroids for managing discomfort and inflammation. Ideally, NSAIDs as well as corticosteroids are used just for temporary management. DMARDs are the preferred treatment [31], [32].

## Complementary therapies

Dietary treatments, consisting of vegetarian as well as Mediterranean diet regimens, have actually been researched in the therapy of RA without persuading evidence of advantage [35], [36].In spite of some favorable end results, there is a lack of proof for the efficiency of acupuncture in placebo-controlled tests of patients with RA [37], [38].Furthermore, thermotherapy and also therapeutic ultrasound for RA have not been researched properly. [39], [40].A Cochrane evaluation of herbal treatments for RA concluded that gamma-linolenic acid (from evening primrose or black currant seed oil) and also Tripterygium wilfordii (thunder god vine) have potential advantages [30].It is very important to inform patients that severe adverse effects have been reported with use herbal therapy [30].

## Conclusion:

Patients with inflammatory joint illness must be recommended to a rheumatology subspecialist, specifically if signs last more than six weeks. Identification of RA at first presentation and also treatment at earlier stage could impact condition path, avoid the advancement of joint erosions or slow down progression of erosive disease In individuals with RA, union therapy with two or more disease-modifying antirheumatic medications is a lot more reliable compared to monotherapy. However, over one biologic agent must not be made use of at one time (e.g., adalimumab [Humira] with abatacept [Orencia] as a result of the high danger of adverse impacts.

To conclude, dynamic course of RA might be minimized or modified by ideal treatment including combination of DMARDs started at earlier duration. Growth of new criteria classify RA patients at very early stage and also allows initiation of therapy for reductions of inflammation as well as lowering illness activity.

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