EXCALIBUR
MEDICAL EDUCATION

HANDLING THE HARD QUESTIONS:

WHAT OUR PATIENTS ARE ASKING US ABOUT RHEUMATOID ARTHRITIS

THE PURPOSE OF THIS DOCUMENT

Patients with newly diagnosed rheumatoid arthritis (RA) often ask many questions about their disease and how it can best be managed. It is important for rheumatologists and other providers involved in the management of RA to be able to properly and effectively communicate appropriate responses to these questions. This pocket guide includes a brief summary of evidence surrounding some of the most common—and challenging—questions rheumatologists and other providers are likely to face from their patients with RA. We hope you find this guide useful for your professional development.

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WHY DID I GET RHEUMATOID ARTHRITIS?

More than 1 million adults in the United States suffer from RA, making it one of the most common chronic diseases in the general population, so you are far from alone.[1] That said, there is no way to say for certain how or why you developed RA—there are a variety of potential factors at play.

RA is a chronic autoimmune disease wherein the lining of the joints—called the synovium—is attacked by rogue immune cells that have lost the ability to recognize the body as "self," leading them to attack healthy tissue. The damage that these immune cells cause leads to inflammation and enlargement of the synovium. This, in turn, causes erosion and degradation of the bone and cartilage. It can also affect other tissues, including the cardiovascular and pulmonary systems.[2,3]

RA can look quite different in different patients, with various potential underlying causes. We know that genetics and environmental factors play important and possibly overlapping roles. Studies have identified more than 100 different genes that are potentially associated with the development of RA.[5] In particular, genetic abnormalities in the human

GENETIC RISK FACTORS (60% OF RISK)

- Susceptibility genes (for example, HLA-DRB1)
- Epigenetic modifications

NON-GENETIC RISK FACTORS (40% OF RISK)

- Smoking
- Microbiota
- Female sex
- Western diet
- Ethnic factors

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leukocyte antigen (HLA; also called the major histocompatibility complex [MHC]) genes, which encode proteins that help the immune system identify foreign materials, show a very strong association with the development of RA.[3]

Environmental factors that have been found to be associated with an increased risk of RA include periodontal disease, disruption of the gut microbiome, and certain infectious agents.[2,3] Perhaps the most notable environmental risk factor, however, is cigarette smoking, which has been shown to significantly increase the risk of RA, particularly in patients with seropositive disease (these are patients with higher levels of anti-citrullinated cyclic peptide [CCP] and/or rheumatoid factor [RF]). Notably, cigarette smoking is also associated with more aggressive RA and poorer treatment outcomes; therefore, smoking cessation is an important component of RA management.[6,7]

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HOW DO YOU KNOW I HAVE RHEUMATOID ARTHRITIS?

RA is diagnosed through a combination of physical symptoms and lab results. There is not one single definitive determinant of the condition, so our diagnosis is based on different results that allow us to reach a diagnosis and rule out other conditions with overlapping presenting characteristics.[1,2]

A physical exam allows us to determine how many of your joints are swollen and tender, as well as which specific joints are impacted. The swelling associated with RA is typically softer and less bony than that associated with osteoarthritis and is centered around the joints rather than the whole digit, as with psoriatic arthritis. The swelling can occur in both small joints (fingers, toes, and wrists) and large joints (knees, ankles, elbows, and shoulders) but is usually absent from the joints closest to the tips of the fingers and toes and from the axial joints of the head and spine. Most patients with RA also report daily morning stiffness lasting at least 30 minutes.[1,2]

Several types of laboratory tests may be ordered to aid in our diagnosis. A blood test can reveal the presence of specific autoantibodies known as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). The presence of these autoantibodies is indicative of the autoimmune-mediated inflammation associated with RA. While approximately 70-80% of patients with RA test positive for these autoantibodies (these patients are dubbed “seropositive”), their absence in the blood (“seronegative”) does not rule out a diagnosis of RA. Blood tests are also used to measure other values such as erythrocyte sedimentation rate (ESR) and levels of serum C-reactive protein (CRP). These so-called acute phase reactants (APRs) are often elevated during the initial phase of RA.[1,2]

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Other blood tests commonly ordered to help determine a possible diagnosis of RA include antinuclear antibody testing, a complete blood count (CBC), and liver and kidney function tests. Finally, radiographs of the hands and feet can help us visualize the characteristic joint erosion that is indicative of RA.[1,2]

In 2010, the American College of Rheumatology (ACR) published classification criteria for RA. While these are not specifically designed to diagnose RA, they can provide us with some guidance. They define "definite RA" as follows:[3]

- Synovitis in at least 1 joint AND
- Absence of an alternative diagnosis that better explains the synovitis AND
- Achievement of a score of ≥6 (out of a possible 10) across 4 assessments:
  - Number and site of involved joints (0-5)
  - Level of seropositivity (RF/ACPA) (0-3)
  - Level of elevated APRs (0-1)
  - Symptom duration (0-1)

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Differentiating Features of Various Forms of Arthritis[1]

Features	Rheumatoid Arthritis	Psoriatic Arthritis	Osteoarthritis	Gout
Onset	Acute/gradual	Gradual	Gradual	Acute
Joint distribution at onset	Symmetric	Asymmetric	Asymmetric	Asymmetric
No. of affected joints	Predominantly polyarticular	30%-50% are oligoarticular	Monoarticular or oligoarticular	Monoarticular or oligoarticular
Sites of hands/feet involved	Proximal	Distal	Distal	Distal
Areas involved	Same joint across digits	All points of digit	Same joint across digits	Usually monoarticular
Purplish discoloration	No	Yes	No	Yes
Spinal involvement	Erosive cervical disease	Axial spondyloarthritis phenotype	Noninflammatory	Absent
Sacroiliitis	Absent	Common	Absent	Absent
Key Radiographic Findings	• Joint space narrowing • DIP not involved • Osteopenia • Bone and cartilage erosions in hands and feet • Ankylosis rare	• DIP classically involved • Joint space narrowing • Bone/cartilage destruction and bone proliferation • Ankylosis • Periostitis (may have “mouse ear’ appearance) • Axial involvement common	• Focal changes that reflect cartilage loss • DIP, PIP, CMC often involved • Periostosis rare • Axial involvement common but non-inflammatory • Central erosions with “gull wing” appearance	• Subcortical bone cysts (tophi) • DIP less common than PsA • Periostosis uncommon • Ankylosis rare
Key Laboratory Finding	• Elevated ESR, CRP • RF is generally positive in 75%-80% patients • Positive ANA • Positive Anti-CCP in 60-80% cases	• RF, ACPA generally negative • HLA-B27 positive in ~25% cases • Elevated ESR, CRP in ~40% cases	• Normal ESP or CRP	• Presence of monosodium urate crystals in synovial fluid • Elevated WBC

Abbreviations: *DIP = distal interphalangeal joint; PIP = proximal interphalangeal joint; CMC = carpometacarpal joint; RF = rheumatoid factor; ACPA = anti-citrullinated protein antibody; HLA = human leukocyte antigens; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ANA = antinuclear antibodies; WBC = white blood cells*

IS THERE A CURE FOR RHEUMATOID ARTHRITIS?

While there is no cure for RA, significant advancements in the management of the condition over the past two decades have dramatically improved patient outcomes. Clinical remission (defined as "the absence of signs and symptoms of significant inflammatory disease activity") or low disease activity is now achievable for the vast majority of patients.[1-3]

Today, RA is treated with disease-modifying antirheumatic drugs (DMARDs), which target the inflammatory process. There are two main kinds of DMARDs: synthetic (small molecule drugs that are administered orally) and biologic DMARDs (made from proteins and other substances found in nature and administered through an infusion or injection). Synthetic DMARDs can be further subdivided into conventional synthetics (e.g., methotrexate, sulfasalazine, leflunomide) and targeted synthetics (e.g., Janus kinase inhibitors, a newer drug class).

Non-steroidal anti-inflammatory drugs (NSAIDs) and other pain medications are commonly prescribed to control RA symptoms, but these do not prevent disease progression. Corticosteroids are also frequently used for short- or medium-term symptom relief, often in combination with DMARDs. While corticosteroids can sometimes positively impact disease activity, their long-term use is generally avoided due to potential side effects.[2–4]

While the management of RA is highly individualized based on symptoms, patient preference, and insurance requirements, a Treat-to-Target (T2T) approach is often followed to assist in the achievement of clinical remission. T2T is a stepwise management strategy that relies on frequent monitoring of disease activity, often every 1-3 months. The steps involved in the T2T strategy include **selection of an appropriate therapeutic goal** (most frequently,

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clinical remission), **treatment initiation, measurement of disease activity** (in patients who are responding, there should be at least 50% improvement in disease activity within 3 months of initiating therapy), and **treatment adjustment** (treatment should be adjusted or changed to achieve or maintain the therapeutic goal).[2]

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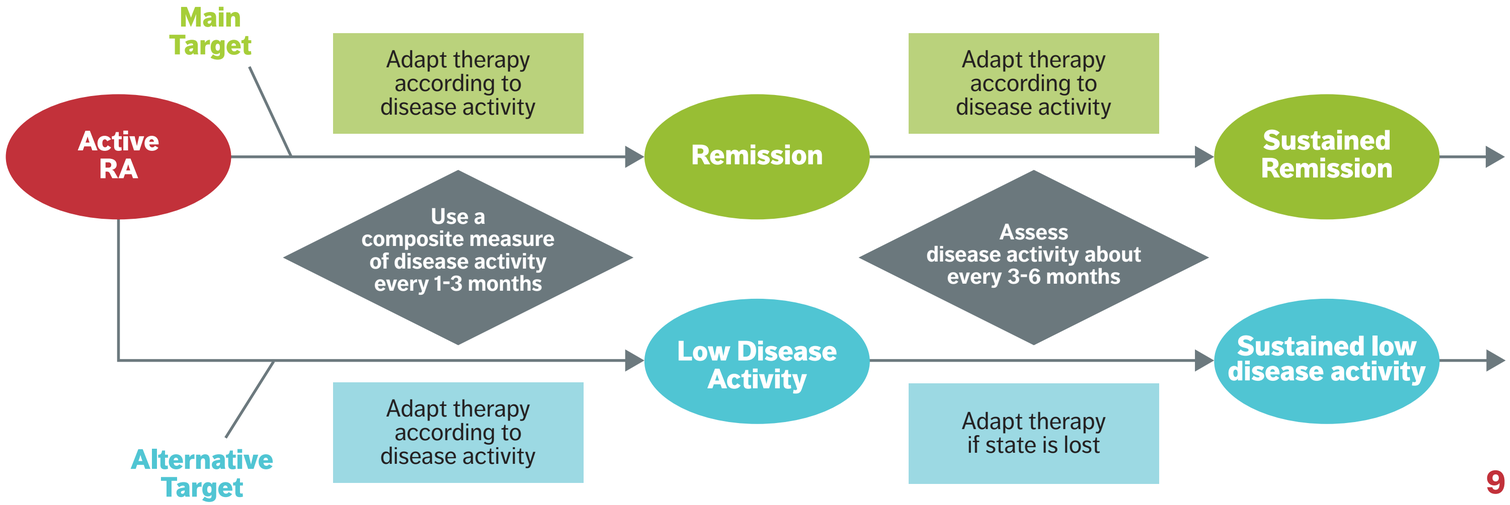
Treat to Target Algorithm for Active RA[5]



AM I EVENTUALLY GOING TO DEVELOP PHYSICAL DEFORMITIES WHEN I GET OLDER?

It is unlikely. Fortunately, RA does not carry the same prognosis as in our grandparents' generation.

While it is true that much of the damage caused by RA is irreversible and will lead to loss of physical function and development of physical deformities without proper medical management, we have numerous tools in our current arsenal.[1] Thanks to the early diagnosis of disease, prompt initiation of treatment, and adherence to a T2T approach, many patients with RA will quickly achieve a state of sustained clinical remission or low disease activity. Achieving this goal prevents progressive joint damage and maximizes the maintenance of physical function. As a result, the rates of physical disability and psychological distress associated with RA have been dramatically reduced over the past several decades.[2]

The prompt initiation of treatment, ideally within the first 12 weeks after diagnosis, is central to optimizing overall outcomes. Studies have consistently shown that patients who receive DMARDs early in the course of their disease have improved functional status compared to patients who initiate therapy after a longer initial duration of symptoms. Earlier time to disease remission is the strongest predictor of sustained remission over a 20-year period, regardless of the type of treatment.[3] Use of the T2T approach is also important in ensuring optimal outcomes; it is associated with decreased disease activity, reduced joint damage progression, increased functional ability, and improved quality of life.[4,5]

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WHAT IF I WANT TO GET PREGNANT?

With careful planning and guidance from medical professionals, women with well-controlled RA can have successful, healthy pregnancies.

Although there is some evidence that women with RA have a more difficult time conceiving, several studies have shown that fertility treatments can help.[1,2] When patients do become pregnant, RA can impact pregnancy outcomes (it has been linked to lower birth weight, increased rate of Caesarian sections, and other complications). However, for women with well-controlled disease, outcomes have been shown to be comparable to the general obstetric population.[1,3]

For women of childbearing age, it is important to receive counseling and education prior to conception. Ideally, for those who wish to conceive, they should establish remission or low disease activity for a period of 3-6 months before attempting to get pregnant, with a treatment regimen that is considered safe during pregnancy.[4,5]

Some agents (e.g., hydroxychloroquine, sulfasalazine, and azathioprine) can be used throughout pregnancy. However, the safety of many other RA medications in pregnant and breastfeeding women has not been well-studied and several (e.g., methotrexate and leflunomide) are contraindicated due to their potential teratogenic effects. NSAIDs are generally considered safe for use during early pregnancy, but they are not recommended during the third trimester due to an increased risk of heart defects in the developing fetus. Glucocorticoids are generally considered safe to use, but women should be counseled about the small increase in risk for malformations and oral

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clefts when glucocorticoids are used in the first trimester.[6]

Certolizumab pegol is the only TNF inhibitor considered compatible with pregnancy throughout all three trimesters. Other TNFs should be discontinued prior to the third trimester of pregnancy, ideally several half-lives prior to delivery. Other biologics such as abatacept and tocilizumab should be discontinued during pregnancy.[7]

For many patients with RA, disease activity actually improves or stabilizes during pregnancy, even when treatment is de-escalated or changed for safety reasons. The reasons underlying this trend are unclear, but it may be related to hormonal changes or the downregulation of the maternal immune system. Conversely, there is an increased risk of disease flare in the postpartum period that can be challenging to manage, especially for women who want to breastfeed.[5,6]

Many patients are concerned about the possibility of their children inheriting RA, and genetic factors do contribute to the risk of RA. In one study of twins with RA, 12% of the risk of RA was attributed to genetic risk factors. In addition to sharing genetic risk factors, children potentially share environmental risk factors for RA with family members, which are also known to contribute significantly to the lifetime risk of RA. As they grow older, children of individuals with RA should be made aware of the risks and of the signs and symptoms of RA so that they can seek prompt evaluation and treatment should these signs appear.[8,9]

Recommended and Best Practice Medication Use Before and During Pregnancy and Breastfeeding

Medication	Pre-conception	During pregnancy	Breastfeeding
CONVENTIONAL MEDICATIONS			
Hydroxychloroquine	++	++	++
Sulfasalazine	++	++	++
Colchicine	++	++	++
Azathioprine, 6-mercaptopurine	++	++	+ Low transfer
Prednisone	+ Taper to <20 mg/d by adding pregnancy-compatible immunosuppresants	+ Taper to <20 mg/d by adding pregnancy-compatible immunosuppresants	+ After a dose of >20 mg, delay breastfeeding for 4 hours
Cyclosporine, tacrolimus	+ Monitor blood pressure	+ Monitor blood pressure	+ Low transfer
NSAIDs (COX2 inhibitors not preferred)	+ Discontinue if the woman is having difficulty conceiving	+ Continue in first and second trimesters; discontinue in third trimester	+ Ibuprofen preferred
TUMOR NECROSIS FACTOR (TNF) INHIBITORS - TNF inhibitors are considered compatible with pregnancy			
Certolizumab	++	++	++
Infliximab, etanercept, adalimumab, golimumab	+ Continue through conception	+ Continue in first and second trimesters; discontinue in third trimester several half-lives prior to delivery	++
Rituximab	+ Discontinue at conception	+ Life-/organ-threatening disease	++
OTHER BIOLOGICS - limited safety data; limited transfer in early pregnancy but high transfer in second half of pregnancy			
Anakinra, belimumab, abatacept, tocilizumab, secukinumab, ustekinumab	+ Discontinue at conception	x Discontinue during pregnancy	+ Expect minimal transfer due to large molecular size, but no available data
NOT COMPATIBLE WITH PREGNANCY			
Methotrexate	xx Stop 1-3 months prior to conception	xx Stop and give folic acid 5 mg/d	x Limited data suggest low transfer
Leflunomide	xx Cholestyramine washout if detectable levels	xx Stop and give cholestyramine washout	xx
Mycophenolate mofetil and mycophenolic acid	xx Stop >6 weeks prior to conception to assess disease stability	xx	xx
Cyclophosphamide	xx Stop 3 months prior to conception	+ Life-/organ-threatening disease in second and third trimesters	xx
Thalidomide	xx Stop 1-3 months prior to conception	xx	xx
Tofacitnib, apremilast, baricitinib	Unable to determine due to lack of data; small molecular size suggests transfer across the placenta and into breast milk		

++ Strongly recommend **+** Conditionally recommend **x** Conditionally recommend against **xx** Strongly recommend against

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WILL I NEED TO TAKE THIS MEDICATION FOR THE REST OF MY LIFE?

Since there is currently no cure for RA, it does require lifelong management to maintain clinical remission or low disease activity. Most patients will need to continue being treated for RA even if they achieve disease remission, but it is unlikely that they will receive the same drug regimen for the rest of their lives as the effectiveness of specific medications tends to wane over time for a variety of reasons. Your treatment regimen is likely to change, often multiple times, to optimize outcomes, which is why coming in for regular follow-up appointments is so important.[1,2]

Some recent studies have found that certain patients can achieve sustained remission following de-escalation of treatment (reduced dose) or even treatment discontinuation. However, attaining drug-free remission is not without significant challenges, and discontinuation of all therapy is not typically recommended outside of the research setting. Treatment de-escalation or drug holidays can result in a disease flare and/or, in some patients, an inability to achieve their prior level of disease control once treatment is reinitiated.[3–5]

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WHAT KINDS OF ACTIVITIES ARE SAFE FOR ME TO DO?

Engaging in various types of physical activity and exercise has been shown to be safe for patients with RA.[1,2] In fact, mounting evidence suggests that regular physical activity and exercise play an essential role in improving patient outcomes, while a sedentary lifestyle can exacerbate the negative impacts of RA.[1,2] The American College of Rheumatology (ACR) suggests that exercise should be one of the mainstays of RA treatment.[3] The Centers for Disease Control and Prevention (CDC) recommends that patients with RA stay as active as their symptoms and overall health allow.[4] Even high-intensity exercise regimens have been shown to be safe for some patients, although in general, the intensity, frequency, and type of exercise should be individualized.[1,2]

Numerous studies have evaluated the safety and effectiveness of different types of exercise and physical activity in patients with RA. These studies clearly demonstrate that increasing physical activity significantly improves both disease-related outcomes (such as fatigue, functional disability, and inflammation) and systemic outcomes (such as body composition and the risk for cardiovascular disease).[1,2] Each of the four main types of exercise (aerobic, strengthening, flexibility, and body awareness exercises) can have a positive impact on patient outcomes.[2,3]

Nutrition may also play an important role in optimizing outcomes for patients with RA. Diet can directly affect RA symptoms and disease activity by impacting inflammatory processes. For example, the consumption of certain foods such as red meat, salt, and trans fats have been linked to inflammation. Diet can also indirectly impact RA outcomes by affecting gut bacteria and altering body composition.[5] A Mediterranean diet that contains plentiful whole grains, fresh fruits and vegetables, seafood, beans, and nuts

WHAT KINDS OF ACTIVITIES ARE SAFE FOR ME TO DO?

is the best studied among patients with RA and has been shown to reduce inflammation and pain.[6] More recent studies suggest that a plant-based diet can have similarly beneficial effects.[7]

For patients who smoke, it is essential to try to stop smoking as soon as possible after a diagnosis of RA. Smoking is a well-established risk factor in the development of RA but also causes accelerated disease progression and lessens the impact of therapy.[8,9] One recent study demonstrated that patients with RA who stopped smoking experienced lower disease activity and reduced rates of cardiovascular events compared to those who continued to smoke.[10]

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WHAT KINDS OF ACTIVITIES ARE SAFE FOR ME TO DO?

General Exercise Guidelines for Patients with RA[3,11]

Type of exercise	Examples	Benefit	ACR Recommendations
Aerobic	• Cycling • Walking • Swimming • Dance • Daily activities/chores (e.g. dogwalking, mowing the lawn)*	• Improved cardiovascular health	• 150 minutes moderate intensity/week • Spread out over a few days
Strength training	• Free weights • Weight machines • Therabands	• Increase muscle mass and strength	• 8-10 exercises (major muscle groups) • 4-5 times/week • Increase intensity gradually over time
Flexibility exercises	• Stretching • Active range-of-motion	• Increase range-of-motion • Better posture • Improved flexibility • Enhanced joint health	• Stretching: 4-5 days/week; hold stretches for 10-15 seconds • Active range-of-motion: 5-10 repetitions/day
Body awareness exercises	• Tai chi • Yoga • Qigong	• Improved stability, balance, proprioception, posture, and coordination • Relaxation	• Per health professional advice

* If performed at moderate intensity (defined as activity that passes the Talk Test [should be able to speak normally] and that doesn't cause an individual to get out of breath or overheated)

WHAT HAPPENS IF MY INSURANCE COMPANY DOESN'T WANT TO PAY FOR MY MEDICATION?

Medical costs for patients with RA are significant, particularly for those receiving biologic DMARDs. With annual costs between $25,000 and $40,000, biologic DMARDs are significantly more expensive annually than traditional DMARDs such as methotrexate.[1,2] While most patients with RA will try a traditional DMARD first, many will need biologic therapy at some point during the course of their disease.

In order to help manage those costs, insurance companies often require prior authorization before a drug is covered. Prior authorization is a common policy wherein the healthcare provider has to provide detailed information to an insurance company before coverage is approved or denied. Alternatively, a stepwise approach to therapy may be required, in which less expensive drugs have to be prescribed before other, more costly drugs, will be covered if the patient fails to respond adequately to treatment.[3]

If a biologic is not covered by your insurance, there are a number of avenues to pursue to help pay for your medications. More and more, patients need to be their own advocate with insurance companies due to the burden of paperwork placed on many practices. You may need to do research on what medications are covered by your plan's formulary. Our healthcare team can also help by providing assistance to find appropriate resources for you. This may include our practice filing an appeal to the insurance company, or helping you apply for savings cards or patient assistance programs that may be offered by drug manufacturers, non-profit organizations, or the state. Both Medicare Part D and Medicaid cover certain biologics for RA, and uninsured patients can apply for Medicaid at any time in the year.[4] As a last resort, we may choose to prescribe less expensive medications for you.[5,6]

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