Rheumatology Nurses Society
Professional Education Series

HANDLING THE
HARD QUESTIONS:

What Our Patients Are Asking Us About RHEUMATIC DISEASE

RNS

The Purpose of This Document

Each day, rheumatology nurses, nurse practitioners, and physician assistants field dozens of questions from their patients with rheumatic diseases, and they need to be able to properly and effectively communicate appropriate responses. This pocket guide includes a brief summary of evidence surrounding some of the most common—and challenging—questions that patients with rheumatoid arthritis, psoriatic arthritis, gout, and systemic lupus erythematosus are asking about. We hope you find this guide useful for your professional development and that it assists you with your day-to-day patient management.

CONTENTS

How did I get rheumatoid arthritis?

There are a variety of factors that may have contributed to your developing rheumatoid arthritis (RA), a chronic, autoimmune disease. In the average individual, the immune system protects the body from disease and foreign substances such as bacteria and viruses through a complex interplay of different cells involved in the immune response.[1]

The ability of the immune system to recognize "self" from "non-self" is key to a properly functioning immune system. However, in individuals with autoimmune conditions such as RA, something in the immune system goes awry. The immune system loses its ability to recognize and tolerate the body as "self." As a result, the immune system mistakenly starts attacking the body's own cells and healthy tissue.[1]

In individuals diagnosed with RA, the immune cells often target the lining of the joints, called the synovium. The damage caused by this process leads to inflammation and, eventually, cartilage and bone destruction. While many people think of RA as just a joint disease, it can also affect other tissues and systems in the body, such as the cardiovascular and pulmonary systems. This system-wide, dysfunctional immune response explains why individuals with RA may experience symptoms such as fatigue, fever, and/or weight loss in addition to red, swollen, and painful joints.[1]

The definitive cause of RA is still unknown; however, it is widely believed to be due to a combination of susceptibility genes, environmental factors, and chance.[1]

More than 100 genes have been associated with an increased susceptibility for developing RA or influencing the degree of disease severity.[2] However, not everyone with an RA susceptibility gene develops RA, suggesting other factors are involved. It is generally accepted that an environmental event of some sort is required to trigger the loss of "self" tolerance and development of RA. Examples of environmental factors associated with the development of RA include smoking, periodontal disease, altered gastrointestinal and respiratory microbiome, and certain infections.[1]

Furthermore, females are 2-3 times more likely to develop RA than males. While reasons for this are not yet fully understood, it is thought to be due to

the effects of some hormones (e.g., estrogen and prolactin, which are both considered proinflammatory hormones) as well as neuroimmunological interactions.[1,3]

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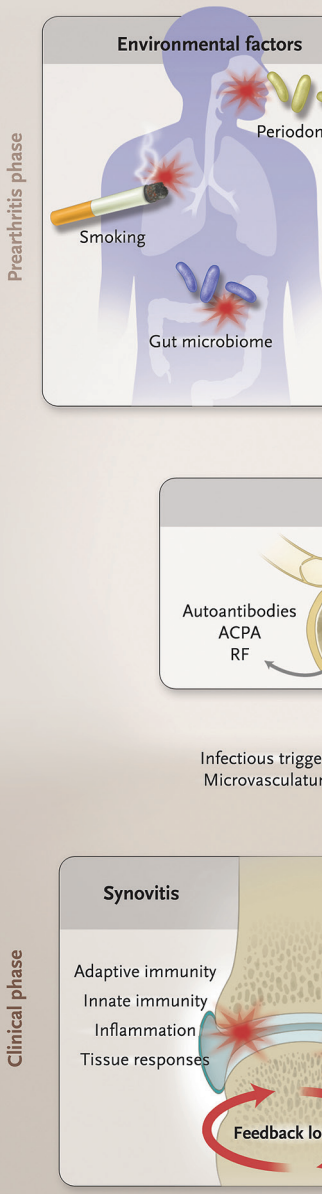
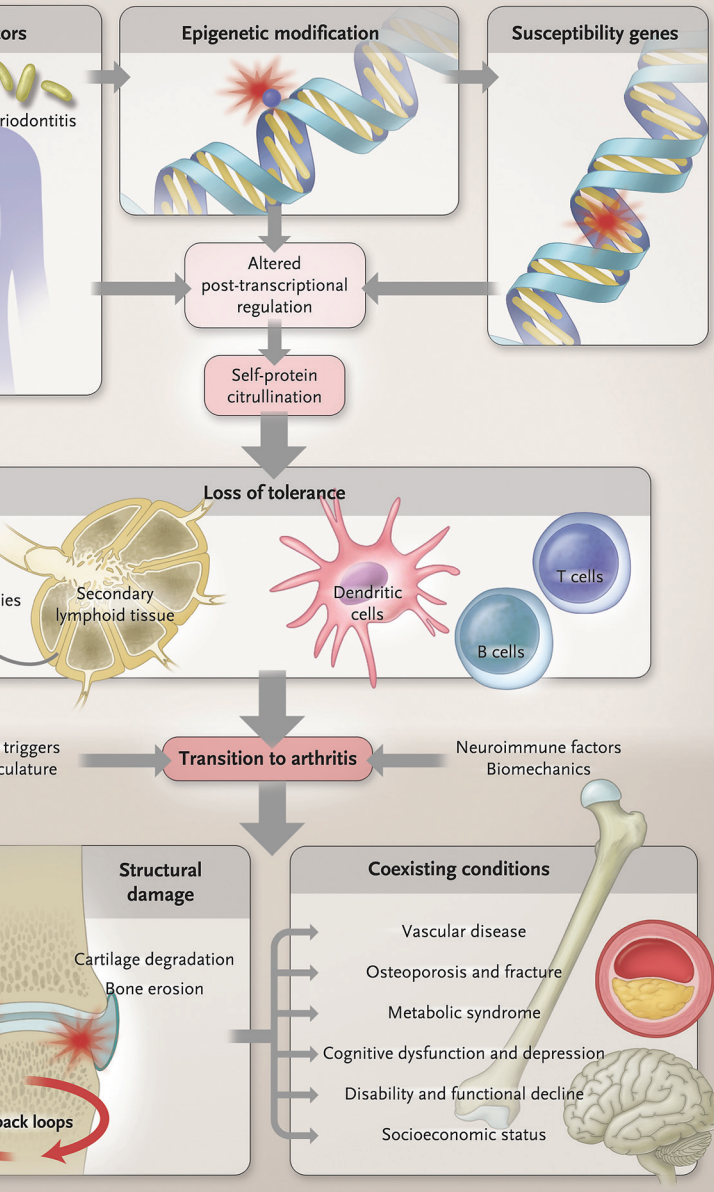


Figure. Multistep Progression to the Development of RA.



McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Eng J Med.* 2011;365(23):2205-2219

Does a diagnosis of RA mean I am going to eventually be crippled or disabled?

Not anymore.

RA is considered a chronic disease. Decades ago, many patients with poorly controlled or untreated RA developed bony joint deformities and progressive and irreversible damage in multiple joints, such as the hands, wrists, feet, spine, shoulder, hips, and knees.[1] These sorts of changes often contributed to reduced functional status and the ability to physically perform activities of daily living without limitations. By the end of their lives, some patients with RA were confined to a wheelchair and had significantly deformed hands and wrists.[2]

Fortunately, over the last several decades, significantly more effective medications and treatment strategies have become available, and outcomes for patients with RA have substantially improved.[3]

Given the impact of RA on functional, radiologic, and structural outcomes, early and intensive treatment with disease modifying anti-rheumatic drugs (DMARDs) is now considered best practice.[4] RA treatment guidelines recommend using a treat-to-target strategy, in which patient response to DMARD therapy is closely monitored every 1-3 months and therapies are adjusted in response to disease activity. The goal of this approach is to rapidly reach a state of sustained remission or low disease activity.[5,6]

Patients who receive DMARD therapy earlier in the disease course (ideally, less than 3 to 6 months after symptom onset) experience greater improvements in functional status over both the short- and long-term compared with those with a longer duration of symptoms prior to starting therapy.[4] Similarly, the treat-to-target approach has been associated with improvements in outcomes, such as decreased disease activity, reduced joint damage progression, increased functional ability, and improved quality of life.[7,8]

Table. Pharmacologic, Nonpharmacologic, and Symptomatic Therapies for RA[3,4]

Non-pharmacologic therapies	Physical therapy, occupational therapy, smoking cessation, weight loss, exercise
Symptomatic treatments	NSAIDs, glucocorticoids, local glucocorticoid injections
Conventional DMARDs	Methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, azathioprine
Tumor necrosis factor inhibitors	Adalimumab*, certolizumab pegol, golimumab, etanercept*, infliximab*
Interleukin inhibitors	Anakinra, sarilumab, tocilizumab
T cell modulator	Abatacept
B cell modulator	Rituximab
Janus kinase inhibitors	Tofacitinib, baricitinib

**Biosimilars have been approved for these reference drugs but are not listed here.*

DMARDs = disease-modifying antirheumatic drug;
NSAID = nonsteroidal antiinflammatory drug

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Will the medications I may be prescribed for my RA increase my risk of getting cancer?

It is unlikely, although the relationship between RA and cancer is complicated.

Compared with the general population, individuals with RA have a slightly elevated baseline risk of developing certain types of cancers, in particular lymphoma and lung cancer. Researchers believe that the elevated risk of lymphoma and lung cancer is likely the consequence of a chronically activated immune system, especially given that people with poorly-controlled RA appear to be at the highest risk for developing lymphoma.[1] However, it is important to remember that the overall malignancy risk in

individuals with RA is only modestly increased (~10%) compared with the general population.[2] As such, a diagnosis of RA does not mean cancer will ultimately develop.

Despite significant research, it is not yet clear whether RA itself is responsible for the increased cancer risk, if medications used to treat RA affect the risk of malignancy, or if it is a combination of both factors.[2]

DMARDs form the backbone of treatment for RA. These therapies work through targeting and modifying immunologic pathways involved in the development of RA.[2] Data from early studies raised concerns that the use of DMARD therapy, in particular biologics, may increase the risk of malignancies in patients with RA.[3] However, robust analyses of more recent data suggest that methotrexate, biologic DMARDs, and synthetic DMARDs are not associated with an overall increased risk for malignancies.[1,4-7]

For instance, recent data from a large (~125,000 patients) collaborative project that pooled data from 11 registries in 9 European countries found no evidence that biologic DMARDs increase the risk of lymphoma and malignant melanoma beyond the normal background risk in patients with RA.[1,3] Similarly, patients receiving biologic DMARDs do not appear to be at increased risk for solid cancers (e.g., breast, lung, colorectal cancers) and non-melanoma skin cancers compared to those treated with conventional DMARDs.[7]

Such findings can be reassuring to patients as the benefits of DMARD therapy for reducing disease activity likely outweigh the risk of treatment-related malignancy.

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How did I get psoriatic arthritis?

As with other autoimmune diseases, there is no single factor that we can attribute to your development of psoriatic arthritis (PsA).

PsA is a chronic inflammatory arthritis, although unlike RA, it affects women and men equally. As a heterogenous condition, PsA may involve either a few or many peripheral joints, the entheses (the area where ligaments, joint capsules, or tendons insert into the bone) or axial skeleton, and/or nail dystrophy.[1,2] Symptoms may include pain in affected joints or tendons, neck or back pain, dactylitis (swelling of entire digits), morning stiffness that lasts more than an hour or improves with activity, fatigue, and difficulties with activities of everyday living.[3] Patients may also have additional symptoms beyond the joints, such as conjunctivitis, colitis, or urethritis.[1]

Typically, individuals with PsA will also have psoriasis, a chronic skin disease. While estimates vary widely, anywhere from 6% to 41% of patients with psoriasis will develop PsA.[2] For the majority of individuals, psoriasis develops before PsA; however, for 15-20% of patients, the signs of arthritis will precede any skin findings.[1] Furthermore, some individuals may have PsA in the absence of skin psoriasis; this usually occurs in people who have relatives with psoriasis.[3]

While the cause of PsA is not entirely clear, it is believed to be immune-mediated, either as a classic autoimmune disease or as a result of inflammation secondary to trauma or physical stress in the entheseal organ (entheses and surrounding tissues). Like many immune-related conditions, PsA is thought to be due to a combination of genetic predisposition combined with a triggering event of some sort, such as infection, drug use, trauma, smoking, or obesity.[1,4,5]

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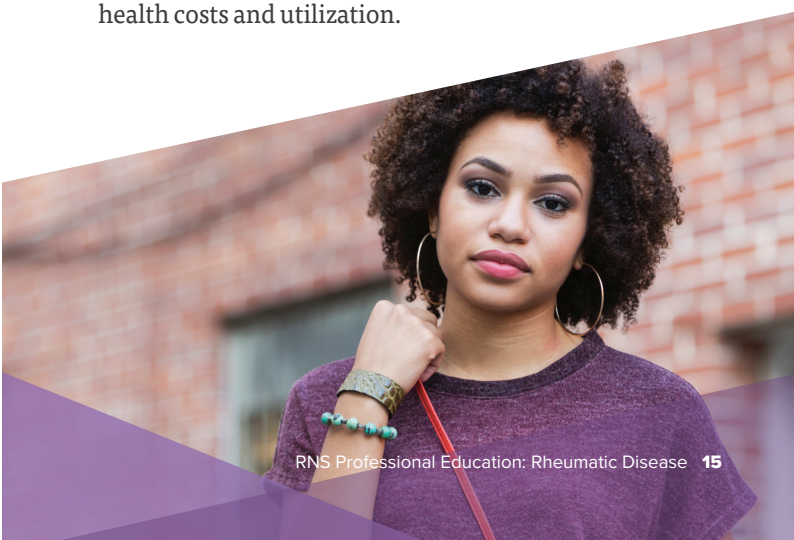
Will my disease ever go away?

Unfortunately, the answer is likely no.

PsA is a heterogenous disease in both presentation and disease course. As such, for some patients, the clinical course of the disease may follow a waxing and waning course, characterized by a series of remissions and flares. Fewer than 20% of individuals with PsA will experience prolonged remission.

Of individuals who develop PsA, an estimated 25-30% will experience relatively mild joint inflammation over time, associated with only limited disability. In contrast, without recommended treatment, up to 60% of affected patients will experience progressive and destructive arthritis.[1] PsA is associated with negative impacts on health-related quality of life as well as higher health costs and utilization.



Similar to other forms of autoimmune arthritis, such as RA, higher levels of disease activity are associated with more progressive joint damage. As such, early identification and initiation of treatment is key to improving long-term outcomes.[2]

Both non-pharmacologic and pharmacologic approaches to the treatment of PsA can reduce inflammation, ameliorate symptoms, and, in some cases, even result in remission. Given the autoimmune underpinnings of PsA, disease-modifying

Table. Pharmacologic, Nonpharmacologic, and Symptomatic Therapies for PsA

Non-pharmacologic therapies	Physical therapy, occupational therapy, smoking cessation, weight loss, massage therapy, exercise
Symptomatic treatments	NSAIDs, glucocorticoids, local glucocorticoid injections
Conventional DMARDs	Methotrexate, sulfasalazine, cyclosporine, leflunomide, apremilast
Tumor necrosis factor inhibitors	Etanercept, infliximab, adalimumab, golimumab, certolizumab pegol
Interleukins	Ustekinumab, secukinumab, ixekizumab, brodalumab
CTLA4-immunoglobulin	Abatacept
Janus kinase inhibitor	Tofacitinib

drugs are typically used in patients with active disease to address the underlying disease process.[2] Similar to treatment approaches for other chronic diseases, a treat-to-target approach to the management of PsA has been associated with improved outcomes.[3]

One study found that 58% of patients with PsA were able to achieve remission, as measured by disease activity score, after one year of treatment with TNF inhibitor therapy.[4] However, while some patients may reach a state of low disease activity or remission with treatment, evidence indicates that most patients (~75%) experience a recurrence or flare within several months after stopping medication.[5] So, while medications may "quiet" the disease activity, they do not cure PsA, and long-term drug-free remission is likely unattainable. In that sense then, the disease will never "go away."

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How likely am I to pass this onto my children?

Given the link between autoimmune disease and genetics, many individuals with PsA and other rheumatic diseases, such as rheumatoid arthritis (RA), worry about the chance of passing the disease onto their children.

To answer this question, researchers often look at how often a condition or disease occurs in multiple generations of a family. Like psoriasis, PsA tends to run in families, with an estimated 40% of individuals with PsA having at least one close family member with either psoriasis or PsA.[1] Similarly, studies have found that individuals with a family history of RA have a 3 to 5 times increased risk of developing RA themselves, especially if the RA is in a first-degree relative.[2]

Specifically looking at PsA, one study found approximately 12% of individuals with the condition reported at least one first-degree relative with confirmed PsA. This same study found that individuals who had at least one first-degree relative with PsA were approximately 48 times more likely to develop PsA compared with individuals without a positive family history.[3] Similar results were reported in another, more recent study, which found approximately 8% of individuals with PsA having an affected first-degree relative.[4]

While data like this support a familial connection, it is important to establish if other factors are at work besides genetics. Twin studies are used to evaluate the relative contribution of genetics and environmental factors to the expression of a trait or disease by comparing the rates of disease development between identical and non-identical twin sets. In the case of PsA, one twin study found the rates of PsA in identical and non-identical twin sets were similar, indicating non-genetic factors also play an important role in disease development.[5]

Unfortunately, the inheritance pattern of PsA is still unknown, and a number of different genes are believed to be involved in its development.[1] Furthermore, PsA is thought to be a multifactorial disease, requiring an environmental trigger in the setting of genetic predisposition.[3] This makes it hard to determine the risk of passing the disease onto a child. While similar numbers for PsA are scarce, scientists believe that at least 10% of individuals inherit one or more of the genes that increase their

risk of developing psoriasis. However, only 2-3% of the overall population develops psoriasis, highlighting the role that environmental triggers play.[6]

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How did I get gout?

Gout is a common condition, thought to affect roughly 4% of the U.S. population. It is the most common type of inflammatory arthritis in men. Overall, men are affected significantly more than women, by an estimated ratio of 5-10:1. Gout tends to occur primarily during or after middle age.[1,2]

Gout is associated with hyperuricemia, or abnormally elevated levels of serum uric acid. This can be due to either the overproduction of uric acid, or much more commonly, the inability of the kidneys to excrete enough uric acid into the urine.[3]

Unlike many other mammals, humans are missing an enzyme called uricase, which breaks uric acid down into a form that can be easily excreted in the urine.[4] When serum uric acid concentrations reach a certain level, the solubility threshold for monosodium urate (the most

common form of uric acid) is reached, and it leaks out of the serum to form crystals.[3] These urate crystals can be deposited throughout various tissues in the body, causing a variety of conditions.[5]

When excess crystals are formed and deposited in the skeletal system (e.g., joints, bursa, tendons, cartilage), the immune system is activated, leading to an inflammatory response and acutely painful, warm, swollen, and red joints. Over time, the frequency and duration of acute attacks can increase and become chronic.[6] This can lead to joint damage and the formation of subcutaneous tophi, which are nodules in and around the involved joint.[7] While gouty arthritis is most common in the big toe, it also commonly affects the mid-foot, ankle, knee, upper limb, and fingers.[2]

Once thought to be a consequence of an indulgent lifestyle, it is now recognized that genetics are the primary contributor to the development of gout.[4] Beyond age, sex, and genetics, other risk factors such as certain medications (e.g., diuretics or aspirin), renal disease, excess weight, hypertension, and dietary and alcohol intake are also believed to increase the risk of developing gout.[7] However, a recent study showed that diet was responsible for less than 1% of variation in serum urate levels; in contrast, 24% of the variation was explained by common genetic factors.[8]

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Are there certain foods and drinks I am going to need to avoid?

The answer is "probably," with the caveat that opinions aren't as strongly held as they were a generation ago.

The onset of gout was once thought to be heavily influenced by food and alcohol intake, but as mentioned in the previous question, the vast majority of gout cases are now known to be due to the kidney's inability to excrete enough uric acid into the urine. However, for some people, hyperuricemia is the result of uric acid overproduction.

Uric acid is a byproduct of the metabolism of purines, which come from both internal and external sources, such as food and drink. For a time, dietary sources of purine-rich foods were believed to

universally increase the risk of gout. However, recent evidence suggests the picture is more complicated, as some purine-rich foods such as beer and high fructose corn syrup have been shown to increase uric acid levels while others, such as purine-rich vegetables (e.g., spinach, asparagus), do not.[1,2]

The overall picture, however, is a bit murky as guidance on dietary modifications in patients with gout is mixed. Several guidelines provide very specific recommendations, claiming that gout patients should avoid or limit their intake of purine-rich animal proteins (e.g., organ meats, shellfish, beef, lamb, pork), foods high in fructose, and sugar-sweetened beverages as well as alcohol, especially beer and spirits. Conversely, low-fat dairy, coffee, vitamin C, cherries, and cherry extracts, as well as certain diets, have been shown to decrease serum urate levels and the risk of gout.[2-5]

Other guidelines are less specific and suggest patients should reach or maintain ideal weight, engage in regular exercise, stop smoking (if applicable), and avoid known dietary triggers that are specific to them, with an emphasis on sugar-sweetened drinks and excess alcohol.[6,7] These less prescriptive recommendations likely reflect the finding that very little high-quality evidence has shown gout-specific dietary modifications (e.g., avoid purine-rich foods) are better than general dietary counseling (i.e., promote weight loss if appropriate, regular exercise, and reduced alcohol intake) on gout outcomes.[5,8]

However, given the frequency of cardiovascular comorbidities in many patients with gout, specific dietary recommendations as well as other lifestyle modifications are likely beneficial from a cardiovascular health perspective.[5]

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Why do I often feel worse right after starting a new medication?

Initial worsening of symptoms is not uncommon in gout patients starting on a new medication, but importantly is not an indicator that their medication is not working.

Medications are a key component of gout management and are used for both the treatment of acute attacks as well as to prevent future attacks.

The first goal when treating gout is to address the acute attack, with medications used as soon as possible to reduce inflammation and control symptoms. Medications may typically include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, intra-articular injections of corticosteroids, and/or colchicine.[1]

The second goal of gout management is to reduce or prevent future acute attacks. As hyperuricemia is a key component in the development of gout, urate lowering therapy (ULT) is recommended for most patients. This is done to achieve serum uric acid levels below saturation thresholds, promote crystal dissolution, and prevent future crystal formation and attacks.[1,2] A number of different drugs are available to reduce uric acid levels, either through reducing the formation of uric acid, increasing the breakdown of uric acid, or increasing the renal excretion of uric acid.[3]

As an acute attack resolves and patients begin ULT, urate crystals that were deposited throughout the body may begin to disperse. While the risk of gout attacks is reduced after approximately 1 year of ULT treatment, ULT does not reduce the risk during the first 6 months. As such, patients may experience a spike in acute flares, which can lead to reduced patient adherence to treatment as they feel their medication might not be working. As such, prophylaxis, typically with colchicine or NSAIDs, is usually used during the first 6 months of ULT to prevent acute flares.[1,2]

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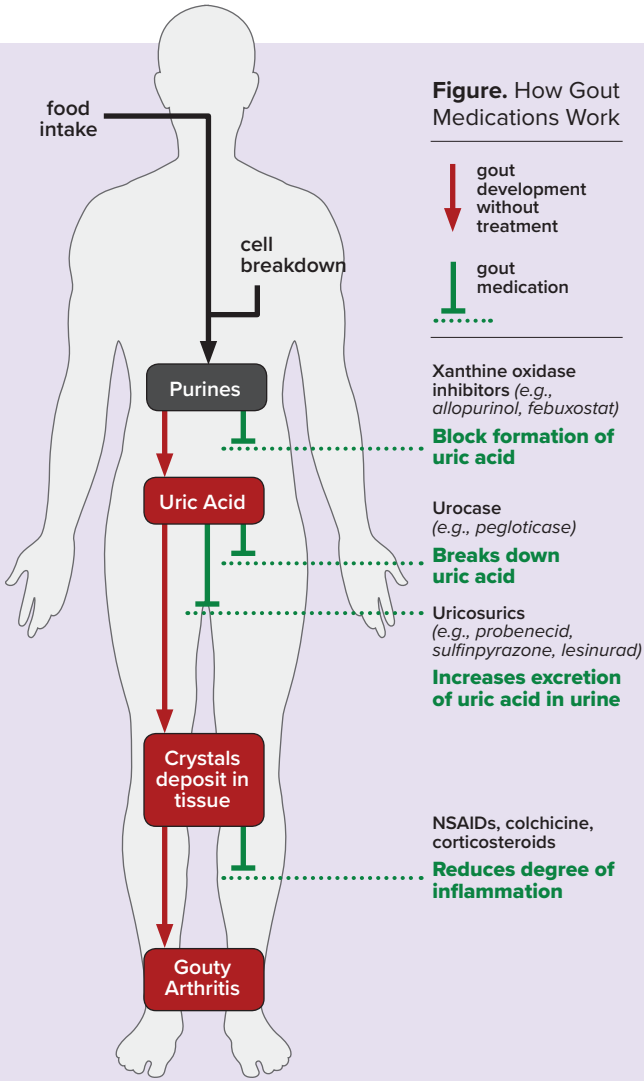

Figure. How Gout Medications Work

How did I get lupus?

Lupus is a chronic, systemic, inflammatory autoimmune disease, with many different clinical signs and symptoms due to its effects on multiple organ systems and tissues. When people talk about lupus, they are often referring to systemic lupus erythematosus (SLE), the most common form of lupus.[1]

The cause of SLE is multifactorial, but is thought to be due to a combination of genetic, hormonal, immunologic, and environmental factors (e.g., ultraviolet light, certain viruses).[1] One of the biggest risk factors for developing SLE is gender. The majority of individuals diagnosed with SLE are female, with women affected 9 times more frequently than men, often during their childbearing years.[2] Race/ethnicity also plays a role, with African Americans, Asians, Hispanics, and Native Americans affected more frequently than Caucasians.[1]

Like all autoimmune diseases, the pathogenesis of SLE is complex and involves many different players in the immune system. In all individuals, cells in the body eventually die; normally, these dead cells are cleared away simply and efficiently. However, in individuals with SLE, the mechanism to clear away dead cells is broken. As such, the dead cells aren't cleared away as quickly as they should, and they begin to break down. As the cells degenerate, proteins that usually live inside the cells become exposed. The immune system doesn't recognize these proteins as "self" and therefore goes into overdrive, leading to cytokine release, inflammation, the production of autoantibodies, and immune complex formation, which are deposited in various tissues throughout the body. The end result is a loss of self-tolerance and an overactive immune system, causing multi-organ inflammation and tissue damage.[1,2,4]

SLE is characterized by varying periods of disease flare-ups and inactivity. In addition to general signs and symptoms of a disease flare such as fever, weight loss, and fatigue, clinical manifestations of SLE can be widespread and involve numerous organ systems and tissue. The skin, musculoskeletal, and pulmonary systems are most frequently affected, although the cardiovascular, gastrointestinal, renal, hematologic, and central nervous systems may all be affected as well. Renal involvement is common in individuals with SLE, with approximately 50% of patients developing nephritis, a major cause of increased morbidity and mortality.[1]

The management of SLE is complex, with the goals of therapy focused on achieving low disease activity or remission in order to reduce flares, minimize organ and tissue damage, and improve long-term survival and quality of life.[5] Hydroxychloroquine forms the backbone of therapy as it reduces disease flares and symptoms. Low-dose glucocorticoids are also frequently used. The selection of other agents, such as immunosuppressive and cytotoxic agents, is typically driven by the specific body systems involved.[6]

Table. Pharmacologic Therapies for SLE

Topical Steroids	Hydrocortisone, triamcinolone, fluocinolone
Antimalarials	Hydroxychloroquine, quinacrine, chloroquine
Glucocorticoids	Prednisone, methylprednisolone, solumedrol
NSAIDs	Many options
Immunosuppressive agents	Azathioprine, mycophenolate, cyclophosphamide, methotrexate, dapsone, thalidomide
B and T cell inhibitor	Mycophenolate mofetil
B lymphocyte stimulator	Belimumab

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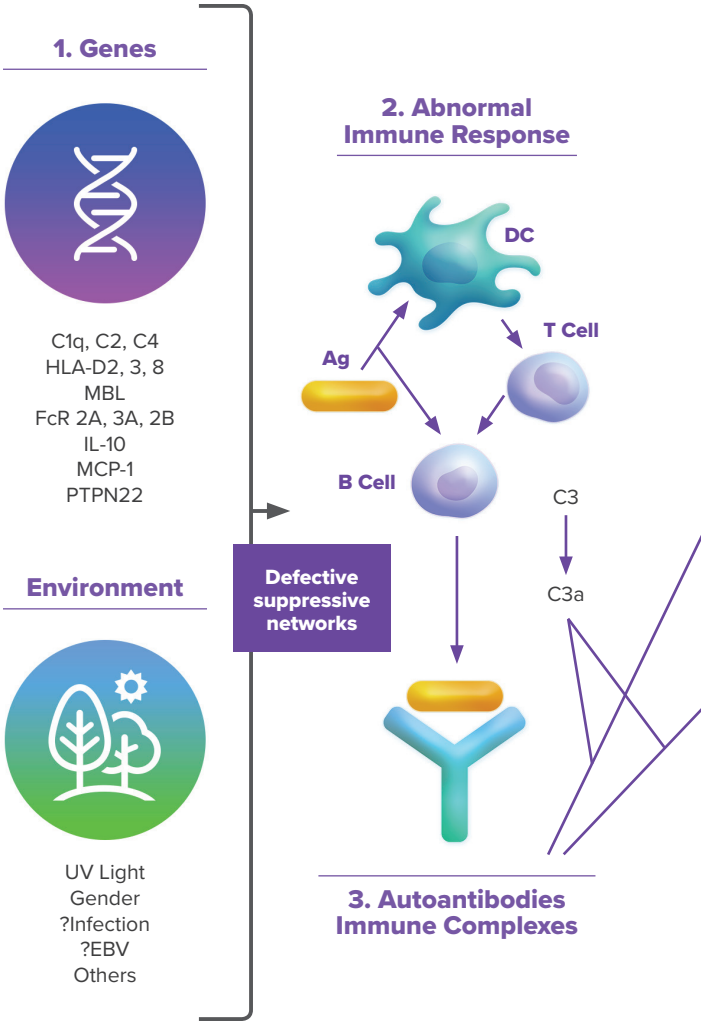
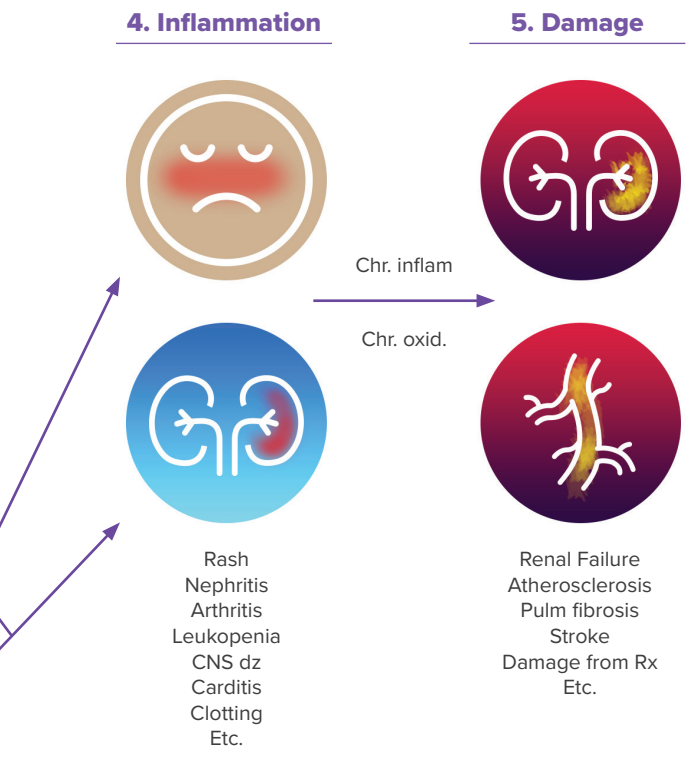


Figure. The Pathogenesis of SLE

In patients who develop SLE, gene-environment interactions result in abnormal immune responses that generate pathogenic autoantibodies and immune complexes that deposit in tissue, activate complement, cause inflammation, and, over time, lead to irreversible organ damage.



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: Harrison's Principles of Internal Medicine, 18th edition. The McGraw-Hill Companies, Inc.

Ag, antigen; C1q, complement system; C3, complement component; CNS, central nervous system; DC, dendritic cell; EBV, Epstein-Barr virus; HLA, human leukocyte antigen; FcR, immunoglobulin Fc-binding receptor; IL, interleukin; MCP, monocyte chemotactic protein; PTPN, phosphotyrosine phosphatase; UV, ultraviolet.

Why are there so many different kinds of lupus?

As mentioned in the previous question, lupus is a heterogenous disease with many clinical presentations, ranging from skin lesions in the absence of any other symptoms to life-threatening, multisystem manifestations. In fact, some researchers believe lupus should be viewed as a syndrome, rather than a single disease.[1]

Beyond SLE, other common lupus types include the following:

- Cutaneous lupus erythematosus, and especially discoid lupus erythematosus, which manifests as a skin rash that may wax and wane with treatment
- Drug-induced lupus, a lupus-like condition caused by certain prescription drugs such as isoniazid or hydralazine. Symptoms usually disappear after the responsible drug is discontinued.
- Neonatal lupus, a rare condition affecting some infants of women with lupus that puts the newborn at risk for congenital heart block. Neonatal lupus usually resolves within a few months, often with no lasting effects.[2,3]

Like SLE, cutaneous lupus erythematosus is believed to be caused by a combination of genetics and environment, with exposure to ultraviolet light thought

to play a key role in both triggering of the disease and causing flares.[2] Patients with cutaneous lupus erythematosus may have either an acute, subacute, or chronic form of the condition. Acute cutaneous lupus erythematosus usually is accompanied by other signs and symptoms of SLE. In contrast, both subacute and chronic cutaneous lupus erythematosus may occur in the absence of SLE.

Furthermore, there are several subtypes of chronic cutaneous lupus erythematosus, including discoid lupus erythematosus, lupus erythematosus profundus, lupus erythematosus tumidus, and chilblain cutaneous lupus.[4]

Both neonatal and drug-induced lupus are considered systemic diseases; as such, they may affect multiple organ systems. Neonatal lupus is believed to be the result of maternal autoantibodies crossing the placenta, whereas drug-induced lupus is the result of an autoimmune response following an exposure to a medication.[2]

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Will I still be able to get pregnant despite having lupus?

Yes, with careful planning, treatment selection, and monitoring, a successful pregnancy is absolutely possible despite a diagnosis of lupus. The same holds true for other rheumatic diseases.

While autoimmune diseases can affect individuals of any age, newly-diagnosed SLE or another rheumatic disease can be particularly devastating to women of childbearing age. Some rheumatic diseases, including SLE, not only disproportionally affect women, but also tend to more commonly strike during childbearing years. Furthermore, rheumatic diseases by their very nature, as well as the medications used to manage them, can directly impact the timing of pregnancy planning as well as pregnancy outcomes.

Most rheumatic diseases have been associated with increased maternal and fetal complications compared with the general population. For instance, both SLE and RA have been associated with higher risks of Cesarean section delivery, preeclampsia, and preterm birth.[1,2] Poorly controlled disease activity has been shown to increase the risk of adverse outcomes, whereas well-controlled disease has been associated with improved outcomes.[3]

A number of the medications used to treat rheumatic diseases can be harmful to developing fetuses. Therefore, family planning counseling, including the use of contraceptives to prevent unintended pregnancies, is an integral part of providing comprehensive care.

When female patients diagnosed with a rheumatic disease are contemplating pregnancy or wish to conceive, disease activity should be well-controlled for at least 3-6 months prior to conception. During this time frame, therapies that have been determined to be unsafe for use throughout pregnancy, such as methotrexate, leflunomide, and non-TNF biologics (after 1st trimester), should be discontinued, with other pregnancy-compatible therapies started or adjusted to reach or maintain no/low disease activity. Therapy may also need to be adjusted during pregnancy in order to ensure safety of the mother and fetus during all trimesters. The choice of therapy during the postpartum period and beyond should focus on drugs that are safe for use during breastfeeding, when relevant.[2-4]

Disease-modifying therapies may also need to be adjusted or changed in male patients with a

rheumatic disease interested in starting a family. For instance, it is recommended that methotrexate be discontinued 3 months prior to attempted conception in men due to the potential impact of the drug on sperm count.[2]

Undoubtedly, pregnancy planning and management in patients with a rheumatic disease is complex and requires a multidisciplinary care team approach. However, with careful planning, treatment selection, and monitoring, pregnancies can be successfully managed with the ultimate outcome—a healthy baby—as the result.

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Table. Pregnancy Classifications in Rheumatic Disease

CATEGORY	RISK	EXAMPLES
A	Controlled clinical studies in humans have failed to demonstrate a risk to the fetus in the first trimester of pregnancy, and no evidence exists suggesting risk in later trimesters.	• Folic acid
B	Reproduction studies in animals have failed to demonstrate evidence of impaired fertility or harm to the fetus. However, no controlled clinical studies have been conducted in humans.	• Anakinra • TNF inhibitors
C	Reproduction studies in animals have either not been performed or have demonstrated evidence of impaired fertility or harm to the fetus. However, the benefit of the drug may still outweigh its risk.	• Hydroxychloroquine • Sulfasalazine • Non-TNF biologics
D	Adverse reaction data in human investigational trials or marketing experience has been demonstrated. However, the benefit of the drug may still outweigh its risk, especially in emergency presentations.	• Azathioprine • Cyclophosphamide
X	Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both. The risk of using the drug clearly outweighs any possible benefit.	• Leflunomide • Methotrexate

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