Autoimmune Diseases

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- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
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Faculty

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Faculty Disclosure

Contributing faculty, Lori L. Alexander, MTPW, ELS, MWC, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the diagnosis, treatment, and care of patients with autoimmune diseases.

Accreditations & Approvals

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A complete Works Cited list begins on page 70.

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NetCE designates this continuing education activity for 15 ANCC contact hours.

IPCE CREDIT™

This activity was planned by and for the healthcare team, and learners will receive 15 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 18 hours for Alabama nurses.

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Special Approvals

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About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective

The purpose of this course is to provide healthcare professionals with the information necessary to diagnose and treat the most common autoimmune diseases according to evidence-based or guideline-endorsed recommendations in order to improve patient quality of life.

Learning Objectives

Upon completion of this course, you should be able to:

1. Describe the impact and pathogenesis of autoimmune diseases in the United States.
2. Recognize genetic and environmental risk factors for autoimmune diseases.
3. Evaluate the general characteristics of autoimmune diseases, including the difficulty in reaching a diagnosis.
4. Identify approaches to the management of autoimmune diseases, with special attentionto considerations for patients with limited English proficiency and/or health literacy.
5. Analyze the epidemiology, clinical manifestations, and diagnostic criteria of autoimmune thyroiditis.
6. Select the appropriate treatment for Hashimoto disease and Graves disease in various patient populations.
7. Appropriately identify and diagnose rheumatoid arthritis according to established diagnostic criteria and clinical manifestations.
8. Outline the recommended treatment of rheumatoid arthritis using pharmacologic and nonpharmacologic interventions.
9. Discuss the importance of follow-up and patient education in the treatment of patients with rheumatoid arthritis.
10. Evaluate the impact and diagnosis of systemic lupus erythematosus (systemic lupus), including indications for appropriate referral.
11. Analyze the available treatments for systemic lupus, including considerations for follow-up and prognosis.
12. Apply the available diagnostic criteria to identify and treat Sjögren syndrome.
13. Evaluate the clinical manifestations of celiac disease
14. Describe the components necessary to diagnose and treat celiac disease.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

The autoimmune diseases are comprised of a great many disorders affecting multiple body systems/organs and sharing a common pathophysiology: immune activation directed against "self." It is difficult to determine the overall burden of autoimmune diseases, because few epidemiologic studies focus on them as a single entity and because many are uncommon and ill-defined. However, the study of individual autoimmune diseases, combined with some data on the diseases collectively, indicates that the burden is substantial in terms of the number of persons affected and the associated morbidity, mortality, and financial cost.

The National Institutes of Health (NIH) estimates that 23.5 million persons (8.5% of the population) have been diagnosed with one or more of the 29 most common and best-studied autoimmune diseases, and the prevalence is considered to be rising [4; 5]. When less well-studied syndromes are taken into account, an estimated 50 million individuals in the United States suffer from autoimmune-mediated disorders, a number greater than that for heart disease (26.6 million) and cancer (14.5 million) combined [1; 2; 309].

Autoimmune diseases are chronic illnesses, with most having no available cure. As a result, lifelong treatment is needed for diseases that cause substantial morbidity, disability, mortality, and costs. Approximately $100 billion in annual direct healthcare costs are attributed to autoimmune diseases [1].

The diagnosis of an autoimmune disease is often difficult to come by; in early-stage disease, the symptoms and signs are often subtle, nonspecific, and confusing [310]. According to a survey conducted by the American Autoimmune Diseases Association, individuals who had been diagnosed with a serious autoimmune disease had seen an average of five physicians over a period of 4.6 years before a correct diagnosis was made [310]. In addition, more than 45% of individuals with an autoimmune disease reported that they had been labeled as a chronic complainer in the early stages of their disease because no cause for their symptoms could be determined [310].

Evidence-based guidelines for diagnosis, management, and/or follow-up are available for some autoimmune diseases, but diagnosis continues to be a challenge because symptoms are often overlapping and definitive diagnostic testing is lacking for most diseases. Problems exist even when guidelines are available; some guidelines predate the emergence of more effective treatment or lack clinical utility [6; 7; 8; 10; 11]. In addition, guidelines are associated with low rates of familiarity and adherence, especially with respect to recommendations for follow-up. For example, despite guidelines recommending routine monitoring of thyroid-stimulating hormone (TSH) levels for individuals taking medication for Hashimoto hypothyroidism, studies have shown that up to 40% of these individuals have abnormal TSH levels [12; 13]. In addition, adherence to some recommendations for the treatment of systemic lupus erythematosus (systemic lupus), the monitoring of its comorbidities, and the prevention of glucocorticoid-induced osteoporosis have been found to be suboptimal [11; 14; 15].

This course provides an overview of the current understanding of the pathogenesis of autoimmune disease and specifically addresses the diagnosis and management of the leading autoimmune diseases in adults: thyroiditis (the most prevalent autoimmune disorder), rheumatoid arthritis, systemic lupus, Sjögren syndrome, and celiac disease (an increasingly prevalent autoimmune disease of the gut) [16; 17]. Although autoimmune mechanisms may be important in the initial pathogenesis of type 1 diabetes, the natural history of this disease is determined primarily by fixed pancreatic islet cell deficiency rather than chronic immune-mediated inflammation; thus, it will not be covered by this course. Each disease section includes details on epidemiology; potential environmental risk factors;

association with other autoimmune diseases; diagnosis, with a focus on established diagnostic criteria and differential diagnosis; treatment options, primarily those based on evidence in guidelines and other systematic reviews and meta-analyses; and recommendations for follow-up. Patient education is highlighted, as self-management is an essential component in the treatment of a chronic disorder [18; 19].

OVERVIEW OF AUTOIMMUNE DISEASES

Autoimmune disease is thought to encompass an array of 80 to 100 disorders, with considerable variation in the body system/organ affected and associated morbidity [1]. Researchers have identified direct evidence (the ability to transfer autoimmune disease) for 15 autoimmune diseases, and there is indirect evidence (the ability to reproduce the autoimmune disease in animal models) and circumstantial evidence (the association of autoantibodies with disease in appropriate clinical settings) for an autoimmune component in more than 80 additional diseases [3].

The autoimmune diseases with the highest reported prevalence rates are Graves disease, rheumatoid arthritis, and Hashimoto thyroiditis; prevalence rates are lower for such diseases as celiac disease and autoimmune hepatitis [21; 22; 23]. Among the other more commonly occurring autoimmune diseases are systemic lupus, Sjögren syndrome, multiple sclerosis, myasthenia gravis, inflammatory bowel diseases (e.g., ulcerative colitis, Crohn disease), pernicious anemia, scleroderma, primary biliary cirrhosis, Addison disease, and thrombocytopenic purpura [24]. Estimates of the prevalence of fibromyalgia have been similar to that of common autoimmune diseases [25].

The prevalence of autoimmune diseases differs according to gender, age, and race/ethnicity. Most autoimmune diseases occur far more frequently in female individuals than in male individuals, and although these diseases do occur at any age, most develop during the middle adult years, which represents the childbearing years for women [310]. Some diseases, such as type 1 diabetes, have an onset primarily in childhood and adolescence, and others, such as rheumatoid arthritis, occur primarily among older adults [21]. Differences in the prevalence of autoimmune diseases according to race/ethnicity are only beginning to emerge, and the variations have been studied only within the context of individual diseases [21].

Many autoimmune diseases follow a progressive course, even with appropriate management, and serious or life-threatening complications may develop. Functional limitations, disability, and poor quality of life are substantial concerns. For example, arthritis and rheumatism are one of the leading causes of disability in the United States, affecting as many as 8.6 million people and causing significant declines in ability to perform activities of daily living [26].

Although no autoimmune disease has been listed among the 10 leading causes of death, the aggregate mortality rate for all autoimmune diseases ranked eighth among the leading causes of death in women younger than 65 years of age in the United States in 1995 (***Table 1***) [27]. Similarly, researchers found that an autoimmune disease was the sixth or seventh most frequent underlying cause of death among female individuals younger than 75 years of age in England and Wales in 2003 [28]. In both studies, rheumatic fever/heart disease, rheumatoid arthritis, multiple sclerosis, and type 1 diabetes were among the leading underlying causes of death [27; 28].

Much is still unknown about how autoimmune diseases develop, but investigators have explored host, genetic, and environmental factors and continue to evaluate potential pathways [29].

DEATHS FOR WOMEN WITH AN AUTOIMMUNE DISEASE AS AN UNDERLYING CAUSE (UNITED STATES, 1995)				
Autoimmune Disease	**Death Counts by Age**			
	25 to 44 Years	**45 to 64 Years**	**≥65 Years**	**All Ages**
Rheumatic fever/heart disease	177	582	2,832	3,613
Rheumatoid arthritis	14	183	1,244	1,442
Multiple sclerosis	254	620	514	1,391
Systemic lupus erythematosus	338	353	356	1,118
Systemic sclerosis (scleroderma)	85	318	490	902
Glomerulonephritis	44	88	745	893
Type 1 diabetes[a]	269	NA	NA	330
Autoimmune hepatitis	12	51	135	201
Idiopathic thrombocytic purpura	21	29	134	188
Myasthenia gravis	9	14	150	174
Autoimmune hemolytic anemia	2	11	77	93
Pernicious anemia[b]	0	2	68	70
Sjögren syndrome[b]	1	16	43	60
Graves disease	4	3	15	24
Thyroiditis	2	2	0	6
Vitiligo[b]	0	0	0	0

[a]Deaths related to type 1 diabetes were included only for individuals younger than 35 years of age.
[b]Diseases without specific International Classification of Diseases categories.

Source: [27] *Table 1*

PATHOGENESIS

The human immune system is a complex, elegant mechanism for responding in balanced (modulated) fashion to a wide range of foreign proteins and other substances (antigens) that gain access to the body, while maintaining tolerance to self. This system provides defense against harmful bacteria, viruses, and even cancer cells. In a subset of the population, on occasion and in response to particular antigenic stimulation, a balanced, modulated response is lost, and unregulated immune activation produces ongoing inflammation and loss of tolerance to "self" [30]. The resulting autoimmunity can lead to a chronic inflammatory state (autoimmune disorder), with potential to cause serious damage to cells, tissues, and organs [31]. Virtually any organ system can be affected; often the dysregulated immune response targets a specific organ, as in thyroiditis, or multiple organs, as in systemic lupus.

In organ-specific diseases, such as thyroiditis, type 1 diabetes, inflammatory bowel disease, or multiple sclerosis, a normal immune response is misdirected against a self-antigen or organ, and inflammation and production of autoantibodies are usually confined to antigens specific to the target organ [31]. Multiple organs are targets in systemic autoimmune diseases, such as systemic lupus, Sjögren syndrome, or systemic sclerosis. In these types of autoimmune diseases, autoantibodies are directed to different autoantigens, typically resulting in chronic activation of innate and adaptive immune cells and an array of clinical manifestations [31].

Some autoimmune diseases are characterized by an organ-specific immune process but are systemic because they also involve autoantibodies to autoantigens outside of a specific organ. For example, rheumatoid arthritis is primarily a joint-selective disease, but other autoantibodies can cause extra-articular manifestations [31].

Organ-specific autoimmune diseases differ according to whether disease is mediated primarily though autoantibodies, autoreactive T cells, or a combination of the two [31]. Systemic autoimmune diseases may be categorized according to the prevailing character of the autoimmune response as cell-mediated, autoantibody-mediated, or immune complex disease. T-cell or B-cell activation causes tissue damage directly by binding to cell-surface autoantigens, or indirectly by forming antibody-antigen complexes that become deposited in tissues. The autoimmune inflammatory process often becomes self-perpetuating, as tissue damage leads to the release of cytokines, activated T cells, and additional self-antigens, thereby stimulating and augmenting the immune response.

The detection of an autoantibody is not necessarily indicative of an active autoimmune disease, as some autoantibodies, such as rheumatoid factor and antinuclear antibodies, are found in individuals without evidence of a specific inflammatory disease process. In addition, autoantibodies can be detected years before a related autoimmune disease develops [33]. Some level of autoimmunity is, in fact, present in all individuals, which means that other factors must be involved in the development of an autoimmune disease [34].

RISK FACTORS

Genetic Factors

Genetics have been found to play a major role in rendering a person susceptible to an autoimmune disease. In general, autoimmune diseases occur concurrently within affected individuals and their families at higher than expected rates, but there are differences in the diseases that cluster within families [4]. The mode of inheritance of an autoimmune disease is complex, and research indicates that the genes involved in autoimmune disorders are pleiotropic (meaning they affect more than one trait) rather than disease-specific [4]. This research suggests that common alleles may have the potential for alternate clinical phenotypes under different sets of genetic and environmental factors, and data support the premise that clinically distinct autoimmune diseases may have common susceptibility genes [4; 35]. Currently, at least 68 genetic risk variants have been associated with various autoimmune diseases, and several loci have been identified as being associated with more than one autoimmune disease [4; 36].

Studies with monozygotic twins have been done to determine the genetic basis for many autoimmune diseases. Reported concordance rates include 12% to 30% for rheumatoid arthritis, 25% to 57% for systemic lupus, 30% for multiple sclerosis, 30% to 50% for type 1 diabetes, 70% to 75% for celiac disease, and up to 80% for Graves disease [22; 30; 37; 38]. The concordance rate does not reach 100% for any autoimmune disease, which means that factors other than genetics must have a role in the pathogenesis [31].

Environmental Factors

The role of environmental factors on the development of autoimmune disease has been studied, but exact triggers and how their interaction with genetic predisposition bears on pathogenesis have not yet been defined [31]. Among the environmental factors that have been found to have influence are infectious agents, stress, sex hormones (estrogens and androgens), and cigarette smoking.

Infectious Agents

Animal models have provided the best evidence of infectious agents inducing an autoimmune disease by immune-mediated mechanisms. On the basis of studies with these models, researchers have theorized that the immune response is triggered by antigens of a micro-organism that closely resembles self-antigens, a mechanism that has been termed molecular mimicry [3]. Another theory is that

autoimmunity is induced by a mechanism known as the bystander effect: the invading micro-organism directly damages tissue during active infection, thereby exposing self-antigens to the immune system [39; 40].

The diseases most often associated with infection as an etiologic factor are multiple sclerosis, type 1 diabetes, rheumatoid arthritis, systemic lupus, myasthenia gravis, and Guillain-Barré syndrome [3; 25; 41; 42; 43; 44]. The micro-organisms most often implicated are viral, including Epstein-Barr virus, hepatitis C virus, parvovirus, and cytomegalovirus [3; 43; 44; 45].

Stress

Several studies in animals and humans have demonstrated that physical and psychologic stress affects the immune system, most probably the result of downstream neuroendocrine alterations that modulate immune function. In response to stress, catecholamines and glucocorticoids released from centers in the brain and the adrenal gland exert an effect on various cell lines in the innate and adaptive arms of the immune system, thereby altering the ambient cytokine profile. This, in turn, impacts the differentiation and number of autoreactive T-cells [294]. It is hypothesized that stress may play a role in the onset and exacerbation of autoimmune disease in genetically susceptible individuals [46; 47; 48]. Inflammatory autoimmune diseases, such as rheumatoid arthritis and systemic lupus, are considered the most likely to be influenced by stress [48]. Psychologic stress as a trigger for autoimmune diseases is further suggested by studies in which as many as 80% of individuals reported emotional stress or major life events before the onset of symptoms, seen primarily in cases of rheumatoid arthritis and Graves disease [25; 47; 48; 49; 50]. In a large cohort study of Iraq and Afghanistan war veterans, men and women with a history of trauma exposure and post-traumatic stress disorder (PTSD) were found to have a significantly higher relative risk for the diagnosis of one or more autoimmune diseases than were veterans having no history of trauma or psychiatric diagnoses [295]. However, most studies have been retrospective and have lacked the statistical power to determine significance [48].

Sex Hormones

Sex hormones and their metabolites and receptors are involved in immunoregulation and the development of autoreactivity through their roles in lymphocyte maturation, activation, and synthesis of antibodies and cytokines [51]. Studies have shown that sex hormones are a factor in the pathogenesis of autoimmunity and that the expression of sex hormones is altered in individuals with autoimmune diseases [51]. Evidence for sex hormones as a causative factor is strongest for systemic lupus because of its incidence trend (i.e., high after puberty and low after menopause) and observed fluctuations in disease activity according to menstrual cycle and pregnancy [51; 52]. More research is needed to better understand the role of sex hormones in autoimmunity and in specific autoimmune diseases.

Cigarette Smoking

Cigarette smoking and exposure to tobacco smoke has also been found to be a potential trigger for autoimmune diseases, most notably rheumatic diseases (rheumatoid arthritis and systemic lupus) and, to a lesser degree, thyroiditis [53; 54]. The exact mechanisms behind the influence of cigarette smoking on the pathogenesis of autoimmune diseases are uncertain [31; 53].

Other Factors

The National Institute of Environmental Health Sciences allocated $2.4 million in grant funding in 2014 to study the role of environmental exposures/toxicants in the development of autoimmunity [314]. In addition to tobacco smoke, factors deemed relevant include exposure to crystalline silica, solvents, and ultraviolet radiation. Research topics include the consequences of environmental exposures on the development of autoimmunity, the consequences of the timing of exposure (e.g., fetal perinatal, prepubertal, pubertal, adult, and aged periods), the interplay between environmental exposures and hormonal factors, and the role of environmental factors in lymphocyte activation [314].

FEMALE PREDOMINANCE OF AUTOIMMUNE DISEASES AND FIBROMYALGIA	
Disease	**Approximate Female-to-Male Ratio**
Hashimoto thyroiditis	10:1
Sjögren syndrome	9:1
Systemic lupus erythematosus	9:1
Antiphospholipid syndrome, secondary	9:1
Primary biliary cirrhosis	9:1
Graves disease	7:1
Scleroderma	3:1
Rheumatoid arthritis	2.5:1
Antiphospholipid syndrome, primary	2:1
Multiple sclerosis	2:1
Myasthenia gravis	2:1
Source: [51; 310]	*Table 2*

GENERAL CHARACTERISTICS

Although each autoimmune disease is a distinct entity with its own constellation of signs and symptoms, many autoimmune diseases share some common characteristics, including female preponderance, similar symptom profiles, difficulty in diagnosis, importance of history and physical examination in diagnosis, and similarity in the approach to disease management.

Female Preponderance

Autoimmune disease exhibits a definite gender bias, with women accounting for nearly 80% of cases overall [21; 24; 55; 56]. The female-to-male ratio varies according to disease, from Hashimoto thyroiditis, which has a female preponderance of 95%, to vitiligo, which has a female preponderance of 52% (***Table 2***) [51; 310] However, a few diseases have been reported to occur more often in men than women, including type 1 diabetes, ulcerative colitis, Guillain-Barré syndrome, and psoriasis [55; 57].

Similar Symptom Profiles

The symptom profiles associated with autoimmune diseases are another shared characteristic. Extreme fatigue is common, and other shared symptoms include low-grade fever, dizziness, and general malaise. In addition, vague, nonspecific symptoms tend to wax and wane over the long-term, causing periods of remission with intermittent disease flare-ups. Clinical presentations with overlapping symptom profiles, along with a high rate of co-occurring autoimmune diseases, make it difficult to confirm the diagnosis of an autoimmune disease [4].

Difficulty in Diagnosis

Evidence of the difficulty in diagnosing autoimmune diseases is demonstrated in the results of surveys that have shown that individuals consult an average of 4 (and as many as 13) healthcare providers, typically over two to five years, before a confident diagnosis is reached [10; 49; 310]. There are several reasons for the difficulty. First, the initial symptoms are often subtle, nonspecific, and intermittent until the disease enters the acute stage. Symptoms can also affect many body organs, making it difficult for specialists in one area to recognize a disease within another specialty area. In addition, because many individual autoimmune diseases are rare, a primary care clinician may be unfamiliar with the clinical manifestations of each disease. Lastly, for the most part these diseases lack a single distinguishing feature or specific laboratory diagnostic test; clinicians must rely on varying combinations of information gathered from the history, physical examination, and laboratory and imaging studies [6; 60; 61; 62; 64]. Diagnostic criteria have been developed to aid in the diagnosis of some autoimmune diseases.

Importance of History and Physical Examination in Diagnosis

A careful history and comprehensive physical examination, often with repeated clinical observations over time, are usually necessary to establish the diagnosis of an autoimmune disease. Clinicians should prompt patients about symptoms that the

patient may not consider important enough to report. Clinicians should also ask about any family and personal history of autoimmune diseases.

Studies within families have shown significantly higher frequencies of autoimmune disease in general and of specific autoimmune diseases among first-degree relatives compared with controls [4]. Studies have also demonstrated that an individual with a diagnosed autoimmune disease is often at increased risk for the co-occurrence of another autoimmune disease [4]. These studies have focused primarily on individuals with an index disease of multiple sclerosis, rheumatoid arthritis, autoimmune thyroiditis (hypothyroidism), type 1 diabetes, inflammatory bowel disease, and vitiligo. Among the most significant findings are a 90-fold and 68-fold higher prevalence of Hashimoto thyroiditis and Graves disease, respectively, among individuals with systemic lupus [65].

Other studies have indicated an increased risk of type 1 diabetes and ulcerative colitis among persons with multiple sclerosis, and an increased risk of rheumatoid arthritis, multiple sclerosis, and a combined category of six other diseases (Addison disease, hemolytic anemia, primary biliary cirrhosis, immune thrombocytopenia purpura, Sjögren syndrome, and systemic sclerosis) among persons with inflammatory bowel disease [66]. In approximately 60% of individuals with Sjögren syndrome, the syndrome is secondary to another autoimmune disease, most commonly rheumatoid arthritis, systemic lupus, or systemic sclerosis [67]. Celiac disease has been associated with the co-occurrence of several autoimmune diseases, most notably Sjögren syndrome and type 1 diabetes [22; 68]. Autoimmune diseases of connective tissue have generally been associated with higher rates of co-occurrence of other autoimmune diseases [69]. Higher-than-expected rates of fibromyalgia have also been found in individuals with autoimmune diseases, most notably systemic lupus, rheumatoid arthritis, thyroiditis, and Sjögren syndrome [17; 25; 70; 71; 72].

Obtaining an accurate history necessitates effective patient-physician communication, which is challenging given the high number of people of various racial/ethnic minorities or with inadequate language proficiency or health literacy [73; 74]. Approaches to overcoming this barrier will be discussed in detail later in this course.

Approach to Disease Management

The specific treatment of autoimmune diseases depends on the particular systems or organs affected, but the overall goals of treatment are similar: to curtail the autoimmune process, reduce inflammation, relieve symptoms, and preserve organ function. This usually requires immunomodulatory/immunosuppressant drugs. Challenges in treatment are related to the complexity of symptoms, the need for long-term medications in order to preserve organ function, and the long-term adverse effects of immunosuppressant drugs. As with diagnostic criteria, practice guidelines for the treatment of autoimmune diseases are available but limited. The long-term management of individuals with autoimmune diseases requires a multidisciplinary approach, including referral to specialists such as rheumatologists, endocrinologists, gastroenterologists, neurologists, nutritionists, physical/occupational therapists, and counselors. This multidisciplinary care is best coordinated by the primary care provider, with clear articulation of specific roles. Because of the influence of stress on the immune system—coupled with the stress of a chronic disease—the management of autoimmune diseases should include stress reduction interventions [47; 48].

There is growing scientific evidence that regular, programmed physical activity is beneficial for a variety of chronic diseases, including autoimmune disease. A 2018 review highlights the salient effects of physical activity on certain aspects of the immune system and autoimmune disease expression [296]. Physical activity leads to an elevation in T-regulatory cells, decreased immunoglobulin secretion, and a decreased production of autoreactive T-cells. In addition, physical activity promotes

the release of IL-6 from muscles, and IL-6 derived from muscle has been shown to induce an anti-inflammatory response through IL-10 secretion and IL-1 beta inhibition. The beneficial role of physical activity is well-documented for patients with rheumatoid arthritis, systemic lupus, and type 1 diabetes; observed outcomes include milder disease course, decreased fatigue, improved joint mobility, enhanced quality of life, and improved cardiovascular disease profile [296].

The management of autoimmune disease is often complicated by the patient's response to the diagnosis and difficulty coping with the disease. Adherence to the treatment plan is often difficult because of denial about the diagnosis, work and life demands, and frustration with the lack of symptom response to treatment [75]. Unresolved symptoms lead to a high rate of complementary and/or alternative therapies used by individuals with autoimmune diseases [25; 49; 75; 77; 79]. The chronic nature of the conditions and the need for adherence to long-term management with frequent follow-up visits is essential for optimal outcomes but is also challenging, especially for individuals in racial/ethnic minority populations who may have different perceptions of health and the disease [80]. A strong, supportive patient-clinician relationship is integral to ensuring adherence and effective management.

Patient-Clinician Relationship in Disease Management

To enhance the patient-provider relationship, healthcare professionals are advised to gain an understanding of the patient's perspective of his or her illness or disease and to ensure that the patient's primary concerns have been addressed [81]. Patient trust in healthcare providers has been rated higher for clinicians who seek the patient's perspective of his or her illness [82]. In turn, the healthcare professional's comprehensive knowledge of the patient and higher levels of patient trust have been reported to be substantial influences on adherence to medical advice, patient satisfaction, and improved health status [82; 83]. In order to manage chronic disease safely and effectively, it is essential that patients have a conceptual understanding of their disease, the prognosis, and the benefits and risks of treatment options.

Effective communication is a cornerstone of the patient-provider relationship. Some communication behaviors that have been found to be positively associated with health outcomes include empathy, reassurance and support, explanations, positive reinforcement, humor, discussion of psychosocial issues, health education and information sharing, courtesy, and summarization and clarification [84]. Other factors essential for effective communication and a successful relationship are knowledge of the patient's language preference; an understanding of and respect for the patient's personal cultural values, beliefs, and practices (referred to as cultural competency); and an awareness of the patient's health literacy level [85; 86; 87].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

Language, cultural competency, and health literacy are significant issues, given the growing percentages of racial/ethnic populations. According to U.S. Census Bureau data from 2018, more than 44.7 million Americans are foreign-born, 67 million Americans (21.9% of the population) speak a language other than English at home, and more than 25.6 million (8.3% of the population) report that they speak English less than "very well" [88]. Clinicians should ask their patients what language they prefer for their medical care information, as some individuals prefer their native language even though they have said they can understand and discuss symptoms in English [89].

The national standards on Culturally and Linguistically Appropriate Services (CLAS) include four standards related to language access services that are mandated for healthcare organizations [85]. Although these standards are not mandated for individual healthcare providers, the Office of Minority Health encourages clinicians to meet the standards to make their practices more culturally and linguistically accessible [85]. These standards are [85]:

- Offering and providing language assistance services, including bilingual staff and interpreter services, at no cost to each patient/consumer with limited English proficiency at all points of contact in a timely manner during all hours of operation
- Providing patients with both verbal offers and written notices (in their preferred language) that inform them of their right to receive language assistance services
- Ensuring the competence of language assistance provided to patients with limited English proficiency by interpreters and bilingual staff and avoiding the use of the patient's family and friends as interpreters
- Making easily understood patient-related materials available and posting signage in the languages of the commonly encountered groups and/or groups represented in the practice area

Convenience and cost lead many clinicians to use "ad hoc" interpreters (e.g., family members, friends, bilingual staff members) instead of professional interpreters. However, professional interpreters are preferred for several reasons. Several states have laws about who can interpret medical information for a patient, so healthcare professionals should check with their state's health officials about the use of ad hoc interpreters [90]. Even when allowed by law, the use of a patient's family member or friend as an interpreter should be avoided, as the patient may not be as forthcoming with information and the family member or friend may not remain objective [90]. Children should especially be avoided as interpreters, as their understanding of medical language is limited and they may filter information to protect their parents or other adult family members [90]. Individuals with limited English language skills have actually indicated a preference for professional interpreters rather than family members [91].

Most important, perhaps, is the fact that clinical consequences are more likely with ad hoc interpreters than with professional interpreters [92]. A systematic review of the literature showed that the use of professional interpreters facilitates a broader understanding and leads to better clinical care than the use of ad hoc interpreters, and many studies have demonstrated that the lack of an interpreter for patients with limited English proficiency compromises the quality of care. The use of professional interpreters improves communication (errors and comprehension), utilization, clinical outcomes, and patient satisfaction with care [93; 94].

Cultural competency is essential for addressing healthcare disparities among minority groups [85]. Among the issues that clinicians should understand are the patients' belief systems regarding health, healing, and wellness; their perceptions on illness, disease, and their causes; their health behaviors and attitudes toward healthcare providers; and the role of the family in decision making [85]. Understanding these aspects is integral to a successful patient-clinician relationship as well as to optimal health outcomes. For example, healthcare professionals should raise the topic of health-related customs, such as the use of complementary and alternative medicines because such use varies substantially among racial/ethnic populations and according to geographic area; may compromise the effect of traditional therapies; and is often not disclosed by the patient [25; 96; 97].

Knowledge of the patient's health literacy is also important, as the patient's understanding of his or her disease and its management is essential to ensuring adherence to the treatment plan and the patient's role in self-management. Yet most individuals lack adequate health literacy. According to the National Assessment of Health Literacy, 14% of individuals in the United States have "below basic" health literacy, which means they lack the ability to understand health information and make informed health decisions [73; 98]. A systematic review of more than 300 studies showed that an estimated 26% of patients had inadequate literacy and an additional 20% had marginal literacy [99].

Health literacy varies widely according to race/ethnicity, level of education, and gender, and clinicians are often unaware of the literacy level of their patients [87; 100]. Predictors of limited health literacy are poor self-rated reading ability, low level of education, male gender, and nonwhite race [100; 101]. Several instruments are available to test patients' literacy levels, and they vary in the amount of time needed to administer and in their reliability in identifying low literacy [73; 87; 100; 102].

Clinicians should adapt their discussions and educational resources to a patient's identified health literacy level and degree of language proficiency. The use of plain language (free of medical jargon), asking patients to repeat pertinent information, regularly assessing recall and comprehension, providing educational resources in a variety of formats (e.g., print, oral, web-based, video), and using culturally appropriate and translated educational materials can all help ensure that patients better understand their disease and its management, ultimately leading to higher quality care.

THYROIDITIS

Thyroiditis is the most common autoimmune disease. Autoimmune thyroiditis encompasses both Hashimoto thyroiditis, also known as chronic lymphocytic thyroiditis, and Graves disease. Hashimoto disease and Graves disease are the leading causes of hypothyroidism and hyperthyroidism, respectively [50; 103]. Hashimoto disease is more common than Graves disease [13; 104].

Hashimoto disease (chronic autoimmune thyroiditis) is characterized by an intense lymphocytic (T cell and B cell) infiltration of the gland and local production of antithyroid antibodies that reach high titer in the serum. Over time, thyroid tissue is gradually destroyed or replaced, thyroid hormone levels decline, and hypothyroidism supervenes. Thus, Hashimoto disease may present as either subclinical or overt hypothyroidism; subclinical disease is the more commonly encountered of the two in the primary care setting [104]. Left untreated, hypothyroidism can cause fatigue, weight gain, mental slowing, heart failure, and elevated lipid levels.

In Graves disease, circulating thyroid antibodies target the TSH receptor, which stimulates the thyroid gland, causing enlargement of the thyroid gland and increased production of thyroid hormone. As with Hashimoto disease, thyroid dysfunction with Graves disease may be subclinical or overt. Mild ophthalmopathy is present in as many as half of individuals with Graves disease, and severe ophthalmopathy occurs in 3% to 5% [50; 105]. This ophthalmopathy is the result of edema and lymphocytic infiltration of orbital fat, connective tissue, and eye muscles, and exophthalmos is the characteristic sign of Graves disease [106]. If not treated, overt hyperthyroidism can result in atrial fibrillation, congestive heart failure, osteoporosis, and neuropsychiatric problems.

EPIDEMIOLOGY

According to the results of the 2007–2012 population-based National Health and Nutrition Examination Survey III (NHANES III) , the prevalence of hypothyroidism in the United States is approximately 3.7% and the prevalence of hyperthyroidism is approximately 3.4% [13; 104]. Subclinical hypo- and hyperthyroidism are far more prevalent than overt disease (3.5% compared with 0.2%, and 3.1% compared with 0.3%, respectively) [104; 283].

Hashimoto thyroiditis usually begins between the ages of 30 and 50 years and is nearly 10 times more common in women than in men [51; 107; 108]. The prevalence of hypothyroidism (subclinical and overt) increases with age; the odds for hypothyroidism are five times greater for individuals 80 years or older than for individuals 12 to 49 years of age [13]. The rate of subclinical hypothyroidism has been reported to be as high as 15% to 20% among women 60 years of age and older [104; 109; 110]. Graves disease typically occurs between the ages of 40 to 60 years and is about eight to nine times more common in women than men [51].

Data on the prevalence of autoimmune thyroiditis among racial/ethnic populations are limited. The prevalence of antithyroid antibodies has been greater in the white and Mexican American populations than in the black population [104]. Among the Mexican American population, the risk for hypothyroidism has been found to be the same as that for the non-Hispanic white population, but the risk for hyperthyroidism is higher [13]. The risk for hypothyroidism is lower and the risk for hyperthyroidism is higher for the non-Hispanic black population compared with the non-Hispanic white population [13].

POTENTIAL ENVIRONMENTAL RISK FACTORS

In individuals with genetic susceptibility, iodine deficiency, infection, smoking, and stress have been identified as environmental triggers for both types of autoimmune thyroiditis [54]. Recent childbirth may be an additional trigger for Graves disease [50].

ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

A coexisting autoimmune disorder is present in approximately 14% of individuals with Hashimoto disease and nearly 10% of individuals with Graves disease [111]. In a British study involving more than 3,000 individuals with autoimmune thyroiditis, rheumatoid arthritis was the most common coexisting autoimmune disorder, appearing in approximately 4% of individuals with Hashimoto disease and 3% of those with Graves disease [111]. Among the other autoimmune disorders that have been found to be associated with Hashimoto thyroiditis are pernicious anemia, systemic lupus, Addison disease, celiac disease, Sjögren syndrome, systemic sclerosis (scleroderma), type 1 diabetes, and vitiligo [111; 112; 113]. The frequency and type of nonthyroidal autoimmune disease in patients with Hashimoto thyroiditis varies with age at presentation. In a study of 1,053 newly diagnosed patients (500 adults and 553 children/adolescents), the prevalence of associated autoimmune diseases was significantly higher in adults, as was the likelihood of a patient suffering from two or more nonthyroidal autoimmune disorders [297]. Furthermore, the cluster of associated diseases was distinctly different in the two cohorts. Rheumatoid arthritis and systemic lupus were encountered almost exclusively in adults (6.4% compared with 0.18% in children/adolescents) and type 1 diabetes and celiac disease in children and adolescents (14.1% compared with 2.2% in adults). The authors concluded that common age-related autoimmune mechanisms may contribute to the pathogenesis of coexisting autoimmune diseases.

Genetic studies have indicated a close relationship between type 1 diabetes and autoimmune thyroid disease, and a fourfold risk of thyroiditis has been found among individuals with type 1 diabetes [4; 38]. In a small study (254 participants), nonthyroid autoimmune diseases were found in approximately 9% of individuals with Graves disease, and the specific nonthyroid diseases varied according to the presence or absence of ophthalmopathy [112]. Type 1 diabetes was the most prevalent disease among individuals who did not have ophthalmopathy (approximately 7%), and vitiligo was the most prevalent autoimmune disease among those who had ophthalmopathy (4%) [112].

CLINICAL MANIFESTATIONS

Both Hashimoto disease and Graves disease may be present with no symptoms or with subtle, nonspecific symptoms, especially with early or subclinical disease. With Hashimoto disease, approximately 20% of individuals have symptoms at the time of diagnosis, although symptoms may not develop until years after thyroid dysfunction [114]. Symptoms of Graves disease are usually present for at least two to three months before diagnosis [50].

The symptoms associated with Hashimoto disease are the same regardless of whether hypothyroidism is present. In addition to nonspecific symptoms, such as fatigue, weakness, lethargy, and muscle aches, hypothyroidism can also affect a variety of body systems (***Table 3***) [108; 113; 115].

SIGNS AND SYMPTOMS OF AUTOIMMUNE THYROID DISEASE		
Body System	**Hashimoto Disease**	**Graves Disease**
General	Fatigue Weakness Lethargy Hypothyroid speech Forgetfulness Increased sensitivity to medications	Fatigue Weakness Sleep disturbances
Psychiatric	Depression	Emotional instability Nervousness, anxiety
Metabolic	Weight gain Cold intolerance	Weight loss Heat intolerance
Skin	Pale, dry, cold skin (may appear jaundiced) Coarse skin Thick, brittle nails Dry, coarse, brittle hair or hair loss	Warm, moist skin Pretibial myxedema Hair loss
Cardiovascular	Slow pulse Bradycardia Diastolic hypertension Peripheral edema	Rapid pulse (≥90 beats/minute) Tachycardia, palpitations, atrial fibrillation Elevated systolic and diastolic blood pressure Edema Dyspnea on exertion
Pulmonary	Slow, shallow respirations	Shortness of breath Increased respiratory rate and depth
Neurologic	Delayed ankle reflexes	Fine finger/hand tremor
Musculoskeletal	Sore muscles Pain and/or stiffness in joints	Proximal muscle weakness or wasting Back pain History of fractures
Digestive	Constipation	Increased appetite Diarrhea Vomiting Abdominal pain
Hematologic	Easy bruising Macrocytic anemia Normocytic normochromic anemia	Easy bruising
Renal	—	Polyuria Polydipsia
Reproductive	Menorrhagia Irregular periods Decreased libido Increased rate of miscarriage, still birth, and fetal death	Amenorrhea Irregular periods Decreased fertility Increased risk for miscarriage
Ophthalmologic	—	Tearing Gritty sensation Eye discomfort/pain Diplopia Exophthalmos
Source: [50; 106; 108; 113; 115]		*Table 3*

DIAGNOSTIC ACCURACY OF CLINICAL FINDINGS FOR THYROIDITIS		
Sign/Symptom	**Sensitivity**	**Specificity**
Hypothyroidism		
Hypothyroid speech	37%	93%
Cool and dry skin	16%	97%
Slow pulse rate	29% to 43%	89% to 93%
Coarse skin	29% to 61%	74% to 95%
Delayed ankle reflexes	48%	86%
Hyperthyroidism		
Eyelid retraction	34%	99%
Eyelid lag	19%	99%
Fine finger tremor	69%	94%
Warm and moist skin	34%	95%
Pulse ≥90 beats/minute	80%	82%
Source: [106]		*Table 4*

Fatigue and weakness are also among the most common symptoms associated with Graves disease, and as with Hashimoto disease, symptoms can be related to many body systems, with the overactivity of the thyroid having the opposite effect [50; 106; 113; 115]. For example, hypothyroidism is typically associated with bradycardia, while hyperthyroidism is usually associated with a rapid, bounding pulse and/or palpitations.

DIAGNOSTIC EVALUATION

Because of the frequency of nonspecific symptoms and the wide array of other symptoms, healthcare professionals should elicit a detailed history, with emphasis on questions related to [115; 315]:

- Appetite, recent unexplained weight loss, or weight gain
- Tightness, fullness, or pain in the neck
- Eye pain or discomfort, changes in visual acuity
- Nervousness and/or anxiety
- Emotional status
- Abdominal pain
- Constipation or diarrhea
- Exertional dyspnea
- Increased perspiration
- Heat or cold intolerance
- Regularity of menstrual cycles
- Sleep disturbances
- Hair loss

The comprehensive physical examination should begin with assessment of blood pressure, weight, pulse, and other vital signs. A slow pulse is a clinically significant finding of hypothyroidism, and a rapid pulse (i.e., 90 beats per minute or more) is a clinically significant finding of hyperthyroidism (***Table 4***) [106]. Among individuals with hyperthyroidism, tachycardia occurs less often among older individuals than younger ones [50].

Palpation and auscultation of the thyroid should be done to determine if the gland is enlarged and if nodules are present. In individuals with hypothyroidism, the thyroid gland may not be palpable or a goiter may be present [113]. An enlarged thyroid gland is a significant sign of hyperthyroidism, occurring in 70% to more than 90% of individuals with the disorder [106]. The goiter associated with hyperthyroidism is typically diffuse and symmetric, which distinguishes Graves disease from toxic nodular goiter, in which nodes are usually felt on palpation of the goiter.

Evaluation of the skin is also important. Skin that is both cool and dry is a clinically significant finding for hypothyroidism; the skin may also feel coarse or appear pale or yellowish [106]. Skin that is both warm and moist is a significant finding for hyperthyroidism. Hair loss is common with both types of thyroiditis.

An eye examination is integral to the diagnosis of Graves disease, as exophthalmos is a hallmark characteristic and is often the first sign of this disease. Eyelid retraction is the most clinically significant finding of hyperthyroidism, followed by eyelid lag; other ophthalmologic signs of Graves disease are periorbital edema and limited eye movements [106].

Hypothyroid speech—a low-pitched, hyponasal voice (as if speaking with a cold), spoken at a slow pace—is found in about one-third of individuals with hypothyroidism [106]. This speech is the finding with the most clinical significance for diagnosis of hypothyroidism [106].

A neurologic evaluation is also useful in the diagnosis. Delayed ankle reflexes are a clinically significant finding of hypothyroidism, and fine finger tremor is a clinically significant finding of hyperthyroidism [106]. Tremor is less likely to occur in older than younger individuals with hyperthyroidism [50].

No single clinical finding, when absent, is significant for ruling out hypothyroidism [106]. The lack of thyroid enlargement, a pulse of less than 90 beats per minute, and the absence of finger tremor are findings with the most significance in ruling out hyperthyroidism [106].

Among the differential diagnoses that should be considered when evaluating an individual with suspected Hashimoto thyroiditis are chronic thyroiditis, thyroid nodules, euthyroid sick syndrome, and lymphoma of the thyroid [106]. The differential diagnosis for Graves disease includes toxic nodular goiter, subacute thyroiditis, and papillary carcinoma of the thyroid [106].

Laboratory Testing

Thyroid function tests can confirm a diagnosis of Hashimoto thyroiditis or Graves disease. The single best screening test for either disease is the sensitive TSH assay (also known as thyrotropin level), and the free thyroxine (T4) level and the total triiodothyronine (T3) level also help confirm the diagnosis [113; 115; 316]. An elevated TSH level with low levels of T3 and free T4 indicates hypothyroidism [108; 113]. Subclinical hypothyroidism is indicated by a repeatedly high TSH level with normal free T4 and T3 levels [108; 113]. In contrast, a low TSH level with increased T3 and T4 levels indicates hyperthyroidism [50]. The patient's history is important to remember when interpreting the results of laboratory testing, as a low TSH level can also be caused by glucocorticoids, dopaminergic drugs, severe illness, pregnancy, diurnal variation, or pituitary dysfunction; elevated TSH levels may be caused by adrenal insufficiency [113]. Thyroid autoantibodies (i.e., thyroid peroxidase and thyroglobulin antibodies) may be helpful in the diagnosis [113; 316].

Other Testing

A radioiodine-uptake scan is not useful in diagnosing hypothyroidism, but it can help distinguish hyperthyroidism from subacute thyroiditis, which is associated with low uptake values, and from multinodular toxic goiter [50]. If a radioiodine-uptake scan is not possible, ultrasonography of the thyroid gland may be done instead, and increased blood flow by Doppler correlates with an increased uptake [50]. Ultrasonography is also useful for detecting nodules and evaluating suspicious structural abnormalities [50; 113]. A fine-needle biopsy should be done to exclude malignancy when a dominant nodule is present [50; 107].

SCREENING FOR THYROID DISEASE

The issue of regular thyroid function screening is controversial. In 1998, the American College of Physicians recommended screening for women older than 50 years of age who have at least one general symptom that could be caused by thyroid disease [116]. Two years later, the American Thyroid Association recommended measuring thyroid function in all adults beginning at age 35 years and every five years thereafter and noted that more frequent screening may be appropriate for high-risk or symptomatic individuals [117]. In 2011, the American Academy of Family Physicians found insufficient evidence to recommend for or against routine thyroid screening in asymptomatic adults, and the American College of Obstetricians and Gynecologists recommended that physicians be aware of the symptoms and risk factors for postpartum thyroid dysfunction and evaluate patients when indicated [118; 119]. In 2004, the U.S. Preventive Services Task Force concluded that the evidence was insufficient to recommend for or against routine screening for thyroid disease in adults. The Task Force noted that while there was fair evidence that TSH testing can detect subclinical thyroid disease in asymptomatic individuals, there was poor evidence that treatment improves clinically important outcomes in adults with thyroid disease detected through screening [120].

Despite the potential for serious adverse events associated with either type of autoimmune thyroiditis, the American Association of Clinical Endocrinologists (AACE) recommends "aggressive case finding" (i.e., using symptoms, family history, and personal history of thyroid damage, autoimmune disorders, or abnormal thyroid exam) rather than universal TSH testing for women of childbearing age before or during pregnancy [113]. There is insufficient evidence to support universal screening in this group, mainly because the impact of outcomes has not been demonstrated. Additionally, the AACE warns of the potential for harm with treatment during pregnancy. If testing is performed, the AACE recommends that measurement of total T4 or a free T4 index, in addition to TSH, be done to assess thyroid status [113].

The AACE recommends hypothyroidism screening for individuals older than 60 years of age, especially women [113]. However, hypothyroidism is common in older patients and the evidence supporting benefit or cost effectiveness is insufficient.

TREATMENT OPTIONS

Both the AACE and the American Thyroid Association have developed guidelines for the treatment of hypothyroidism and hyperthyroidism [113; 115]. Treatment of either thyroid dysfunction must be tailored to the individual patient, and the patient should have a clear understanding of the indications and implications of all forms of therapy, including risks, benefits, and side effects. Clinicians should also encourage the patient to be an active participant in the decision-making process regarding the type of therapy. The goal of treatment for either condition is to achieve a euthyroid state.

Hashimoto Disease

The AACE states that most primary care clinicians can diagnose and treat hypothyroidism, but the organization recommends consultation with an endocrinologist for patients with [113]:

- Age 18 years or younger
- Pregnancy (or planned pregnancy)
- Cardiac disease
- Disease that is unresponsive to treatment
- Another endocrine disease
- A goiter, nodule, or other structural change in the thyroid gland
- Unusual causes of hypothyroidism or hypothyroidism caused by medications or medical conditions

Overt hypothyroidism involves lifelong thyroid replacement medication, typically levothyroxine. Various brands of the medication are available, and the AACE recommends using a high-quality brand, with the same brand used throughout treatment in order to maintain consistency [113].

Levothyroxine is prescribed as a daily, oral dose, and treatment begins with a low dose and is gradually titrated up according to the results of TSH testing [113; 115]. An initial daily dose of 25–50 mcg has been recommended; lower doses may be more appropriate for older individuals or those with cardiovascular disease [107; 108]. The AACE notes that the mean full replacement dosage is 1.6 mcg/kg per day [113]. Clinical evaluation of the patient and TSH testing should be done every four to eight weeks after a change in dose [113].

When titrating the dose of levothyroxine, healthcare professionals must consider the effects of other drugs the patient takes. Many drugs, including cholestyramine, ferrous sulfate, sucralfate, calcium, and some antacids containing aluminum hydroxide, can interfere with levothyroxine absorption [113]. Also, rifampin and sertraline may accelerate levothyroxine metabolism, calling for a higher replacement dose [113].

It should be noted that a small cohort of patients will retain signs of neurocognitive dysfunction, despite normal serum TSH and free T4, perhaps because more than half of the T3 in the brain is produced locally [317]. Results of a large clinical trial demonstrated that patients carrying a polymorphism in the Dio2 gene are particularly prone to this outcome, and combination treatment with liothyronine is beneficial for patients with persistent neurocognitive symptoms in spite of normal serum concentrations of TSH and free T4 [317].

Hashimoto Disease Without Hypothyroidism

Recommendations have also been made for individuals who have Hashimoto disease without hypothyroidism (i.e., who have a goiter but normal TSH levels). Treatment is not required for individuals who are asymptomatic and have a small goiter. However, many endocrinologists prescribe levothyroxine for patients with a goiter, even if the level of TSH is normal, with a goal of decreasing the size of the goiter [107].

Subclinical Hypothyroidism

The appropriate approach to subclinical hypothyroidism has been debated. Proponents of treatment note that although subclinical hypothyroidism is usually asymptomatic, treatment has been shown to offer benefit in reducing the risks of several adverse events, including cardiovascular events, hyperlipidemia, and neuropsychiatric effects [121; 122; 123; 124; 125]. In addition, subclinical hypothyroidism can progress to overt hypothyroidism, with a wide range in risk of progression (3% to 20%) [108; 113].

Despite a recommendation to treat subclinical hypothyroidism, there is no consensus on the TSH level that should prompt treatment [113; 126]. The AACE recommends treatment for individuals with subclinical hypothyroidism and a TSH level greater than 10 IU/mL especially if patients have symptoms of hypothyroidism, positive anti-thyroid peroxidase antibodies (TPOAb), or evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors for these diseases [113]. Treatment should also be considered for individuals who have a strong family history of thyroid disease, who are pregnant, who have a history of heavy tobacco use, and/or who have severe lipidemia [108]. As with the treatment of overt hypothyroidism, the dose should be adjusted according to the TSH level. The TSH target recommend by AACE guidelines for non-pregnant patients should be the normal range of a third generation TSH assay (or between 0.45 and 4.12 mIU/L, when not available), and the level should be determined every six to eight weeks until the target has been reached [113]. More studies are needed before thyroxine replacement therapy can become the standard of care for subclinical hypothyroidism [108; 113].

Hypothyroidism During Pregnancy

Hypothyroidism (even if mild) during pregnancy can have serious adverse effects for both the mother (e.g., hypertension, pre-eclampsia, postpartum hemorrhage) and fetus (e.g., spontaneous abortion, fetal death or stillbirth, low birth weight, abnormal brain development) [113]. The AACE states that pregnant women who have or have had positive levels of serum TPOAb and with a TSH greater

than 2.5 mIU/L should be treated with levothyroxine [113]. Additionally, treatment should be considered if they have or have had positive levels of serum TPOAb, particularly when there is a history of miscarriage or hypothyroidism [113]. Women with positive levels of serum TPOAb or with a TSH greater than 2.5 mIU/L who are not being treated with levothyroxine should be monitored every 4 weeks in the first 20 weeks of pregnancy for the development of hypothyroidism [113].

Thyroid function should be monitored every 4 weeks during the first half of pregnancy and at least once between 26 and 32 weeks' gestation to ensure that the requirement for L-thyroxine has not changed; the dose of thyroxine should be adjusted accordingly [113]. Some clinicians may prefer to continue regular monitoring throughout gestation. The upper limit of the normal range should be based on trimester-specific ranges for that laboratory. If ranges are not available in the laboratory, the following upper normal TSH reference ranges are recommended [113]:

- First trimester: 2.5 mIU/L
- Second trimester: 3.0 mIU/L
- Third trimester: 3.5 mIU/L

Graves Disease

As noted, the goal of treatment of Graves disease is to make the thyroid function normally or to disable the gland completely and treat the resultant hypothyroidism. The three primary treatment options are radioactive iodine (usually ^{131}I), antithyroid drugs, or thyroidectomy. In addition, treatment with a beta blocker is recommended to provide relief of symptoms (such as tremor, palpitations, and sweating) until a euthyroid state is reached [115].

Treatment with Radioactive Iodine

Treatment with ^{131}I is considered to be the treatment of choice for most people; however, pregnancy and breastfeeding are absolute contraindications [115]. A pregnancy test should be obtained 48 hours before treatment with ^{131}I for all women of childbearing age who are sexually active.

The isotope is given orally (as a capsule or in water), and there is no consensus on the optimal dose [127]. The dose is usually determined with a dose-calculation algorithm, and the typical dose range is 5–15 mCi of ^{131}I [115; 127]. Randomized trials have shown no significant differences in outcome between the use of calculated doses and fixed doses, and fixed doses are now used in many institutions [128; 129].

Treatment with antithyroid drugs may be indicated for some individuals, particularly older individuals or those with cardiac disease, before administration of ^{131}I. Antithyroid drugs should be stopped one week before treatment with radioactive iodine is begun and should not resume until approximately six weeks after treatment.

The American Thyroid Association and the AACE recommend that individuals be followed up within the first one to two months after treatment to monitor the transition to a euthyroid and/or hypothyroid state [115]. Hypothyroidism can occur at any time after treatment, but most commonly occurs within two to six months [50]. Treatment with partial replacement doses of levothyroxine can usually begin two months after treatment. The timing of thyroid-replacement treatment depends on the findings of laboratory testing and clinical evaluation [115].

The cure rate for treatment with radioactive iodine is more than 80% [130]. Retrospective studies have shown that factors associated with a lack of response to ^{131}I are a young age, a large thyroid, severe thyrotoxicosis, previous exposure to antithyroid drugs, and a higher ^{131}I uptake value [131; 132]. When necessary, a second dose should be given at least 6 to 12 months after the initial treatment, and antithyroid drugs should be stopped before and after a second treatment [127].

Treatment with ^{131}I is safe, with the primary side effects being acute radiation thyroiditis and hypothyroidism; there is no adverse effect on fertility or on offspring conceived after treatment [50; 115]. Radioactive iodine administration is the recommended modality for women who wish to become pregnant four to six months after treatment.

The findings of some studies have suggested an increased risk for some types of cancer after treatment with ^{131}I, but the results of other studies have demonstrated conflicting data, with no increases in the incidence of cancer [133; 134].

Treatment with Antithyroid Drugs

Antithyroid drugs (thionamides) interfere with thyroid hormone synthesis by preventing iodine from combining with tyrosine residues in thyroglobulin [135]. This approach is usually the treatment of choice for pregnant women, children and adolescents, and individuals who have severe Graves ophthalmopathy [127; 135]. The goal of treatment is to achieve remission, defined as a biochemical euthyroid state for a minimum of one year after discontinuing treatment [115; 135].

The most frequently prescribed antithyroid drugs are methimazole and propylthiouracil [135]. Methimazole has become the preferred drug in the United States, especially after a 2009 U.S. Food and Drug Administration (FDA) Safety Alert noting reports of severe liver injury and acute liver failure (some fatal) in both adults and children treated with propylthiouracil [136]. The FDA recommended that physicians should "carefully consider" the choice of drug for newly diagnosed Graves disease and that propylthiouracil should not be used in children and adolescents unless the patient is allergic to or intolerant of methimazole and no other treatment options are available [136]. The FDA now requires a boxed warning on the label of propylthiouracil to alert clinicians about the risk of liver damage.

The AACE and the American Thyroid Association recommend the use of methimazole for nearly every patient; however, propylthiouracil should be used during the first trimester of pregnancy, for treatment of thyroid storm, and in patients with minor reactions to methimazole who refuse radioactive iodine therapy or surgery [115]. Antithyroid drug therapy can be given in two ways: a titration regimen or a block-replace regimen. With a titration regimen, the initial dose is high and the dose is tapered over time. With a block-replace regimen, a high dose of an antithyroid drug is given, followed by levothyroxine once a euthyroid state has been reached. No difference in efficacy has been found between the two methods, according to a systematic review of the literature published in 2010 [138]. The block-replace regimen, however, was associated with a higher rate of adverse effects [138].

The starting dose depends on the severity of the hyperthyroidism, and the typical starting doses have been 10–40 mg/day for methimazole and 100–600 mg/day (in divided doses) for propylthiouracil [115; 130]. The starting dose is tapered according to the results of thyroid function testing, which should be done once a month until symptoms start to resolve and then every two to three months [127; 130]. The results of thyroid function testing are also considered when tapering the dose; testing should be done every month. Use of a block-replace regimen requires less frequent testing [130]. Typical maintenance doses are 5–20 mg/day of methimazole or 100–200 mg/day of propylthiouracil [127; 130].

Two starting doses of methimazole (15 mg/day and 30 mg/day) and propylthiouracil (300 mg/day) were compared in a small randomized study in Japan (240 participants) [137]. Overall, the 30 mg/day dose of methimazole normalized the serum free T4 level in significantly more individuals than the 15 mg/day dose or propylthiouracil at 12 weeks [137]. The higher dose of methimazole was also significantly more effective in the subgroup with severe hyperthyroidism (free T4 level: 7 ng/dL or greater), but there was no difference among the three treatments in the subgroup with mild or moderate disease (free T4 level: less than 7 ng/dL) [137].

With regard to duration of therapy, one year of treatment has been reported to offer better rates of remission than six months of treatment [50]. However, there has been no significant difference in remission rates at two years between individuals treated for longer than 18 months compared with those treated for 18 months [50]. A systematic

review indicated that the optimal duration of a titration regimen was 12 to 18 months [138]. The AACE and the American Thyroid Association recommend methimazole be continued for 12 to 18 months, at which point it should be tapered and discontinued if the TSH level is normal [115]. If disease is not in remission after 12 to 18 months, thyroidectomy or 131I should be considered; low-dose methimazole is recommended if these options are refused or contraindicated.

Hyperthyroidism will recur after antithyroid drug therapy in approximately 30% to 60% of individuals [50; 130]. Studies have suggested that recurrence after antithyroid drug therapy is associated with several factors, including [50; 127; 135]:

- Severe hyperthyroidism
- Long duration of symptoms before initiation of treatment
- Age younger than 40 years
- Male gender
- Family history of autoimmune thyroid disease
- History of cigarette smoking
- Presence of clinical ophthalmopathy
- High serum T3 and T4 concentrations
- Large goiter at diagnosis and/or at end of therapy

However, the association between recurrence and any of these individual factors has not been strong enough to warrant use as a risk stratification factor [127]. Thyroid function tests should continue for 6 to 12 months (at 1- to 3-month intervals) to diagnose relapse early; patients should be vigilant about recognizing the signs of hyperthyroidism [115]. Another course of antithyroid drug therapy, treatment with radioactive iodine, or surgery can be used to treat recurrent hyperthyroidism [130].

Side effects occur in approximately 5% of individuals receiving antithyroid drugs [130]. The most common side effects are rash, arthralgia, gastrointestinal problems, and changes in taste/smell [130]. The most serious side effect, occurring in about 0.1% to 0.3% of individuals, is agranulocytosis [50]. The risk of agranulocytosis increases with higher drug doses and with age and can occur at any time during the course of treatment [50; 137].

Thyroidectomy

Surgery was once frequently used to treat hyperthyroidism, but it is now the least-used treatment option. The AACE and the American Thyroid Association recommend that the specific indications for thyroidectomy are a large goiter, especially with compressive symptoms (which may be resistant to radioactive iodine treatment); severe ophthalmopathy (because of the risks associated with radioactive iodine); or an allergy or intolerance to antithyroid drugs [115]. The primary advantage of thyroidectomy is that it provides definitive treatment of hyperthyroidism with none of the hazards associated with radioactive iodine, the other option with a good cure rate [127; 138]. In addition, surgery offers a rapid normalization of thyroid function [127]. Thyroidectomy usually results in hypothyroidism, occurring in 12% to 80% of individuals during the first year and at a subsequent annual rate of 1% to 3% [127].

Thyroidectomy is associated with a low rate of complications and a mortality rate of nearly zero [50; 115; 127]. This is particularly true if the surgery is performed by a high-volume thyroid surgeon [115]. Total thyroidectomy is recommended over subtotal thyroidectomy because it has been associated with similar complication rates but better cure rates (near 0% recurrence versus 8% recurrence at five years, respectively) [115; 139].

Treatment of Subclinical Hyperthyroidism

There is no consensus on whether subclinical hyperthyroidism should be treated. Treatment is generally unnecessary in younger individuals, but the AACE and the American Thyroid Association recommend that individuals 65 years of age or older with a TSH level persistently less than 0.1 mU/L should be strongly considered for treatment or treated using the same principles as outlined for overt hyperthyroidism [115].

Treatment During Pregnancy

As with hypothyroidism, hyperthyroidism can have serious adverse effects during pregnancy, and the goal of treatment is to maintain a euthyroid state with the lowest possible dose of an antithyroid drug. In general, propylthiouracil has been the preferred drug because it crosses the placenta less than methimazole and because methimazole has caused rare cases of embryopathy (including aplasia cutis) [115; 136]. Propylthiouracil is considered more appropriate during the first trimester, even given the FDA warning regarding liver damage [136]. Methimazole should be used when antithyroid treatment is started after the first trimester [115; 141]. Pregnant women with Graves disease should be followed up at intervals of three to four weeks (or more frequently, if necessary); pregnancy has an ameliorative effect on hyperthyroidism, and it may be possible to lower the dose of the antithyroid drug or to discontinue its use in the third trimester [115; 141]. The lowest possible dose should be used to keep total T4 and T3 levels slightly above the normal range [115]. Women treated for hyperthyroidism during pregnancy should be re-evaluated at six weeks postpartum, as disease can worsen at that time [115; 141].

The Endocrine Society asserts that subtotal thyroidectomy may be indicated during pregnancy as therapy for maternal Graves disease if 1) a patient has a severe adverse reaction to antithyroid drug therapy, 2) persistently high doses of antithyroid drug are required, or 3) a patient is nonadherent to antithyroid drug therapy and has uncontrolled hyperthyroidism. The optimal timing of surgery is in the second trimester.

(https://academic.oup.com/jcem/article/97/8/2543/2823170. Last accessed July 23, 2020.)

Strength of Recommendation/Level of Evidence: C (At least fair evidence that the service can improve health outcomes but the balance of benefits and harms is too close to justify a general recommendation)

Treatment of Ophthalmopathy

The primary problems caused by Graves ophthalmopathy are dryness, redness, and edema. The AACE and the American Thyroid Association recommend that the overall evaluation and management of the condition is best done in a multidisciplinary clinic combining endocrinologists and ophthalmologists with experience treating Graves ophthalmopathy [115]. Many nonpharmacologic measures for symptoms related to mild Graves ophthalmopathy, including artificial tears for lubrication, sunglasses to decrease photophobia, eye protectors during sleep, and elevation of the head of the bed to decrease periorbital edema, have been recommended Other interventions include a diuretic at bedtime, application of cool compresses to the eyes, increased fluid intake, and avoidance of secondhand smoke, ceiling fans, and contact lenses. Treatment may include glucocorticoids, retro-orbital radiation, or surgery. In 2020, the first medication was approved for the treatment of thyroid eye disease. Teprotumumab is administered as an IV infusion to adults with thyroid-associated ophthalmopathy [293].

Treatment of Thyroid Storm

A complication of Graves disease is thyroid storm, a syndrome characterized by exaggerated signs and symptoms of hyperthyroidism accompanied by fever and altered mental status. Thyroid storm is most often precipitated by a concurrent illness or injury and may also occur following discontinuation of treatment with antithyroid drugs or with radioactive iodine [115; 142]. The diagnosis of thyroid storm relies on clinical evaluation, as laboratory testing cannot distinguish thyroid storm from uncomplicated hyperthyroidism [115]. Thyroid storm is a complex, life-threatening syndrome, and an endocrinologist should be involved in the care. Individuals with thyroid storm should be treated in the intensive care unit, with treatment consisting of an antithyroid drug, a drug that inhibits release of thyroid hormone from the thyroid gland, and agents that decrease the peripheral effects of thyroid hormone [115; 142].

POINTS OF EMPHASIS IN PATIENT EDUCATION FOR AUTOIMMUNE THYROID DISEASE TREATMENTS	
Treatment	**Education Points**
Hashimoto Disease	
Levothyroxine	Take drug: • At same time every day • With full glass of water • When stomach is empty • Avoid the use of antacids
Graves Disease	
Radioactive iodine	Abstain from close personal contact for one week after treatment (two weeks for children and pregnant women). Avoid pregnancy for 4 to 6 months after treatment.
Antithyroid drugs	Recognize signs and symptoms of agranulocytosis (fever, sore throat, mouth ulcers), and stop taking drug if they occur.
Source: [50; 108; 113]	*Table 5*

FOLLOW-UP AND PROGNOSIS

The AACE and the American Thyroid Association recommend annual follow-up visits for patients with either Hashimoto or Graves disease, after a stable TSH level has been achieved [115]. Both organizations recommend that a TSH level be determined at least annually [115]. This monitoring is important, as studies have shown that as many as 40% of individuals taking thyroid medication do not have a TSH level within the normal range [12; 13]. Clinicians should also ask direct questions about compliance with drug therapy.

Routine follow-up visits provide healthcare professionals with the opportunity to evaluate patients for signs or symptoms of other autoimmune diseases, especially those that have been reported to be associated with thyroiditis, such as rheumatoid arthritis, systemic lupus, pernicious anemia, and vitiligo [111; 112]. In addition, because of the strong association between thyroiditis and type 1 diabetes, the patient should be evaluated closely for signs of this disease [4; 38; 112].

For patients with Hashimoto disease, clinicians should carefully examine the thyroid during follow-up visits, as lymphoma of the thyroid is a serious, yet rare, complication [107]. The FDA recommends that patients taking propylthiouracil for Graves disease be closely monitored for signs and symptoms of liver injury, especially within the first six months after the start of treatment [136]. Individuals with subclinical hypothyroidism should be followed up annually to determine if there are clinical or biochemical signs of loss of thyroid function, indicating progression to overt hypothyroidism [108; 113].

The prognosis for individuals with autoimmune thyroid disease is good, and associated mortality for either autoimmune thyroid disease is low [27]. Remission and mortality vary according to treatment, as discussed.

PATIENT EDUCATION

A member of the healthcare team should explain the particular type of thyroid disease to the patient, focusing on how the patient can participate in his or her own care. Patient education should emphasize the importance of adhering to drug therapy and the recognition of signs and symptoms of complications (***Table 5***) [108; 113; 138]. For example, women should understand the increased risk of birth-related events associated with autoimmune thyroid disease [113]. In addition, clinicians should highlight the need for patients to report any changes in symptoms or the occurrence of new symptoms, which may indicate the response to therapy or the development of another autoimmune disease. Clinicians may also refer patients to reliable online educational resources.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic disease characterized by inflammation of synovial tissue that can lead to long-term damage of the joint, resulting in chronic pain, loss of function, and disability. A cytokine network, which includes tumor-necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6, has an integral role in the development of the inflammatory response [48]. The disease is also associated with several extra-articular manifestations and comorbidities [143; 144]. The course and severity of the illness vary considerably, and the disease tends to progress over time, with the occurrence of intermittent disease flares.

Most mortality studies in patients with rheumatoid arthritis have found increased death rates compared with the general population; one-third to one-half of the premature deaths in patients with rheumatoid arthritis are due to cardiovascular conditions such as ischemic heart disease and cerebrovascular accidents [149; 319]. It is unclear whether cardiovascular disease results from rheumatoid arthritis or if it precedes the onset [148].

EPIDEMIOLOGY

An estimated 1.5 million American adults are affected by rheumatoid arthritis [145]. The yearly incidence of rheumatoid arthritis is approximately 53 per 100,000 for women and about half that (27.7 per 100,000) for men [145]. The prevalence of rheumatoid arthritis increases steadily with age in both sexes, being highest in the 65 to 74 years of age group [145]. However, the incidence is much higher for women in all age groups compared with men.

In most cases, updated statistics and costs related to rheumatoid arthritis are included as part of the larger category of related arthritic or rheumatic conditions. There were 20.8 million office visits for primary rheumatic conditions in 2015, totaling nearly 2.1% of all ambulatory care visits that year (2.3% for women, 1.9% for men) [146]. An estimated 23% (54.4 million) of adults in the United States reported having doctor-diagnosed arthritis between 2013 and 2015, and 50% of adults 65 years of age or older reported an arthritis diagnosis (i.e., some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia) [148]. By 2040, an estimated 78.4 million Americans 18 years of age or older are projected to have diagnosed arthritis [148].

Overall, rheumatoid arthritis and related arthritic diseases have a significant impact in the United States, causing disability and premature mortality. Although many people with rheumatoid arthritis work full-time, about 10% of those with rheumatoid arthritis become severely disabled and unable to do simple daily living tasks. Many report significant limitations in vital activities such as walking, stooping/bending/kneeling, climbing stairs, and social activities [149]. Rheumatoid arthritis can shorten a patient's life expectancy by an average of three to seven years. However, individuals with severe forms of rheumatoid arthritis may die 10 to 15 years earlier than expected [149]. It has been found that people with rheumatoid arthritis are 2.3 times as likely to die as other people of the same age [148].

There are significant costs associated with rheumatoid arthritis, and these arthritic-related disease costs continue to increase. In 2013 (the year with the most recently available data), the total cost attributed to arthritis and other rheumatic conditions in the United States was $303.5 billion, up from $128 billion in 2003 [147; 150]. Medical expenditures (direct costs) for arthritis and other rheumatic conditions in 2013 were $140 billion, up from $80.8 billion in 2003 [150]. Earnings losses (indirect costs) for arthritis and other rheumatic conditions in 2013 were $164 billion, up from $47 billion in 2003 [147; 160]. Individuals with rheumatoid arthritis are far more likely to change occupation, reduce work hours, lose their job, retire early, and be unable to find a job compared with people without arthritis [148].

POTENTIAL ENVIRONMENTAL RISK FACTORS

Environmental factors that have been linked to rheumatoid arthritis include infection, smoking, and stress/depression. Among the infectious microorganisms thought to be associated with rheumatoid arthritis are Epstein-Barr virus, *Mycobacterium tuberculosis*, *Escherichia coli*, *Proteus mirabilis*, retroviruses, parvovirus B19, and hepatitis C virus [3]. Approximately 8% to 15% of individuals have reported the onset of rheumatoid arthritis-related symptoms within a few days after an infectious illness [151].

There is emerging evidence that the community of intestinal microbes (gut microbiota) has both beneficial and adverse effects on immune regulation and the maintenance of human health. The gut microbiota composition (microbiome) is now considered to have a role as mediator of inflammation locally and at extra-intestinal sites. Several studies have linked alterations in the gut microbiome (dysbiosis) to the pathogenesis of rheumatoid arthritis and other autoimmune diseases [298]. In a study comparing the oral, salivary, and gut microbiomes of patients with rheumatoid arthritis to that of healthy controls, patients with rheumatoid arthritis were found to have a distinct dysbiosis marked by depletion of *Hemophilus* spp. and an overabundance of *Lactobacillus salivarius* [299]. These alterations in the microbiome could be correlated with clinical measures and used to stratify patients on the basis of their response to therapy. Specifically, the degree of *Hemophilus* spp. depletion correlated with levels of serum autoantibodies, and the amount of *Lactobacillus salivarius* present correlated with the level of rheumatoid disease activity. The observed dysbiosis partially resolved after treatment of the rheumatoid arthritis. Functional alterations in the transport and metabolism of iron, sulfa, zinc, and arginine were also found in the microbiota of individuals with rheumatoid arthritis in this study.

Smoking has also been identified as a significant risk factor for the development of rheumatoid arthritis, and greater smoking intensity (number of cigarettes per day) and longer smoking history further increase the risk [152]. The risk remains increased for at least 20 years after smoking cessation [152]. Research indicates that the risk of developing rheumatoid arthritis is nearly double for current smokers compared with nonsmokers [320].

Psychologic stress has been thought to play a role in the pathogenesis of rheumatoid arthritis by triggering the inflammatory process and exacerbating disease activity [47; 48]. In a prospective cohort study of female nurses, women with high PTSD symptomatology were found to have an elevated risk for rheumatoid arthritis [300]. The risk increased with increasing number of PTSD symptoms and was independent of cigarette smoking history. Rheumatoid arthritis is also strongly associated with major depression (attributable risk of 18.1%), probably through its role in creating functional limitation [318].

In addition, because evidence of rheumatoid arthritis-associated antibodies has often been found many years before the onset of clinical symptoms, early environmental factors have been thought to be a contributor to the disease [153]. High birth weight and early breastfeeding cessation are two such early factors [153].

ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

As noted, autoimmune diseases of connective tissue are more likely to be associated with other autoimmune diseases [69]. Studies have shown that the coexistence of rheumatoid arthritis, thyroiditis, and type 1 diabetes is high [4; 111]. In addition, features of systemic lupus are common in individuals with rheumatoid arthritis; in one study, four or more lupus features were found in approximately 16% of individuals with rheumatoid arthritis within 25 years after diagnosis [154]. This finding is significant because the co-occurrence of systemic lupus features and rheumatoid arthritis was associated with increased overall mortality [154].

As many as 25% of individuals with rheumatoid arthritis also have Sjögren syndrome, and the risk of rheumatoid arthritis appears to be higher in individuals who have inflammatory bowel disease [4; 67; 144]. An inverse relationship between rheumatoid arthritis and multiple sclerosis has been reported [4]. Fibromyalgia is also commonly found in association with rheumatoid arthritis, with reported rates ranging from 17% to 57% [17; 155].

CLINICAL MANIFESTATIONS

Pain and stiffness in multiple joints are the primary characteristics of rheumatoid arthritis; approximately one-third of individuals with the disease initially have pain in only one joint [156]. Other common symptoms of rheumatoid arthritis include fatigue, weakness, generalized muscular aches, and anorexia [151]. Approximately 46% of individuals with rheumatoid arthritis have extra-articular manifestations, the most common of which is rheumatoid nodules, followed by pulmonary fibrosis, dry eye syndrome, and anemia of chronic disease [143; 144; 151]. Rheumatoid nodules are soft, poorly delineated subcutaneous nodules, and they also occasionally affect internal organs such as the pleura, sclera, vocal cords, and vertebral bodies [143; 151]. Other frequently occurring extra-articular manifestations include pericarditis, pleuritis, vasculitis, cervical myelopathy, and neuropathy [143]. No reliable predictors of extra-articular manifestations have been identified, but they have been reported to be associated with male gender, smoking, more severe joint disease, worse function, high levels of inflammatory markers, and a positive rheumatoid factor and antinuclear antibody (ANA) titer [144].

DIAGNOSTIC EVALUATION

When evaluating a patient for suspected rheumatoid arthritis, healthcare professionals should focus both the history and the physical examination on the joints. Questions about symptoms related to the joint should help determine which joints are involved, when joint pain occurs (e.g., during activity, at rest), how long pain and stiffness last, and how pain limits function.

The most commonly involved joints are the wrist joints and the proximal interphalangeal and metacarpophalangeal joints; the distal interphalangeal joints and sacroiliac joints are typically not affected [156]. Affected joints may become warm and tender after long periods of inactivity, and joint symptoms are usually bilateral. Small joints of the hands and feet are not usually painful at rest. Morning joint stiffness associated with rheumatoid arthritis usually lasts more than one hour, in contrast to osteoarthritis, in which morning stiffness usually resolves within 30 minutes after waking [157]. For most individuals, symptoms develop over a long period of time (weeks to months); symptoms develop over days to weeks in approximately 15% of patients [156].

The findings on physical examination are usually normal, except for an occasional low-grade fever. The involved joint(s) may feel warm and boggy and may be tender to the touch, but there is usually no accompanying erythema [156]. Affected joints have limitations in the range of motion, and the strength of muscles near affected joints is usually decreased. The patient may keep an affected joint in flexion to avoid pain related to extension. Lymph nodes in the epitrochlear, axillary, and cervical regions may be enlarged. Rheumatoid nodules are often found in pressure areas (e.g., the elbows and finger joints) and the extensor surface of the forearm [151].

Diagnostic Criteria

In 1988, the American Rheumatism Association (now known as the American College of Rheumatology [ACR]) published its Criteria for the Classification of Rheumatoid Arthritis, and these criteria remained the standard for several years [158]. However, the criteria were criticized for a lack of sensitivity to early disease. In 2010, the ACR and the European League Against Rheumatism (EULAR) collaborated on a new classification system that focuses on features of earlier stages of rheumatoid arthritis that are associated with persistent and/or erosive disease, rather than defining the disease by its late-stage features [159]. The impetus

2010 ACR/EULAR CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS[a]		
Category	**Criteria**	**Score**
Joint involvement	1 large joint (shoulder, elbow, hip, knee, ankle)	0
	2 to 10 large joints	1
	1 to 3 small joints (MCP, PIP, second to fifth MTP, thumb IP joints), with or without involvement of large joints	2
	4 to 10 small joints, with or without involvement of large joints	3
	>10 joints (at least 1 small joint and any combination of any other joints)	5
Serology (at least 1 test result is needed for classification)	Negative RF and ACPA	0
	Low-positive RF or low-positive ACPA	2
	High-positive RF or high-positive ACPA	3
Acute-phase reactants (at least 1 test result is needed for classification)	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of symptoms	<6 weeks	0
	≥6 weeks	1

[a]See text for initial criteria and descriptions of criteria.
ACPA = anti-citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IP = interphalangeal; MCP = metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal; RF = rheumatoid factor.

Source: [159] Reprinted with permission, from Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69:1580-1588. *Table 6*

for this change in focus was the need for earlier diagnosis in order to begin disease-modifying drugs as soon as possible [159].

The new classification criteria apply only to newly presenting individuals, and two requirements must first be met: there must be evidence of currently active clinical synovitis (i.e., swelling) in at least one joint as determined by an expert assessor, and the synovitis must not be better explained by another diagnosis [159]. The ACR/EULAR note that all joints may be assessed, except for the distal interphalangeal joints, the first metatarsophalangeal joint, and the first carpometacarpal joint, as these are most often involved in osteoarthritis [159]. Individuals who are eligible according to the first two criteria are then evaluated by four additional criteria related to joint involvement, serologic testing, acute-phase reactants, and duration of symptoms (***Table 6***) [159]. The classification system includes a scoring system, with a possible total of 10 points; a score of 6 or more indicates "definite" rheumatoid arthritis. Although a person with a score of less than 6 does not have definite rheumatoid arthritis, the score may increase on subsequent testing.

The ACR/EULAR recommended serologic testing involves a rheumatoid factor and an anti-citrullinated protein antibody (ACPA) [159]. A positive rheumatoid factor has long been known as an indicator of rheumatoid arthritis, and studies have shown that this test is positive in approximately 69% to 90% of people with the disease [160; 161]. However, the test may be positive in healthy individuals as well as in individuals with other rheumatic diseases (e.g., Sjögren syndrome, systemic sclerosis, systemic lupus), with chronic infections, or with pulmonary disease [160]. The false-positive rate of rheumatoid factor for rheumatoid arthritis

has been reported to be 15% [161]. As a result, the sensitivity and specificity of the test are 69% and 85%, respectively [161]. Testing for ACPA began in the late 1990s, and although the sensitivity of the test (67%) is similar to that of the rheumatoid factor, its false-positive rate is lower, yielding a specificity of 95% [161]. According to the ACR/EULAR classification scoring system, the highest score is given if the results of either the rheumatoid factor or the ACPA test is highly positive, and no points are given if both tests are negative [159]. An ANA titer has a reported sensitivity of about 40% among individuals with rheumatoid arthritis, and false-positive results are common [160]. The ANA titer is not part of either the 1988 or 2010 diagnostic criteria [158; 159].

Other recommended baseline laboratory testing includes a complete blood cell count (CBC) with differential, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) [8; 162]. However, the ESR and CRP results should be interpreted with caution, as the tests are normal in about 40% of people with rheumatoid arthritis [163]. Baseline renal and hepatic functioning should also be determined, not because these tests are sensitive or specific for rheumatoid arthritis but because they are important in guiding the choice of medications [162].

Radiographic evaluation has been recommended as part of the diagnostic work-up for rheumatoid arthritis, but the findings on conventional radiographs of involved joints are often normal, especially in early-stage disease [8]. The findings on imaging studies are not part of the 2010 classification criteria for rheumatoid arthritis [159]. However, imaging studies may be helpful in the differential diagnosis and in establishing baseline images for comparison during follow-up. An analysis of 11 studies of magnetic resonance imaging (MRI) as a diagnostic tool showed a wide range in sensitivity and specificity, with the authors concluding that the data are inadequate to justify widespread use of MRI in the diagnosis of rheumatoid arthritis [164].

Differential Diagnosis

A wide range of medical conditions should be considered in the differential diagnosis of rheumatoid arthritis, including [151; 156; 165]:

- Connective tissue diseases (e.g., systemic lupus, systemic sclerosis)
- Psoriatic arthritis, gout, and other forms of arthritis
- Fibromyalgia
- Polymyalgia rheumatica
- Thyroid disease
- Sarcoidosis
- Hemochromatosis
- Still disease
- Viral arthritis
- Paraneoplastic syndrome (when onset is after 55 years of age)

Overlapping signs and symptoms can make it challenging to distinguish rheumatoid arthritis from many of these conditions, especially connective tissue diseases and other forms of arthritis. A positive ANA titer may help distinguish systemic lupus from rheumatoid arthritis, and determination of a TSH level can aid in a diagnosis of hypothyroidism [156; 160]. Early in the course of rheumatoid arthritis, self-limited viral syndromes should be considered, especially hepatitis B and C, parvovirus, rubella (infection or vaccination), and Epstein-Barr virus [3].

TREATMENT OPTIONS

The primary goal of treatment for rheumatoid arthritis was once to alleviate symptoms using a pyramid approach, but the advent of disease-modifying drugs as a standard of care has shifted the focus to early remission and/or the prevention of further joint damage using a treat-to-target approach [166; 323]. This approach is a tightly controlled, aggressive strategy tailored to each patient, with modifications to the individual medication regimen to achieve a particular target (remission, or alternatively, low disease activity) in a specific

period of time (usually six months) [166]. Treatment goals are to preserve the structural integrity of the joint, enhance function and quality of life, minimize pain and inflammation, and control systemic complications [9; 156]. These goals are achieved through a combination of disease-modifying drugs, anti-inflammatory agents, and nonpharmacologic measures. Surgery is sometimes needed when medical treatment options fail. In addition, treatment of complications or comorbidities associated with rheumatoid arthritis is often needed.

Several guidelines for the treatment of rheumatoid arthritis exist. In 2016, the ACR published updated guidelines on the use of disease-modifying antirheumatic drugs and biologic agents and emphasizes the use of the treat-to-target approach [9]. Updated ACR guidelines are anticipated to be published in late 2020 [285]. The EULAR has developed guidelines for the management of early rheumatoid arthritis and for the use of disease-modifying drugs (updated in 2019) [162; 166; 284].

A 2012 meta-analysis of four studies comparing tight control with usual care found that applying a treat-to-(any)target approach approximately doubled remission rates in patients with early rheumatoid arthritis with high disease activity [323]. One small-scale study comparing early aggressive treatment (i.e., methotrexate) with usual care (i.e., using milder drugs initially, with intensification of treatment as needed) found that there was approximately 50% remission in each group at the study endpoint (two years) [326]. However, during the course of the study, 23 of 24 patients in the conventional care group had progressed to aggressive treatment (with methotrexate) and most were given intra-articular corticosteroids much more frequently than those in the tight control group. It is interesting to note that the aggressive treatment (methotrexate) is not considered aggressive by today's standards, as treatment with adalimumab was started only in patients who had poor response six months after initiation of treatment. Progression of joint damage (i.e., lack of radiographic remission) occurred among a minority of participants even in the aggressive treatment group who were considered to have clinical remission (based on assessment scores); on average, radiographic and functional scores were similar in both groups at the end of the study [326]. The authors emphasize that their results do not indicate an advantage of one treatment strategy over another; instead factors such as patient preference and risk versus benefit (e.g., weighing the severe side effects of the stronger disease-modifying antirheumatic drugs [DMARDs] against their rapid response) should guide the treatment decision [326]. In addition, the measures of remission are ill-defined, and to progress from low disease activity (which may be a satisfactory target) to clinically defined remission may require a medication regimen greater than what is safe or tolerable. Most clinicians in the study were unwilling to push for remission if their patient's disease was reduced to an acceptable level with conservative treatment.

Disease-Modifying Antirheumatic Drugs

Early treatment is essential to achieving optimal outcomes with disease-modifying drugs, and the EULAR guideline recommends that treatment with disease-modifying drugs begin immediately following the diagnosis [166; 284]. DMARDs are antimetabolite/cytotoxic agents, and several nonbiologic and biologic disease-modifying drugs are now available, allowing clinicians and patients to select a specific drug after considering several factors. In its recommendations for the use of disease-modifying drugs, the ACR discussed the use of 13 drugs (five nonbiologic and eight biologic agents) and noted that other drugs were not included because they were used infrequently, were associated with a high incidence of adverse events, or were not recommended for other reasons (***Table 7***) [9; 167]. For example, anakinra, an IL-1 antagonist, has been found to be less effective than the other biologic agents and so was omitted from the review of the literature informing the guidelines [167; 168]. Since the publication of the guidelines, three additional nonbiologic agents in the Janus kinase (JAK) inhibitor family (tofacitinib, baricitinib, and

RECOMMENDED DISEASE-MODIFYING ANTIRHEUMATIC DRUGS APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

Agent	Indication[a]	Dose and Administration	Most Common Adverse Effects
Nonbiologic Agents			
Methotrexate	Any disease duration, any degree of disease activity, with or without poor prognosis features	12–25 mg PO, IM, or SC weekly	Nausea, diarrhea, fatigue, mouth ulcers, rash, alopecia
Leflunomide	Any disease duration, any degree of disease activity, with or without poor prognosis features	100 mg PO daily for 3 days, then 10–20 mg PO daily	Nausea, diarrhea, rash, alopecia; highly teratogenic, even after use is discontinued
Hydroxychloroquine	Short or intermediate disease duration, low disease activity, no poor prognosis features	200–400 mg PO daily	Nausea, headache, possible retinopathy
Sulfasalazine	Any disease duration, any degree of disease activity, no poor prognosis features	2–3 g PO daily (in divided doses)	Nausea, diarrhea, headache, mouth ulcers, rash, alopecia, oligospermia (reversible)
Tofacitinib[b]	Moderately to severely active disease despite treatment with methotrexate or intolerance of methotrexate	5 mg daily	Infections, headache, diarrhea
Baricitinib[b]	Moderately to severely active disease with inadequate response to one or more anti-tumor necrosis factor-α agents. Maybe used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs	2 mg PO daily	Infection, upper respiratory tract infection, nausea
Upadacitinib[b]	Moderately to severely active disease with intolerance of methotrexate. May be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs	15 mg PO daily	Upper respiratory tract infection, nausea
Biologic Agents			
Anti-tumor necrosis factor-α agents (adalimumab, etanercept, infliximab)	In combination with methotrexate: Disease duration of less than 3 months, high disease activity, features of poor prognosis, and no previous treatment with disease-modifying drugs Alone: Inadequate response to methotrexate monotherapy AND disease duration >3 months, moderate disease activity, and poor prognosis features OR disease duration >3 months, high disease activity, with or without poor prognosis features	Adalimumab: 40 mg SC every 2 weeks Etanercept: 25 mg SC twice weekly or 50 mg SC weekly Infliximab: 3 mg/kg IV at weeks 0, 2, and 6, then every 8 weeks	Infusion reactions, increased risk of infection (especially fungal)
Golimumab (anti-tumor necrosis factor-α)	In combination with methotrexate: moderate-to-severe disease	50 mg SC monthly	Serious infections, upper respiratory infection, nasopharyngitis
Abatacept	Inadequate response to methotrexate-based combination or sequential administration of other nonbiologic agents, moderate-to-high disease activity, and features of poor prognosis	500–1,000 mg (depending on body weight) IV at weeks 0, 2, and 4, then every 4 weeks	Headache, nasopharyngitis, dizziness, urinary tract infection, bronchitis

Table 7 continues on next page.

RECOMMENDED DISEASE-MODIFYING ANTIRHEUMATIC DRUGS APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

Agent	Indication[a]	Dose and Administration	Most Common Adverse Effects
Rituximab	In combination with methotrexate: Inadequate response to methotrexate-based combination or sequential administration of other nonbiologic agents, high disease activity, and features of poor prognosis	1,000 mg IV at week. 0 and 2, then every 24 weeks	Upper respiratory infection, bronchitis, nasopharyngitis, urinary tract infection
Tocilizumab	Alone or in combination with methotrexate: Moderate-to-severe disease refractory to 1 or more anti-tumor necrosis factor-α agents	4–8 mg/kg IV monthly	Serious infection, upper respiratory infection, nasopharyngitis, headache, hypertension
Sarilumab	Moderately to severely active disease with an adequate response or intolerance to one or more DMARDs Do not use in combination with biologic DMARDs	200 mg SC every 2 weeks	Increased serum alanine aminotransferase, increased serum aspartate aminotransferase, neutropenia, antibody development, erythema at injection site

[a]Disease duration defined as short (less than 6 months), intermediate (6 to 24 months), or long (more than 24 months). Degree of disease activity is defined according to scores on one of several validated disease activity instruments; presence of poor prognosis features is defined as functional limitation, extra-articular disease, positive rheumatoid factor and/or positive anti-citrullinated protein antibody test, and/or osseous erosions on radiograph.
[b]JAK inhibitors (tofacitinib, baricitinib, and upadacitinib) should not be used in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine.

Source: [9; 20; 286; 287; 288; 308; 321] *Table 7*

upadacitinib) and one additional biologic agent (sarilumab) have received FDA approval for the treatment of rheumatoid arthritis [286; 287; 288; 308; 321]. These additional drugs are included in the updated EULAR guidelines and are expected to be included in the forthcoming update to the ACR guidelines [284; 285].

In patients with symptomatic early rheumatoid arthritis with moderate-to-severe disease activity, the American College of Rheumatology recommends the use of DMARD monotherapy over double or triple therapy.

(https://www.rheumatology.org/Portals/0/Files/ACR%202015%20RA%20Guideline.pdf. Last accessed July 23, 2020.)

Level of Evidence: Moderate

Among the recommended nonbiologic agents are methotrexate, generally considered to be the standard first-line treatment; the antimalarial drug hydroxychloroquine; the JAK inhibitors tofacitinib, baricitinib, and upadacitinib; and sulfasalazine and leflunomide, drugs developed specifically for rheumatoid arthritis [9]. The biologic agents include five anti-TNF-α agents (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) and three non-TNF-α agents, including abatacept, a selective costimulation modulator; rituximab, an anti-CD20 monoclonal antibody that depletes B lymphocytes; and tocilizumab and sarilumab, IL-6 receptor antagonists [9].

Methotrexate is the most commonly prescribed DMARD and is still considered the so-called anchor drug for the treatment of rheumatoid arthritis [9; 166]. It can be given alone or in combination with one or two other nonbiologic agents. Leflunomide, a competitive inhibitor of an intracellular enzyme needed for de novo pyrimidine synthesis, is a newer DMARD with comparable efficacy that can be substituted for methotrexate and may be particularly useful for patients with intolerance of or contraindications to methotrexate [156; 324; 325]. Patients for whom monotherapy with methotrexate has failed may benefit from the addition of leflunomide, either with methotrexate or other DMARDs [325].

The ACR recommends basing the decision regarding initial treatment with a DMARD on the duration of disease (early or established) and degree of disease activity (low, moderate, or high) [9]. Previous guidelines had also considered prognosis, but this is now considered encompassed by disease activity. Additional factors to consider when choosing a drug are side effect profiles, cost, and access to care.

The treat-to-target approach for patients with early high disease activity typically involves initiation of methotrexate and/or another DMARD(s) immediately upon diagnosis [9; 166; 323]. Initial combination therapies with DMARDs, particularly those including a biologic anti-TNF-α agent, appear to provide earlier clinical improvement and less joint damage progression in patients with early highly active disease. These therapies can be withdrawn successfully, and fewer treatment adjustments are needed than with initial monotherapies [9; 25; 166; 327; 328]. Patients with active disease are monitored closely (every one to three months), and it is recommended that treatment adjustments be made if there is no improvement at three months (or if the six-month target has not been reached) [9; 166]. For patients with low-to-moderate disease activity or high disease activity without poor prognostic features, DMARD monotherapy is usually given initially.

As discussed, comparative studies of methotrexate, leflunomide, and sulfasalazine have provided no evidence that points to the benefit of one of these drugs over the others; similarly, evidence suggests similar benefit among biologic agents [167; 170; 171; 326]. In addition, a combination of nonbiologic drugs, methotrexate, and a biologic drug have led to better clinical response rates and functional outcomes than either methotrexate or a biologic agent alone, especially in early active disease [170; 172]. However, one systematic review showed no significant advantage of a methotrexate-based combination compared with methotrexate monotherapy among patients receiving initial treatment with a disease-modifying drug [173]. That review did show significant reductions in pain and improvement in physical function for methotrexate-based combinations among patients in whom disease had not responded to methotrexate monotherapy [173].

Several precautions should be taken before beginning treatment with a disease-modifying drug. The ACR recommends determining baseline CBC, liver function studies, and creatinine level before beginning or resuming treatment with any of the drugs; these laboratory tests should also be done after any significant increase in dose [9]. Individuals receiving methotrexate or leflunomide should also be tested for hepatitis B or C infection. If an individual's vaccinations are not current, influenza vaccine should be administered before treatment with a nonbiologic agent is begun, and pneumococcal vaccine should also be given before treatment with DMARDs. Both vaccinations are recommended before treatment with a biologic agent begins [9]. Routine tuberculosis screening should also be done to identify latent tuberculosis infection in individuals who are being considered for therapy with a biologic agent or tofacitinib.

In previous guidelines, acute hepatitis B or C infection was considered a contraindication for most DMARDs and biologic agents. However, in its 2016 update, the ACR recommended that patients with active hepatitis B or C who are receiving effective antiviral treatment may be managed the same as patients without hepatitis [9]. Certain medications may be preferred for other high-risk conditions, including congestive heart failure, treated or untreated malignancy, and serious infection [9].

Anti-Inflammatory Medications

Anti-inflammatory medications are used to reduce joint pain and swelling associated with rheumatoid arthritis. Because these drugs do not change the course of disease, they must be used in conjunction with a disease-modifying drug. Treatment typically begins with a nonselective nonsteroidal anti-inflammatory drug (NSAID); a cyclooxygenase-2 (COX-2)-selective inhibitor and/or glucocorticoids may also be used. A gastroprotective agent (proton-pump inhibitor) should be prescribed with an NSAID for individuals at high risk for gastrointestinal complications [176].

There is good evidence that nonselective NSAIDs and COX-2 inhibitors have comparable efficacy and that COX-2 inhibitors are comparable to each other [177]. Although COX-2 inhibitors have better tolerability in general compared with NSAIDs, there is considerable variability across individual drugs in terms of protection against serious gastrointestinal events [177]. A large, double-blind, randomized trial involving nearly 4,500 individuals with rheumatoid arthritis or osteoarthritis demonstrated that the COX-2 inhibitor celecoxib was associated with lower risks of adverse gastrointestinal events than a nonselective NSAID plus a proton-pump inhibitor (diclofenac plus omeprazole) [178].

The adverse event profiles of both nonselective NSAIDs and COX-2 inhibitors should be considered when selecting a specific drug for an individual patient. All individuals treated with NSAIDs should be monitored for long-term complications such as gastrointestinal bleeding, nephrotoxicity, cardiovascular events (e.g., myocardial infarction, stroke), and gastric ulcers and bleeding [176; 177]. The increased risk of cardiovascular events associated with some COX-2 inhibitors has been well publicized, prompting the FDA to re-evaluate the risks and benefits of the COX-2 inhibitors; special care should be taken when prescribing these drugs [177]. Although certain COX-2 inhibitors (such as celecoxib) are still available, they are labeled with strong warnings and a recommendation for prescribing the lowest possible dose for the shortest possible duration [20].

In addition to their anti-inflammatory properties, glucocorticoids may substantially reduce the rate of further joint erosion and should be considered as a temporary adjunct to treatment with disease-modifying drugs [162; 179]. However, because of the substantial risk of adverse effects, glucocorticoids should be given for the shortest time and at the smallest dose possible, and treatment should be discontinued gradually—over at least one month—to avoid rebound effects [8]. Administration of a glucocorticoid as an intra-articular injection may reduce swelling and inflammation in a single joint, but the clinical benefit is short term [162].

Complementary/Alternative Medicine

Many individuals with rheumatoid arthritis turn to complementary and alternative medicine to alleviate symptoms. The use of complementary and alternative medicine among individuals with rheumatoid arthritis has ranged from 28% to 90%, and the rates of use among all individuals vary across racial/ethnic populations [77; 180; 181]. Most herbal supplements used by individuals with rheumatoid arthritis are safe, but the evidence of their benefit has been weak to moderate [182; 183]. Despite the wide use of complementary and alternative medicine, most individuals (63% to 72%) do not report the use to their healthcare providers [96; 181]. Because of this, clinicians should ask direct questions about the use of complementary and alternative medicine approaches and initiate discussions about their use.

Aside from supplementation with several specific types of oils, the only complementary therapy currently endorsed by the U.S. Department of Health and Human Services for patients with rheumatoid arthritis is to consume a nutritious, balanced diet [329]. Some argue that the typical American diet, which is based on animal proteins (many of which are now devoid of significant levels of nutrients and/or are heavily processed) and typically consisting of high levels of animal fats (e.g., cheese, butter, ice cream) and simple carbohydrates promotes inflammation [334]. However, others argue that restricting the intake of good quality food sources of nutrients, such as fish and real cheese, can lead to dietary deficiencies. A growing body

of evidence supports the belief that proper nutrition from food, or more specifically, avoidance or correction of nutritional deficiencies, can prevent the development of inflammatory disorders in genetically predisposed individuals. One group of researchers writes that, "diet can affect transgenerational gene expression via 'reversible' heritable epigenetic mechanisms" [330]. It is believed that certain anti-inflammatory bioactive food components (e.g., carotenoids, organosulfurs, polyphenols, phytosterols, tocopherols, tocotrienols) can lessen the rates and negative effects of acetylation, methylation, oxidation, phosphorylation, ribosylation, SUMOylation, and ubiquitination.

One food-sourced supplement, fish oil, is a proven, powerful rheumatoid arthritis therapy and contains several bioactive components, such as the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). A 2010 meta- and mega-analysis of randomized controlled trials confirmed the efficacy of fish oil for the relief of joint pain and found a significantly reduced use of anti-inflammatory drugs in patients with long-standing rheumatoid arthritis [331]. NSAIDs can cause an increased cardiovascular risk, and reduced morbidity and mortality among participants in the research groups was also attributable to fish oil supplementation, as atherosclerosis and NSAID use are both reduced with this therapy. Past research was limited to long-standing cases of rheumatoid arthritis; it is unclear whether fish oil can prevent joint damage in recent-onset rheumatoid arthritis [331]. Though fish oil is most often studied, krill oil (from a small, shrimp-like crustacean) has also shown similarly beneficial results [332]. It should be noted that concerns over bleeding risks (e.g., hemorrhagic stroke) related to a high intake of fish oil have been shown to be unfounded [333]. However, blood thinning is a side effect, and patients should be advised to eat foods rich in vitamin K1 while taking these supplements.

Nonpharmacologic Therapy

Physical therapy and/or occupational therapy can help individuals improve their ability to carry out activities of daily living at home, at work, and socially [162]. In addition, physical therapists can provide instruction in a program of range-of-motion and strengthening exercises, in joint protection, and in ways to conserve energy. Evidence of benefit from nonpharmacologic approaches is lacking, however. An overview of systematic reviews found that there was unclear benefit (low quality of evidence) for most nonpharmacologic therapies, including balneotherapy, electrical stimulation, transcutaneous electrical nerve stimulation, assistive devices, and splints [183]. The exceptions were comprehensive occupational therapy and joint protection, which were shown to improve function (with no difference in pain) according to high-quality evidence, and low-level laser therapy, which was shown to reduce pain and improve function according to evidence of moderate quality [183].

Regular participation in activities such as walking or aerobic exercises is recommended, as they can help improve joint mobility, muscle strength, and aerobic fitness; decrease fatigue; and maintain psychologic well-being [8; 184]. Also, because emotional stress can exacerbate disease activity, stress management interventions should be encouraged [47; 48]. Several randomized controlled trials have indicated that significant improvements in pain management and function have resulted from cognitive-behavioral therapy that has focused on therapist-guided training in coping strategies (e.g., relaxation, goal setting, imagery, and cognitive restructuring of negative thoughts related to pain) [48].

Surgical Intervention

The goals of surgical intervention for rheumatoid arthritis are to restore function and quality of life, prevent further deterioration of the joint, relieve pain, and correct deformity [185]. Surgery is reserved for patients who have structural joint damage that causes high pain levels, loss of range of motion, or severely limited function (severe disability and/or inability to work) despite pharmacologic and nonpharmacologic therapy [334]. The challenge with surgical treatment is that many joints are often involved; priority should be given to the joint that causes the greatest disability and pain [185]. Among the options for surgical treatment are synovectomy, carpal tunnel release, resection of the metatarsal heads, specialized hand surgery, arthrodesis, and joint replacement [185]. The preoperative functional status is an important factor in the postoperative outcome, making early referral for surgery important [334].

Treatment of Extra-Articular Manifestations

The overall management of individuals with rheumatoid arthritis includes clinical assessment and follow-up for extra-articular manifestations of rheumatoid disease [144]. As indicated earlier, a variety of conditions are seen involving major organs: cardiac (e.g., pericarditis, myocarditis), pulmonary (e.g., pleuritis with effusion, interstitial pneumonitis, pulmonary fibrosis), ocular (e.g., scleritis, anterior uveitis, peripheral ulcerative keratitis), vasculitis, neuropathy, osteopenia, and osteoporosis. Because extra-articular manifestations are associated with a poor prognosis, they should be identified early and managed promptly with the assistance of subspecialty consultation. Because the underlying pathophysiology often centers on inflammation and vasculitis, treatment primarily relies on glucocorticoids [144].

FOLLOW-UP AND PROGNOSIS

Close follow-up is needed for individuals with rheumatoid arthritis to evaluate response to treatment, ensure control of symptoms, and monitor for treatment side effects and disease-related comorbidities.

Response to Treatment

Both the ACR and the EULAR recommend that evidence of disease activity be evaluated, through subjective and objective measures, at each follow-up visit [9; 162]. The follow-up assessment may include:

- Self-reports of degree of joint pain, duration of morning stiffness, limitation of function, and duration of fatigue
- Tender and swollen joints on physical examination
- Evidence of disease progression on physical examination (e.g., loss of motion, instability, malalignment, and/or deformity)
- Elevated ESR or CRP level
- Progression of radiographic damage of involved joints (with use of radiographic assessment scales)
- Global assessment of disease activity (by the physician and the patient)
- Standardized questionnaires to assess functional status and/or quality of life

The recommended follow-up interval is every one to three months until remission is achieved, and adjustments to the doses and/or choices of monotherapy or combination therapy with disease-modifying drugs should be made if the response is inadequate [9; 162; 166]. Treatment with DMARDs can lead to some level of remission in approximately 30% to 40% of individuals, but sustained remission is less common (17% to 20%), and most individuals will have persistent disease [151; 156; 335]. Again, achieving low disease activity with a conservative medication regimen may be a better course than seeking clinical remission with aggressive therapy [326].

Monitoring and Treatment of Drug Side Effects

A systematic approach to long-term drug monitoring is necessary because of the potential for serious adverse events associated with the long-term use of DMARDS and glucocorticoids [186].

Among the side effects of long-term use of disease-modifying drugs are infection; bone marrow suppression; gastrointestinal, hepatic, renal/genitourinary, cardiovascular, and neurologic effects; pulmonary toxicity; and skin reaction/rash [186]. Infusion site reactions are also commonly associated with anti-TNF-α agents [186]. It is recommended that individuals treated with leflunomide, methotrexate, or sulfasalazine have a CBC, liver function studies, and a serum creatinine at baseline and then every 2 to 4 weeks for the first three months after the beginning of treatment; every 8 to 12 weeks during the three- to six-month period, and every 12 weeks subsequently [20]. Individuals taking rituximab should have a CBC and platelet count done every two to four months, and individuals treated with tocilizumab should have neutrophils, platelets, and liver enzymes, as well as CBC, platelet count, and liver function studies, as indicated, assessed every four to eight weeks [20].

Individuals receiving hydroxychloroquine are at risk for severe retinopathy, and ophthalmologic follow-up is important for early detection and minimization of toxicity [187]. The reported incidence of retinopathy associated with hydroxychloroquine is low, especially within the first five years of use at a low dose (less than 400 mg/day), but the potential severity calls for ophthalmologic follow-up [187; 188]. The American Academy of Ophthalmology (AAO) recommends a complete ophthalmologic examination within the first year after treatment [187]. If the results are normal, subsequent eye examinations should be performed annually after five years of treatment in all patients considered to be at low risk for hydroxychloroquine-related toxicity based on presence of the following factors [187]:

- Duration of use: Longer than five years
- Cumulative dose: >1,000 g (total)
- Daily dose: >400 mg/day (>6.5 mg/kg ideal body weight for short individuals)
- Older age
- Kidney or liver dysfunction
- Retinal disease or maculopathy

For people at high risk for toxicity (i.e., those who are treated with higher doses of hydroxychloroquine and/or for longer than five years), the AAO recommends an annual eye examination [187]. Age older than 60 years, the presence of renal or hepatic disease, and obesity are also factors that increase the risk for hydroxychloroquine-related retinopathy [187]. The AAO emphasizes that these are minimum recommendations that balance cost with risk, and more frequent screening may be appropriate.

All drugs used to treat rheumatoid arthritis are associated with a high risk of conventional and opportunistic infections, and measures to prevent infection should be taken. The ACR recommends that in addition to receiving an influenza vaccination before beginning treatment with DMARDs, individuals should receive the vaccination annually thereafter [9]. In addition, a pneumococcal vaccination should be given every five years [9]. All vaccines should be given based on age and risk. If hepatitis and/or human papillomavirus (HPV) risk factors are present, the hepatitis B and/or HPV vaccine should be administered. Live vaccines (e.g., herpes zoster) should be avoided only in individuals already receiving a biologic disease-modifying drug [9]. Targeted prophylaxis for individuals at high risk for infection may also be appropriate [43; 186].

The use of glucocorticoids, especially over the long term, is associated with a wide range of potential adverse events, including osteopenia/osteoporosis, hypertension, cataracts, glaucoma, dyspepsia, weight gain, avascular necrosis of bone, Cushingoid changes, and adverse psychologic effects [186].

AMERICAN COLLEGE OF RHEUMATOLOGY RECOMMENDATIONS FOR USE OF BISPHOSPHONATES DURING TREATMENT WITH GLUCOCORTICOIDS WITH A DURATION OF AT LEAST THREE MONTHS

Age/Dose	Risk Factor[a]	Treatment Recommendation
All adults taking >2.5 mg/day prednisone	—	Optimize calcium intake (1,000–1,200 mg/day), vitamin D intake (600–800 IU/day), and lifestyle modification
Adults >40 years of age taking any dose of prednisone	Low	Optimize calcium and vitamin D intake and lifestyle modifications over treatment with bisphosphonates, teriparatide, denosumab, or raloxifene
	Moderate	Treat with an oral bisphosphonate over calcium and vitamin D alone. Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, denosumab, or raloxifene
	High	reat with an oral bisphosphonate over calcium and vitamin D alone Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, denosumab, or raloxifene
<40 years of age	Low	Optimize calcium and vitamin D intake and lifestyle modifications over treatment with bisphosphonates, teriparatide, or denosumab
	Moderate to high	Treat with an oral bisphosphonate over calcium and vitamin D alone Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, or denosumab

[a]Ten-year risk of a major osteoporotic fracture, as defined with use of the FRAX calculator. (adjusting by 1.15 for major osteoporotic fracture and 1.2 for hip fracture if glucocorticoid treatment is >7.5 mg/day), bone mineral density, and history of fracture.

Source: [189] *Table 8*

The ACR updated their guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis in 2017 [189]. The ACR recommends daily calcium intake (dietary plus supplement) of 1,000–1,200 mg and supplemental vitamin D (600–800 IU) in conjunction with lifestyle modifications (e.g., maintaining a balanced diet and recommended weight, smoking cessation, regular weight-bearing or resistance training exercise, and limiting alcohol intake to one to two alcoholic beverages daily)_to prevent osteoporosis in all individuals taking glucocorticoids [189]. The ACR guidelines also include recommendations for the use of bisphosphonates according to an individual's age, risk factors, and dose and duration of the glucocorticoid , noting that risk is best assessed with a combination of the Fracture Risk Assessment (FRAX) tool (adjust and increase the 10-year risk generated with FRAX by 1.15 for major osteoporotic fracture and 1.2 for hip fracture if glucocorticoid treatment is >7.5 mg/day) and bone mineral density(***Table 8***) [189; 190]. In addition, baseline dual x-ray absorptiometry, height, prevalent fragility fractures, and serum 25-hydroxyvitamin D level should be obtained before the start of treatment with glucocorticoids and should be monitored throughout the course of treatment [189]. Better adherence to the ACR guidelines are needed, as one study showed that a baseline bone scan was done in only 39% of patients and appropriate treatment was also prescribed for only 39% [11].

COMORBIDITIES ASSOCIATED WITH RHEUMATOID ARTHRITIS		
Comorbidity	**Prevalence**	
	Lifetime	**Current**
Any gastrointestinal problem	50%	15%
Hypertension	47%	32%
Any psychiatric problem	36%	16%
Depression	34%	15%
Any endocrine problem	30%	20%
Any genitourinary problem	30%	4%
Cataract	27%	10%
Any lung problem	25%	12%
Any cardiovascular problem	22%	9%
Source: [191]		*Table 9*

Prevention of Comorbidities

Other comorbidities are prevalent among people with rheumatoid arthritis, and hypertension, gastrointestinal problems, and psychiatric problems/depression are the most common current and lifetime comorbidities (***Table 9***) [191]. In addition, the association between rheumatoid arthritis and an increased risk for cardiovascular disease and events is well-documented, including its impact on mortality. Follow-up care should include patient assessment and preventive strategies for these comorbidities, as well as treatment as appropriate. Individuals with rheumatoid arthritis should also be monitored for signs and symptoms indicative of autoimmune diseases commonly found in association with rheumatoid arthritis, such as thyroiditis, type 1 diabetes, Sjögren syndrome, and inflammatory bowel disease [4; 111; 144].

Prognosis

Of all the autoimmune diseases, rheumatoid arthritis is a leading cause of mortality, especially among women older than 65 years of age [27; 28]. Studies have consistently shown higher rates of mortality for individuals with rheumatoid arthritis than for the general population [192; 193; 194]. Furthermore, the increasing survival rates documented for the population at large since the 1950s and 1960s have not been found for individuals with rheumatoid arthritis [195]. The increased mortality has been linked to several factors, including extra-articular manifestations, markers of disease severity, and diminished function within the first year [193; 194]. By far, cardiovascular disease has been thought to confer the greatest risk for increased mortality [193; 194].

A meta-analysis of observational studies demonstrated that mortality related to cardiovascular disease is increased by about 50% in individuals who have rheumatoid arthritis (compared with individuals who do not have the disease) [196]. The increased risk cannot be explained by an increased incidence of traditional cardiovascular disease risk factors [197; 198; 199]. The underlying inflammatory mechanism is thought to have a role, and the increased use of disease-modifying drugs is expected to help improve survival in addition to function [194; 200]. To date, only methotrexate has been shown to be associated with a reduced risk of cardiovascular disease among individuals with rheumatoid arthritis [201]. The increased risk of cardiovascular disease highlights the need for clinicians to assess traditional and nontraditional cardiovascular risk factors, such as hypertension, obesity, smoking, hyperlipidemia, inflammation, insulin resistance, and family history of cardiovascular disease, and provide counseling, preventive measures, and treatment as appropriate [202].

POINTS OF EMPHASIS IN PATIENT EDUCATION REGARDING PREVENTION OF COMORBIDITIES ASSOCIATED WITH RHEUMATIC DISEASES AND THEIR TREATMENT	
Comorbidity/Complication	**Preventive Measures**
Infection	Wash hands frequently. Avoid situations that increase the risk of infection (e.g., crowded areas, public transportation, children and adults who have been recently vaccinated with live vaccines). Take precautions against injuries. Remain up-to-date on influenza vaccination.
Osteopenia/osteoporosis	Increase dietary intake of calcium and vitamin D. Take calcium and vitamin D supplements as prescribed. Engage in regular weight-bearing and muscle-strengthening activities. Stop smoking. Avoid excessive use of alcohol.
Cardiovascular disease	Maintain proper weight (reduce weight if necessary). Eat a healthy diet, low in fat, salt, and sugars. Engage in regular exercise/activities. Take any medications as prescribed (e.g., for hypertension, hyperlipidemia, or diabetes). Reduce stress. Stop smoking. Avoid excessive use of alcohol.
Source: [3; 189; 269]	*Table 10*

PATIENT EDUCATION

Education and self-management are valuable components of an overall treatment plan for a chronic illness such as rheumatoid arthritis [18; 162]. Studies have demonstrated that patient education improves function, patients' global assessment, adherence to the treatment plan, and psychologic status [48; 183].

Clinicians should emphasize the importance of noting new symptoms that may be related to adverse effects of treatment drugs and the need for strategies to minimize these effects [186]. For example, clinicians should counsel patients treated with glucocorticoids and/or immunosuppressant agents about ways to prevent osteoporosis and reduce the risk of infection and should emphasize to all patients the importance of modifying lifestyle factors that increase the risk for cardiovascular disease (***Table 10***).

Given the high rate of complementary and alternative medicine use, along with a substantial lack of disclosure of such use, clinicians should emphasize the importance of discussing the use of herbal and/or dietary supplements. Education should focus on the risk of disease progression if alternative approaches or supplements are used to replace conventional therapies and the potential for interactions between herbal supplements and treatment drugs.

Patient education should be tailored to address individual needs. Healthcare professionals should emphasize to patients that adhering to the management program will alleviate their symptoms, improve their function, and enhance their quality of life. Clinicians should also refer patients to reliable educational resources.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus is a chronic inflammatory autoimmune disorder of the connective tissue, primarily affecting the skin, joints, blood, and kidneys; however, other body systems/organs can also be affected. The disease process in systemic lupus is complex, with an often unpredictable course and a prognosis that varies from mild to severe to life-threatening. As with other autoimmune diseases, systemic lupus is characterized by recurring remissions and exacerbations (flares).

Improved treatment options have led to longer survival for people with systemic lupus [75]. Unfortunately, along with longer survival has come an increased risk for chronic diseases, especially cardiovascular disease. In addition, the disability caused by systemic lupus can be substantial. Studies and surveys have shown that the symptoms of fatigue, pain, and neurocognitive dysfunction cause many individuals with systemic lupus to stop working. Approximately 50% of individuals stop working within 13 years after diagnosis [203]. A large telephone survey found that the percentage of individuals with systemic lupus who were working decreased from 74% to 54% between the time of diagnosis and a follow-up interview one to two years later [204]. The number of people who stop working increases with longer time from diagnosis [204].

EPIDEMIOLOGY

The prevalence of systemic lupus has ranged from 72.8 to 143.7 per 100,000, with higher rates (127 to 280 per 100,000) among women [32; 59]. The incidence of systemic lupus has nearly tripled since the 1950s [194]. Approximately 161,000 to 322,000 adults in the United States have systemic lupus, according to prevalence and population estimates [56]. A 2017 systematic review, based on epidemiologic reports in 2013 and updated in 2016, estimates that the annual incidence of systemic lupus in North America is 23.2 cases per 100,000 population and the prevalence is 241 persons per 100,000 [301].

The prevalence rates for lupus are 5 to 10 times higher among women than men, reflecting the female preponderance of the disease [32; 59; 63]. Most women affected by the disease are of childbearing age; the average age at the time of diagnosis of adult-onset systemic lupus is 39.3 years [59]. About 3% to 18% of cases have an onset after 50 years of age [207]. The risk of the disease is 20 to 30 times more likely for the sibling of a person who has systemic lupus [42; 290].

Some researchers have evaluated prevalence according to race/ethnicity, and rates of systemic lupus are higher among black, Asian, Hispanic, and Native American populations than among the white population [32; 59; 63; 234; 322]. Studies have shown that the prevalence of systemic lupus is two to three times higher among black women than white women and about twice as common among black men compared with white men [32; 59; 63].

POTENTIAL ENVIRONMENTAL RISK FACTORS

Several environmental factors have been evaluated as contributors to the development of systemic lupus, and the strongest evidence has been found for infection, cigarette smoking, and hormones. These same factors have been associated not only with a higher incidence of systemic lupus but also with disease of greater severity and/or increased disease activity [31].

A strong association has been identified between systemic lupus and Epstein-Barr infection, with research demonstrating that an immune response to the Epstein-Barr virus plays an important role in the development of systemic lupus in at least some individuals with systemic lupus [3; 41; 42; 43].

The role of gut microbiota in the pathogenesis of systemic lupus has also been investigated. One group has reported that translocation of *Enterococcus gallinarum*, an intestinal gram-positive bacterium, can trigger autoimmunity in mice and humans [302]. The series of experimental observations reported by this group, demonstrating a causative role for *E. gallinarum* in a mouse model of systemic lupus, is the subject of a recent review

[303]. In the initial phase, administration of oral antibiotics directed against gram-positive bacteria was shown to improve survival, reduce serum levels of autoantibodies, and diminish the permeability of the bowel in lupus-prone mice. Increased bowel permeability, of the sort present in this mouse model, may lead to translocation of bacterial products from the gut having the potential to induce inflammation. *E. gallinarum* is somewhat unique in this regard, as it is known to promote the production of interferon-alpha, an immune mediator implicated in the pathogenesis of systemic lupus. The group found that live bacteria, principally *E. gallinarum*, escaped the mouse intestine and could be cultured from adjacent lymph nodes, mesenteric veins, and liver. When the intestines of healthy mice were colonized with *E. gallinarum*, the bowel became leaky and these mice produced antibodies to double-stranded DNA. Using a polymerase chain reaction assay, the group also found that DNA from *E. gallinarum* was present in the livers of a small group of patients with systemic lupus but not in specimens obtained from healthy controls. Finally, they showed that human hepatocytes, when co-cultured with *E. gallinarum*, produce interferon-alpha.

As discussed, tobacco smoking has been linked to the inflammatory response in rheumatic diseases. It is thought that smoking can trigger immune responses to anti-double-stranded DNA, antibodies that are relatively specific for systemic lupus [53; 211; 212; 213]. A meta-analysis of nine studies demonstrated a small but statistically significant association between current smoking and development of systemic lupus [214]. No association was identified between past smoking and the development of systemic lupus [214].

The mechanisms of sex hormones as a risk factor in the development of systemic lupus are unclear. A review and meta-analysis found that levels of sex hormones are altered in the presence of systemic lupus, but strong evidence of causal relationships was lacking [215]. Sex hormones and systemic lupus are more closely related among women than among men. Levels of dehydroepiandrosterone/dehydroepiandrosterone-sulfate (DHEA/DHEAS), progesterone, and testosterone are lower and estradiol and prolactin are higher among women with systemic lupus, whereas an increased prolactin level is the only abnormality confirmed among men with systemic lupus [215]. The effect of exogenous hormones has been debated, with some studies showing slightly increased risk for systemic lupus among women taking oral contraceptives or hormone-replacement therapy [52; 216]. Evaluation of 262 incident cases of systemic lupus in the Nurses' Health Study (total of 238,308 subjects) indicated that early age at menarche, oral contraceptive use, early age at menopause, surgical menopause, and postmenopausal use of hormones were each associated with an increased risk of systemic lupus [52]. However, the development of systemic lupus in children and in women after menopause, as well as the greater severity of disease among men, calls into the question the role of estrogen [216]. Although more research is needed to determine the exact relationships of sex hormones to the development of systemic lupus, it is agreed that the disease involves a complex interaction of multiple sex hormones, including estrogen, prolactin, DHEA, and testosterone [216].

ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

Other autoimmune diseases occur frequently in individuals with systemic lupus. In one study, 41% of subjects with systemic lupus had at least one other autoimmune disease and approximately 5% had two or more autoimmune diseases in addition to systemic lupus [217]. Among the most common autoimmune diseases in individuals with systemic lupus are thyroiditis, rheumatoid arthritis, antiphospholipid antibody syndrome, and Sjögren syndrome; in addition, fibromyalgia often co-occurs with systemic lupus.

MOST COMMON SIGNS AND SYMPTOMS OF SYSTEMIC LUPUS ERYTHEMATOSUS	
Organ/Body System	**Symptoms**
General	Fatigue Low-grade, unexplained, episodic fever Weight loss Generalized adenopathy
Cutaneous	Butterfly-shaped rash on face Photosensitivity Alopecia Oral mucosal sores, ulcers Raynaud phenomenon
Musculoskeletal	Arthralgia, arthritis Myalgia, muscle tenderness
Cardiovascular	Pericarditis Pericardial effusion Myocarditis
Respiratory	Pleuritic pain Pleurisy (with coughing and dyspnea)
Renal	Glomerulitis, glomerulonephritis
Neurologic	Cognitive dysfunction Headache Seizures Cranial or peripheral neuropathy
Gastrointestinal	Abdominal pain Nausea/vomiting
Ocular	Dry eye syndrome, uveitis, scleritis
Source: [188; 220]	*Table 11*

With regard to thyroiditis and systemic lupus, the prevalence of the two diseases in a single individual has varied widely [218]. In one study, autoimmune thyroiditis was found in 18% of individuals with systemic lupus [217]. Other researchers found that the prevalence of Hashimoto thyroiditis was 90-fold higher among individuals with systemic lupus than among the general population; the prevalence of Graves disease was 68-fold higher [65]. Subclinical thyroid disease has been found more often than overt disease [218].

Researchers believe that there is a common genetic susceptibility to both systemic lupus and rheumatoid arthritis, as genetic studies have shown that several loci are associated with an increased risk for both diseases [154]. Antiphospholipid antibody syndrome and Sjögren syndrome have each been found in about 14% of individuals with systemic lupus [217].

Systemic lupus has also been found to be a significant risk factor for fibromyalgia, with fibromyalgia occurring in 22% to 65% of individuals with systemic lupus [17; 70; 155]. However, race/ethnicity substantially affects the co-occurrence of these two diseases, with significantly positive associations among white populations but negative associations among black and Mexican populations [71; 219].

CLINICAL MANIFESTATIONS

The clinical manifestations of systemic lupus vary widely, and symptoms may develop abruptly or insidiously. The classic sign of active systemic lupus is a butterfly-shaped rash in the malar area of the face, which is present in up to 90% of cases [7]. Discoid rash may also occur elsewhere on the body, and approximately 40% of individuals have photosensitivity, with a rash resulting from sunlight exposure [220].

Joint pain occurs in approximately 90% of individuals and is usually symmetrical and typically involves the proximal joints of the fingers [220]. Other common symptoms are general and nonspecific. Nearly all individuals with systemic lupus note fatigue; nearly 80% have a low-grade, unexplained fever; and about 50% have unintentional weight loss or alopecia [220]. Other symptoms vary depending on the body systems affected (***Table 11***) [188; 220].

The clinical manifestations of systemic lupus often differ among older individuals. Malar and discoid rash, photophobia, arthritis, and glomerulonephritis are less common in the older population compared with the younger population, whereas fever, serositis, dry eye syndrome, and lung disease are more common in the older population [207].

DIAGNOSTIC EVALUATION

The diagnosis of systemic lupus is challenged by the waxing and waning of symptoms over time and variations in the degree of disease severity and in the organ systems involved. Because of the lower prevalence and differences in clinical manifestations among older individuals, diagnosis is especially challenging for that population and is often delayed [207].

The malar rash associated with systemic lupus can be easily misdiagnosed as rosacea or seborrheic dermatitis, but it is usually asymptomatic, lacking symptoms such as burning, itching, and tingling, that accompany other facial rashes [75]. The differential diagnosis of systemic lupus includes several other autoimmune disorders, such as early rheumatoid arthritis, undifferentiated connective tissue disease, vasculitis, and idiopathic thrombocytopenia purpura [7].

Diagnostic Criteria

Criteria for the classification and diagnosis of systemic lupus have been established by the ACR and was updated in 2019 (***Table 12***) [221; 222]. The updated criteria include a positive ANA at least once as obligatory entry criterion, followed by seven clinical and three immunologic manifestations, weighted from 2 to 10. A score of ≥10 is needed for a definitive diagnosis of systemic lupus [221; 222]. Because the criteria are based on the presence of signs and symptoms at any time during the course of the illness, an individual with early or atypical disease may not meet the criteria for definitive diagnosis. It is not uncommon for people with systemic lupus to meet only two of the clinical criteria, with the diagnosis subsequently confirmed by laboratory testing [75].

A positive ANA titer (≥1.80 on Hep-2 cells or an equivalent positive test) is required as diagnostic entry criterion. The ANA titer is highly sensitive for systemic lupus, with a positive result in approximately 93% to 100% of individuals with the disease [230; 231]. However, the specificity is low, and a positive titer will also be found in 60% to 80% of people with systemic sclerosis and 40% to 70% of people with Sjögren syndrome, as well as in a substantial number of healthy individuals [230]. After a patient has tested positive, additive criteria may be considered. A negative ANA titer (less than 1:160 on standard substrate) essentially rules out a diagnosis of systemic lupus.

Physical examination can identify some of the diagnostic criteria, including constitutional, mucocutaneous, serosal, and musculoskeletal symptoms; however, the absence of these signs may not necessarily exclude systemic lupus as a potential diagnosis because of the waxing and waning of symptoms.

Seizure, psychosis, and delirium are the three neurologic criteria for the classification of systemic lupus, but many other neuropsychiatric disorders occur in conjunction with the disease [221]. Neuropsychiatric disorders have been reported in up to 80% of adults with systemic lupus and more than 90% of children with the disease [223; 224]. The disorders may be evident before, at the time of, or after the diagnosis of systemic lupus [225]. In various studies of patients with systemic lupus (mainly adults), the most common manifestations of neuropsychiatric lupus were headache (87%), cognitive impairment (66%), and mood disorders (26%) [223; 226].

CLASSIFICATION CRITERIA OF THE AMERICAN COLLEGE OF RHEUMATOLOGY FOR THE DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS		
Entry Criterion		
Domain	**Criteria**	**Weight**
Positive antinuclear antibody (ANA) titer	ANA titer of >1.80 on Hep-2 cells or an equivalent positive test (ever)	Must be positive to continue to additive criteria
Additive Criteria, Clinical		
Constitutional	Fever	2
Hematologic	Leukopenia Thrombocytopenia Autoimmune hemolysis	3 4 4
Neuropsychiatric	Delirium Psychosis Seizure	2 3 5
Mucocuteanous	Non-scarring alopecia Oral ulcers Subacute cutaneous OR discoid lupus Acute cutaneous lupus	2 2 4 6
Serosal	Pleural or pericardial effusion Acute pericarditis	5 6
Musculoskeletal	Joint involvement	6
Renal	Proteinuria >0.5 g/24h Renal biopsy Class II or V lupus nephritis Renal biopsy Class III or IV lupus nephritis	4 8 10
Additive Criteria, Immunology		
Antiphospholipid antibodies	Anti-cardiolipin antibodies OR Anti-β2GP1 antibodies OR Lupus anticoagulant	2
Complement proteins	Low C3 OR low C4 Low C3 AND low C4	3 4
SLE-specific antibodies	Anti-dsDNA antibody OR Anti-Smith antibody	6
Source: [221; 222]		*Table 12*

Laboratory testing can help to identify the remaining clinical criteria, including hematologic, renal, neuropsychiatric disorders. The work-up should include a CBC with differential, platelet count, chemistry profile (especially kidney and liver function studies), and urinalysis [220; 227]. Evidence of renal involvement may include proteinuria or red blood cell casts and leukocytes in the urine [220]. Hematologic testing may indicate anemia (in about 40%), thrombocytopenia (in about 25% to 35%), and leukopenia (in about 15% to 20%) [227]. Metabolic abnormalities (e.g., uremia, electrolyte imbalance, or ketoacidosis) may be signs of neurologic disorders; seizures or psychosis are other signs [75].

Other laboratory testing includes , as well as anti-double-stranded DNA, antibody to Sm nuclear antigen (anti-Sm), antiphospholipid antibodies, anti-Ro/SSA, and anti-La/SSB antibodies (***Table 13***) [7; 228; 229].

ANTIBODY TESTING FOR SYSTEMIC LUPUS		
Diagnostic Test	**Prevalence[a]**	**Comments**
Antinuclear antibody titer	93% to 100%	Positive titer also found in systemic sclerosis (up to 80%) and Sjögren syndrome (up to 70%), as well as many healthy individuals
Anti-double-stranded DNA	70% to 80%	Positive test highly specific for systemic lupus Associated with greater risk of skin disease and lupus nephritis
Anti-Ro	30% to 40%	Also associated with Sjögren syndrome (up to 70%) Associated with greater risk of skin disease, lupus nephritis, and fetal heart problems
Antiphospholipid antibodies	20% to 30%	Associated with greater risk of thrombosis and pregnancy loss
Anti-Sm	10% to 30%	Positive test highly specific for systemic lupus Associated with greater risk of lupus nephritis
Anti-La	15% to 20%	Associated with Sjögren syndrome (up to 50%) Associated with fetal heart problems
[a]Among people with systemic lupus.		
Source: [160; 230; 231; 232; 270]		*Table 13*

Anti-double-stranded DNA and anti-Sm tests can help confirm a diagnosis of systemic lupus, as they have greater specificity than the ANA titer; however, they are not as sensitive as the ANA titer [232]. The prevalence of positive anti-Ro/SSA and anti-LA/SSB titers is also low, and these titers are more often positive among older people [207]. Serum complement levels may also be useful, as decreased levels indicate active or impending exacerbation of disease [7; 75; 228; 229]. The prevalence of positive anti-double-stranded DNA titers and of decreased complement levels is lower among older individuals than among younger ones [207].

The presence of antiphospholipid antibodies is determined with testing for anticardiolipin antibodies or for lupus anticoagulant [7; 75]. About 20% to 30% of people with systemic lupus have antiphospholipid antibodies, which increase the risk for thromboembolism and pregnancy loss [232].

REFERRAL

The ACR recommends that primary care providers refer patients with suspected lupus to a rheumatologist to confirm the diagnosis and to evaluate the activity and severity of disease [7]. The rheumatologist will establish a treatment plan, and when the disease is mild-to-moderate, the primary care provider can monitor the clinical course of the disease and drug-related toxicities. Because of the range in systems/organs that may be affected, a variety of other specialists may be needed during the course of disease. In addition, referral to physical and occupational therapies, social workers, and psychologists may also be appropriate.

TREATMENT OPTIONS

Data from large, randomized, controlled trials in the treatment of systemic lupus are lacking, creating a weak evidence base for recommendations. The ACR published guidelines for the management of systemic lupus in 1999, before the advent of many of the drugs currently used [7]. The EULAR published guidelines in 2008, acknowledging the lack of strong evidence, and updated their guidelines for the management of systemic lupus erythematosus in 2019 [233; 289]. One of the challenges of treating systemic lupus is that very few drugs have FDA approval for use, leading researchers to evaluate the efficacy and safety of drugs approved for other conditions, most notably rheumatoid arthritis [235; 236]. Several drugs have been used in clinical practice, with their use depending on the severity of disease (***Table 14***) [7; 75; 186; 225]. First-line treatment

TREATMENT OPTIONS FOR SYSTEMIC LUPUS			
Agent	**Typical Dose[a]**	**Indication**	**Side Effects**
Nonsteroidal anti-inflammatory drugs (NSAIDs)	At or near the upper limit of the dose range	Mild-to-moderate arthritis, fever, mild serositis	Gastrointestinal bleeding, renal and hepatic toxicity
Immunosuppressants/ cytotoxic agents	Dose varies	Usually used in conjunction with a low-dose glucocorticoid	Infection, leukopenia, anemia, thrombocytopenia, myelosuppression, lymphoma, gastrointestinal effects, alopecia
Antimalarial Agents			
Hydroxychloroquine	200 mg PO twice daily	Preferred first-line treatment; effective for arthritis and rash and for preventing disease flares	Dizziness, nausea and diarrhea (usually resolves over time), macular damage
Glucocorticoids			
Prednisone (low dose)	≤10 mg PO daily	Usually used in conjunction with hydroxychloroquine	Osteopenia/osteoporosis, infection, hypertension, avascular necrosis of bone, weight gain, glaucoma, cataracts, psychologic effects
Prednisone (moderate dose)	≤20 mg PO daily	Moderate disease (without organ involvement) with inadequate response to first-line treatment	
Methylprednisolone (high dose)	40–60 mg PO daily or 1 g IV daily X3	Lupus nephritis, cerebritis, thrombocytopenia	
Topical	Low or intermediate dose	Facial lesions	Skin atrophy, infection, contact dermatitis
	Intermediate dose	Lesions on trunk or extremities	
	High dose	Lesions on palms or soles	
Azathioprine	25–150 mg PO daily	Nonarthritic disease refractory to antimalarial agent and/or glucocorticoids; maintenance therapy for lupus nephritis, neuropsychiatric lupus	Hepatitis, pancreatitis
Methotrexate	7.5–20 mg PO weekly	Mild-to-moderate disease refractory to first-line treatment; lupus nephritis, neurologic complications	Hepatic fibrosis, cirrhosis, pulmonary infiltrates, stomatitis, mucositis; teratogenic
Cyclophosphamide	IV, dose varies	Digital vasculitis; disease with organ involvement (lupus nephritis, cerebritis)	Irreversible ovarian or testicular failure (with long-term use); nausea, alopecia, herpes zoster; teratogenic
Mycophenolate mofetil	1.5–3 g PO daily	Mild-to-moderate lupus nephritis (induction and maintenance therapy); refractory thrombocytopenia; cutaneous manifestations; uncontrolled disease	Diarrhea, nausea; teratogenic
Leflunomide	10–20 mg PO daily	Mild-to-moderate disease refractory to first-line treatment	Diarrhea, alopecia, rash; teratogenic
Topical Calcineurin Inhibitors			
Tacrolimus or pimecrolimus	0.1%	Severe cutaneous lesions resistant to other agents	Peeling and burning sensation
Monoclonal Antibody			
Belimumab	10 mg/kg IV every 2 weeks for 6 weeks, then every 4 weeks	Adjunctive therapy for autoantibody-positive, mild-to-moderate systemic lupus	Nausea, fever, diarrhea, nasopharyngitis, insomnia; possibly teratogenic
Rituximab	375 mg/m^2 IV once weekly for 4 doses OR 500–1,000 mg on days 1 and 15	Mild-to-moderate disease refractory to first-line treatment; lupus nephritis	Nausea, fever, fatigue, cytopenias, lymphopenia; possibly teratogenic
[a]For most drugs, the typical dose may vary, as no recommended dose has been established because of the lack of FDA approval.			
Source: [7; 20; 75; 186; 225; 236]			*Table 14*

has not changed significantly since 1993, with most physicians relying hydroxychloroquine and prednisone as the initial approach [247].

The goals of treatment of systemic lupus are to reduce inflammation, alleviate symptoms, achieve and maintain remissions, and prevent organ damage, all while minimizing the risk of treatment side effects. The approach to the treatment of older individuals with newly diagnosed systemic lupus is the same as that for younger individuals, but treatment is complicated in older people because of a greater likelihood of comorbidities and an increased risk of treatment-related toxicity [207].

Mild Disease (No Organ Involvement)

The cornerstone of treatment of mild systemic lupus without major organ involvement is typically an antimalarial drug and a low-dose glucocorticoid (usually prednisone), two of only three drugs approved by the FDA for use in systemic lupus. Antimalarial agents include chloroquine and hydroxychloroquine, and the latter is preferred because of its better side effect profile [7]. Antimalarial agents offer many benefits. They can alleviate joint-related, cutaneous, constitutional, and serosal manifestations of systemic lupus; they can prevent disease flares; they are well tolerated; they have been associated with a lower risk of infection than other treatment approaches; and they have a protective effect on survival [237; 238]. Despite all these advantages, hydroxychloroquine is underutilized in practice [239].

A low-dose oral glucocorticoid is typically used in conjunction with an antimalarial agent to provide further relief of symptoms. For most patients with mild disease (and no major organ involvement), prednisone at a dose of 5 mg per day is effective, although some patients may need 10 mg per day [75]. NSAIDs may also be used to provide symptomatic relief of joint manifestations [7]. The use of both glucocorticoids and NSAIDs should be carefully considered because of their associated toxicity [7]. Glucocorticoids should be given at the lowest possible dose that suppresses manifestations of disease activity and prevents flares [75].

Although antimalarial drugs usually resolve systemic lupus-related rash, the mainstay of treatment for this manifestation is a topical glucocorticoid, available as a cream, liquid, or gel [7]. Intermediate-dose rather than high-dose topical glucocorticoids should be used on areas where atrophy is more likely, such as the face [7]. Novel therapies for cutaneous lesions are calcineurin inhibitors, most notably tacrolimus and pimecrolimus [236]. The use of these immunomodulators has been shown to be effective, but studies have been small [236]. The FDA has approved tacrolimus and pimecrolimus for the treatment of moderate and severe atopic dermatitis in adults and children but has not approved them for use in systemic lupus [236].

If the disease response to antimalarial drugs and tolerable doses of glucocorticoids (i.e., daily dose of prednisone of 10 mg or less) is inadequate, treatment with an immunosuppressant should be considered as a glucocorticoid-sparing approach [75]. Methotrexate and leflunomide have been evaluated in mild-to-moderate systemic lupus, and many studies have indicated benefit, especially with regard to joint- and skin-related symptoms, but the data have been conflicting [75; 235]. Azathioprine is often the drug of choice for nonarthritic manifestations that have not responded to antimalarial treatment and low-dose glucocorticoid [75]. Because of the increased risk for infection associated with immunosuppressants, screening for tuberculosis and chronic viral infections should be completed before treatment with an immunosuppressant agent begins [43].

It has been hypothesized that biologics may be the next frontier of lupus treatment. In 2011, the FDA approved belimumab, the first new drug for lupus in more than 50 years [243]. Belimumab, a monoclonal antibody against B-lymphocyte stimulator, has been associated with better clinical response compared with placebo [243; 251]. More research is necessary to determine if the drug is effective in black patients and patients with severe manifestations, especially those with nephritis and neurologic disease [291]. Belimumab is approved to treat patients with active, autoantibody-positive lupus who are receiving standard therapy [243]. It

is administered via an intravenous infusion at an initial dose of 10 mg/kg every two weeks for six weeks; the maintenance dose is 10 mg/kg every four weeks [20].

Though not FDA approved for the treatment of systemic lupus erythematosus, rituximab has shown promise in the management of lupus [291; 292]. Like belimumab, rituximab is a monoclonal antibody that selectively depletes B cells. Many open-label studies have shown improvements in lupus symptoms with the use of rituximab, including in patients with severe and/or refractory disease, but two large randomized, double-blind studies failed to show major clinical response compared with placebo [291; 292]. Additional research is ongoing.

Systemic lupus often affects the eyes, with about one-third of patients having dry eye syndrome (keratoconjunctivitis sicca) [188]. Symptoms are usually relatively mild (e.g., irritation and redness), and artificial tear drops can be used to treat milder forms of the condition [188]. Pain in the eye or significant visual impairment at any time during the course of disease warrants immediate referral to an ophthalmologist [188].

Neuropsychiatric disorders have been shown to have a persistent negative effect on quality of life for people with systemic lupus [223; 224]. According to EULAR guidelines, appropriate treatment depends on the cause of the disorder: glucocorticoids and immunosuppressants are recommended for disorders that reflect an immune/inflammatory process, and antiplatelet/anticoagulation therapy is recommended for disorders thought to be related to antiphospholipid antibodies [225]. Prophylaxis with low-dose aspirin may be of benefit for people with positive results on testing for antiphospholipid antibodies, as thromboembolic events occur in approximately 50% of these patients [75].

Systemic lupus is associated with reduced exercise capacity and decreased muscle strength, which are exacerbated by disease-related fatigue and sleep disturbances [240; 241; 242]. To address these issues, routine exercise should be part of the overall treatment plan for people with mild-to-moderate disease [242; 244]. Individuals with systemic lupus who participated in a supervised cardiovascular training program had significant improvements in exercise tolerance, aerobic capacity, quality of life, and depression [245]. Exercise programs should focus on aerobic exercises as well as strength training to improve isometric strength and should begin with a formal, supervised program, as adherence has been better for such programs than for home-based ones [242].

Uncontrolled or Moderate-to-Severe Disease

Uncontrolled systemic lupus is defined as the persistence of clinical manifestations during treatment. Several manifestations indicate uncontrolled disease, including [7]:

- Pleurisy, pericarditis, and/or arthritis not controlled by NSAIDs
- Rash not controlled by topical therapies
- Vasculitis
- Digital ulcers
- Muscle weakness and/or elevated creatine phosphokinase despite glucocorticoid therapy
- Any central nervous system manifestation
- Continuing evidence of active renal disease, cardiopulmonary disease, or hematologic manifestations despite therapy

The primary care provider should refer patients with uncontrolled disease to a rheumatologist [7]. Moderate doses of a glucocorticoid may be effective for moderately severe disease without major organ involvement (e.g., arthritis, dermatitis, serositis, systemic symptoms) [75]. Glucocorticoids should be tapered as tolerated until a maintenance level can be established [75].

As systemic lupus progresses to moderate-to-severe disease, it can affect any major organ system. However, the kidneys are most commonly involved. Lupus nephritis occurs in 50% to 60% of individuals with systemic lupus within 10 years of diagnosis and leads to end-stage renal disease in 17% to 25% of patients [169]. The prevalence of lupus nephritis

is higher in the black, Hispanic, and Asian populations than in the white population and is higher in male patients than female patients [169]. The goal of treating nephritis is to reduce the risk of end-stage renal disease and death, but controlling proteinuria and preventing disease flares are also important aims [169].

Recommended treatment for proliferative lupus nephritis is a glucocorticoid plus another immunosuppressant agent (cyclophosphamide or mycophenolate mofetil) [169; 227]. In 2012, the ACR published a guideline for the treatment and management of lupus nephritis [169]. This guideline outlines an approach to treatment focused on the stage of disease (as determined by renal biopsy) and improvement in symptoms over time. Very early disease (class I or II) generally does not require immunosuppressive therapy [169]. For more advanced disease, the recommended induction therapy is cyclophosphamide or mycophenolate mofetil with glucocorticosteroids for three days, which is replaced by prednisone [169]. After six months, response to therapy is assessed and changes in the regimen are made. Mycophenolate mofetil is preferred over cyclophosphamide for black and Hispanic patients. In addition, all patients with systemic lupus erythematosus with nephritis should be treated with a background of hydroxychloroquine, unless contraindicated [169].

The American College of Rheumatology Task Force Panel recommends that all patients with clinical evidence of active lupus nephritis, previously untreated, undergo renal biopsy (unless strongly contraindicated) so glomerular disease can be classified.

(https://www.rheumatology.org/Portals/0/Files/ACR%20Guidelines%20for%20Screening,%20Treatment,%20and%20Management%20of%20Lupus%20Nephritis.pdf. Last accessed July 23, 2020.)

Level of Evidence: C (Consensus opinion of experts, case studies, or standard of care)

Biologic agents, including anti-TNF-α factors, IL-6 inhibitors, co-stimulation blockers, and anti-CD20 agents, have also been evaluated for efficacy in systemic lupus but have not been as successful as in rheumatoid arthritis, due to a lack of efficacy and/or high rates of adverse events [251]. Rituximab had preliminary success in treating resistant lupus manifestations, including central nervous system, vasculitic, hematologic, and renal manifestations; however, as noted, the results of two large phase II/III placebo-controlled, randomized controlled trials were negative [235; 251].

Anifrolumab is a human monoclonal antibody to type 1 interferon subunit 1 recently investigated for the treatment of moderately to severely active systemic lupus [304]. In a phase 3 trial, patients were randomly assigned to intravenous anifrolumab (180 subjects) or placebo (182 subjects) every 4 weeks for 48 weeks, and the end-point was a clinical response at 52 weeks. Applying a standard clinical assessment tool designed to measure reduction in baseline disease activity, 47.8% in the anifrolumab group had a favorable response compared with 31.5% in the placebo group. Although the difference favoring anifrolumab was significant, the character and quality of benefit realized was only modest. Patients who received anifrolumab were more likely to have reductions in the glucocorticoid dose and in the severity of skin disease than were patients who received placebo. However, differences with respect to counts of swollen and tender joints and the annualized rate of lupus flares were not significant. While the overall number of adverse events was the same in both groups, the frequency of herpes zoster was higher with anifrolumab (7.2%) than with placebo (1.2%) [304].

Approximately 50% of people with systemic lupus seek symptomatic relief with complementary and alternative methods [252]. However, data and evidence of efficacy are lacking on a variety of these methods, including herbal medicines, dietary supplements, and acupuncture. However, small trials involving vitamin D supplements, tumeric, and omega-3 fatty acids show some promise [252]. In addition, counseling and therapy may improve quality of life and mood [248].

QUALITY INDICATORS FOR FOLLOW-UP CARE FOR PATIENTS WITH SYSTEMIC LUPUS	
Patient Population	**Recommendation**
All	Discuss risks and benefits of any newly prescribed medication. Obtain baseline studies before beginning treatment with any new medication and monitoring for drug toxicity, as recommended. Assess cardiovascular risk factors annually.
Receiving immunosuppressant treatment	Recommend annual influenza vaccination.
Receiving prednisone at a dose of ≥10 mg/day for at least 3 months (or other glucocorticoid equivalent)	Attempt to taper dose, add a steroid-sparing agent, or escalate dose of existing steroid-sparing agent.
Proteinuria ≥300 mg/day	Begin treatment with an ACE inhibitor or an ARB.
Proteinuria ≥300 mg/day and two or more blood pressure readings (including the most recent reading) with a systolic pressure >130 mm Hg or diastolic pressure >80 mm Hg over 3 months	Begin treatment for hypertension or change current antihypertensive agent (or increase dose).
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.	
Source: [227]	*Table 15*

Treatment During Pregnancy

Pregnancy in women with systemic lupus is associated with risks for both the mother and the fetus, and pregnant women should be managed as high-risk obstetric patients [75]. Pregnancy may cause disease flares, especially in the third trimester and postnatal period, but flares are usually mild and can be controlled without excessive risk to either the mother or the fetus [75; 233]. Many treatment agents may be used during pregnancy, including hydroxychloroquine, prednisone, and azathioprine; evidence suggests that mycophenolate mofetil, cyclophosphamide, and methotrexate should be avoided [233]. Systemic lupus increases the risk for fetal loss, especially in women who have antiphospholipid antibodies [75; 233]. A history of lupus nephritis, antiphospholipid antibodies, and anti-Ro and/or anti-La antibodies are associated with increased risk for pre-eclampsia, miscarriage, stillbirth, premature delivery, intrauterine growth restriction, and fetal congenital heart block [233]. Heparin and aspirin are usually given throughout pregnancy to reduce the risk of miscarriage and thrombotic events.

Pregnant patients with symptomatic lupus nephritis may be treated with hydroxychloroquine (for mild disease) or prednisone plus azathioprine (for clinical active disease) [169]. In cases of severe persistent disease, delivery after 28 weeks may be necessary [169].

FOLLOW-UP AND PROGNOSIS

Follow-up care is essential for individuals with systemic lupus not only to evaluate the response to treatment but also to monitor for drug-related adverse events and to prevent infection and common comorbidities [7; 169; 227; 233; 253]. The EULAR has established evidence-based guidelines for following up patients with systemic lupus, and an expert panel in the United States proposed several quality indicators for follow-up care (***Table 15***) [227]. Better adherence to the quality indicators is needed, as a survey of 200 patients in a rheumatology clinic showed low rates of adherence, especially for assessment of cardiac risk factors [15]. Having a primary care physician within the care network increased the likelihood that care met quality indicators [15].

The ACR recommends follow-up visits every 3 to 6 months for individuals with mild disease; the later EULAR guidelines recommend follow-up assessment every 6 to 12 months, although the guidelines note that this frequency is arbitrary [7; 253]. Individuals with more severe disease and/or organ involvement may need follow-up at more frequent intervals.

Disease Activity/Response to Treatment

Disease activity should be assessed by a validated instrument, and the most widely used tools are the Systemic Lupus Activity Measure (SLAM), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Lupus Activity Index (LAI), British Isles Lupus Assessment Group (BILAG) index, and the European Consensus Lupus Activity Measure (ECLAM) [253; 254; 255]. The EULAR also recommends evaluation of quality of life through patient history and/or a patient global assessment at each visit and annual assessment of organ damage [253].

Laboratory testing every 6 to 12 months should include urinalysis, CBC, ESR, CRP, albumin, and creatinine levels [253]. Anti-double-stranded DNA titer and serum complement levels should also be obtained, as an increase in the anti-double-stranded DNA titer and decreases in the serum complement levels often signal a disease flare [75; 253]. As defined by an international panel of experts, a flare is "a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment" [256]. Early treatment with a glucocorticoid may reduce the total dose needed to suppress the flare [75].

Because of the risk for lupus nephritis, patients should be followed up closely for signs of progression of disease to the kidneys. For patients who have persistently abnormal urinalysis results or elevated serum creatinine level, a urine protein/creatinine ratio (or 24-hour urine for protein), urine sediment, and ultrasound of the kidney should be done, and referral for a biopsy should be considered [253]. When evidence of renal disease is found, CBC, serum creatinine level, urinalysis with microscopic evaluation, and quantitative testing of urinary protein should be done at three-month intervals [227; 253].

Approximately 50% to 60% of neuropsychiatric manifestations occur within the first year after diagnosis, and patients should be evaluated carefully for relevant signs and symptoms [225]. A focused history can be used to elicit information about such symptoms as seizures, paresthesias, numbness, weakness, headache, epilepsy, and depression [253]. Clinicians should also assess patients for cognitive impairment by asking questions about problems with multitasking, household tasks, or memory [253]. If cognitive impairment is suspected, the patient should be evaluated further [253].

Monitoring and Treatment of Drug Side Effects

Infection, osteopenia/osteoporosis, and bone marrow suppression are the major side effects of treatment for systemic lupus; gastrointestinal, hepatic, renal/genitourinary, cardiovascular, and neurologic effects may also occur [186]. Recommended testing for individuals receiving methotrexate, mycophenolate mofetil, or azathioprine is a CBC and platelet count every three months [227]. Individuals treated with methotrexate should also have liver function studies done every three months [227]. A serum glucose level should be obtained yearly for patients treated with glucocorticoids [227]. Monitoring during treatment with cyclophosphamide should be done monthly, with a CBC, platelet count, and urinalysis [227]. No laboratory testing is recommended to monitor treatment with hydroxychloroquine.

Prevention of Infection

Infection has been estimated to be responsible for 30% to 50% of morbidity and mortality among individuals with systemic lupus and is a leading cause of mortality [43; 257]. Approximately 80% of infections are caused by bacterial micro-organisms, with the skin, respiratory tract, and urinary tract accounting for more than two-thirds of affected sites [42].

Viral infections occur less commonly, and parvovirus B19 and cytomegalovirus are the most common viral micro-organisms [42; 258]. Symptoms related to viral infections often mimic disease flares [258]. Women with systemic lupus are at increased risk for infection with the human papillomavirus (HPV)-16 virus and thus are at risk for premalignant cervical lesions [42]. Factors associated with heightened risk for infection include [42; 43]:

- Active disease
- Neutropenia/lymphopenia
- Low serum complement levels
- Involvement of major organ systems (e.g., kidney, lung, central nervous system)
- Treatment with immunosuppressive agents

Treatment with antimalarial drugs has been shown to have a significant protective effect against infection, further confirming that treatment with antimalarial agents should be the standard of care unless contraindicated [257; 259].

In anticipation of the need to administer glucocorticoids and possibly other immunosuppressive drugs, clinicians should perform purified protein derivative skin testing early in the management course of a patient with lupus. A positive skin test indicates latent tuberculosis and the need for isoniazid prophylaxis whenever immunosuppressive drugs are used. Other measures to prevent infection include timely pneumococcal and influenza vaccinations for individuals with stable disease [43; 257; 258].

Prevention of Osteoporosis

As noted, long-term use of glucocorticoids is associated with a wide range of potential adverse events, including osteopenia/osteoporosis, hypertension, cataracts, glaucoma, dyspepsia, weight gain, avascular necrosis of bone, Cushingoid changes, and adverse psychologic effects [186; 189]. Of these side effects, osteoporosis is of particular concern, with a prevalence of 4% to 24% among patients with systemic lupus [253]. According to the updated 2017 ACR guidelines, the following are recommended for the prevention and treatment of glucocorticoid-induced osteoporosis [189; 190]:

- Daily calcium intake (dietary plus supplement) of 1,000–1,200 mg, supplemental vitamin D (600–800 IU), and lifestyle modifications (balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing or resistance training exercise, limiting alcohol intake to one to two alcoholic beverages per day) to prevent osteoporosis in all individuals taking glucocorticoids
- Use of bisphosphonates according to an individual's risk (noting that risk is best assessed with the FRAX tool, which provides a better overall clinical risk profile than bone mineral density alone)
- Dual x-ray absorptiometry, height, prevalent fragility fractures, and serum 25-hydroxyvitamin D level at baseline (before treatment starts) and at intervals throughout the course of treatment

Prevention of Treatment-Related Eye Disease

As discussed, hydroxychloroquine increases the risk for retinopathy, although this toxicity is rare at doses of less than 6.5 mg/kg/day for fewer than five years [187; 188]. Still, ophthalmologic follow-up is important for early detection and minimization of this potentially serious side effect [187]. The AAO recommends a complete ophthalmologic examination within the first year after treatment [187]. Routine examination of the eyes should be done for patients treated with glucocorticoids who are at high risk for cataracts and glaucoma, and studies indicate that adherence to this recommendation is suboptimal [8; 253].

Prevention of Comorbidities

The EULAR guidelines recommend a high index of suspicion and prompt evaluation for comorbidities commonly associated with systemic lupus, such as atherosclerosis, hypertension, dyslipidemia, and non-Hodgkin lymphoma [233]. Among patients with systemic lupus, the prevalence of hypertension or dyslipidemia has been reported to range from approximately 11% to 75% [191; 253]. Racial disparities exist, with cardiovascular events occurring

COMORBIDITIES ASSOCIATED WITH SYSTEMIC LUPUS		
Comorbidity	**Prevalence**	
	Lifetime	**Current**
Any gastrointestinal problem	61%	27%
Any psychiatric problem	58%	34%
Depression	57%	34%
Hypertension	56%	37%
Any lung problem	42%	21%
Any endocrine problem	38%	25%
Any genitourinary problem	37%	6%
Any cardiovascular problem	32%	13%
Source: [191]		*Table 16*

at a younger age in black women and men [260; 261]. Although the increased risk of cardiovascular disease in the systemic lupus population cannot be fully explained by traditional cardiovascular risk factors, experts agree that such risk factors should be evaluated at least annually and that modifiable risk factors should be treated according to established guidelines [233; 253].

Hypertension and cardiovascular problems are among the most common comorbidities in individuals with systemic lupus (***Table 16***) [191]. Hypertension is the leading current comorbidity, and any gastrointestinal problem is the leading lifetime comorbidity. Psychiatric problems and depression are the second and third leading current and lifetime comorbidities [191]. Follow-up care should include patient assessment and preventive strategies for these comorbidities, as well as treatment as appropriate.

The risk of cancer is slightly increased for individuals with rheumatic diseases in general and for systemic lupus specifically [262; 263]. Although several types of cancer have been reported to occur more frequently, the risk is greater for hematologic cancers, especially non-Hodgkin lymphoma [262; 263; 264]. The underlying link between cancer and systemic lupus is unknown, but both the disease itself and medication exposure are thought to be factors [263]. The risk for HPV infection and cervical dysplasia are increased, making patients with lupus at a greater risk for virus-associated malignancies (e.g., cervical cancer, anal cancer) [249; 265]. Clinicians should assess patients for signs and symptoms of cancer and should ensure that routine cancer screening is carried out [253; 262; 263]. Shorter intervals for gynecologic evaluation are reasonable for women with systemic lupus due to the increased risk for cervical cancers [265].

It is interesting to note that the risk of certain other malignancies, specifically breast, ovarian, endometrial, and prostate cancers, appears to be decreased in patients with systemic lupus erythematosus, likely due to a combination of factors, including long-term use of medications and potential exogenous hormone use [249; 250].

Because of the high percentage of thyroiditis and the potential for polyautoimmunity among people with systemic lupus, clinicians should carefully consider the possibility of these diseases during follow-up, especially among those at highest risk [65; 218]. The highest risk for polyautoimmunity has been associated with female sex, articular involvement, familial autoimmunity, and positive anti-Ro titer [217].

Systemic lupus often has a substantial impact, with disease-related symptoms interfering with quality of life and ability to work [203; 204; 223; 224; 266]. In a survey study, the factors significantly associated with workplace activity limitations were older age, greater disease activity, fatigue, poorer health status, lower job control, greater job strain, and working more than 40 hours per week [266]. Healthcare professionals should ask patients about their ability to cope with the disease and should suggest support groups or counseling as appropriate.

Prognosis

Systemic lupus is one of the leading causes of death among autoimmune disorders, and its associated mortality is higher than that expected for the general population [27; 209]. Mortality among women is consistent across all age-groups [27]. Survival has improved substantially over the years, from a four-year survival of 50% in the 1950s to a five-year survival rate of 95% today [75; 194; 209; 232]. Ten-year and 15-year survival rates have been reported to be approximately 90% and 80%, respectively [209; 267]. Improved survival is thought to be the result of earlier diagnosis, recognition of mild disease, increased use of ANA testing, and better treatment options [194]. Lower survival rates are associated with an older age at the time of diagnosis and male gender, and mortality rates are twofold to threefold higher among the black population than among the white population [209; 260; 261; 267].

PATIENT EDUCATION

In a study of patients with lupus (predominantly women), the majority of participants indicated that they were very interested in a patient education program. Patients expected a broad range of topics to be covered as part of the program, including pregnancy, possible outcomes of the disease, specific information related to different treatments, and the management of fatigue and pain [246]. In addition, patients should receive clear information regarding management of complications, minimizing sun exposure, and physical activity.

The risk of complications and side effects associated with systemic lupus and its treatment makes it imperative for patients with lupus to understand the measures needed to prevent complications. Education should focus on the importance of the identification and prompt reporting of signs and symptoms related to drug toxicity and to following measures to prevent infection and comorbidities, especially osteoporosis and cardiovascular disease. In addition, clinicians must emphasis the importance of routine cancer screening, especially for cervical cancer, not only because of the increased risk of cancer, but also because the rate of cancer screening has been reported to be lower among individuals with systemic lupus [253; 268]. Patients should also become familiar with the signs and symptoms of disease flares, to aid in early identification and treatment.

Education about avoiding sun exposure is also essential, as ultraviolet rays can induce or exacerbate both cutaneous and systemic flares of systemic lupus [7; 227]. Healthcare professionals must emphasize protective measures such as the use of a sunscreen that shields against both ultraviolet A and B rays, wearing protective clothing, and avoiding exposure to the sun during its hottest periods (typically 10 a.m. to 4 p.m.) [269]. Individuals should also be reminded that fluorescent and halogen lights may emit ultraviolet rays [269]. Education regarding sun avoidance should be documented at least once in the medical record, according to quality indicators established for the treatment of systemic lupus [227].

Healthcare professionals should also counsel patients about the many benefits of regular exercise and the need to avoid exhaustion and to rest when they sense the beginning of a flare [7]. Patient education must emphasize that, although it does not seem intuitive, regular exercise or recreational activities will help alleviate the severe fatigue often associated with systemic lupus as well as enhance overall well-being and reduce the risk of cardiovascular disease [242; 244; 245].

SJÖGREN SYNDROME

Sjögren syndrome is a systemic chronic inflammatory condition characterized primarily by decreased function of lacrimal and salivary glands, enlargement of the parotid gland, and often, extraglandular manifestations. The clinical hallmark of the disease is the triad of dry mouth and eyes, fatigue, and joint pain [305]. The syndrome is classified as primary when it develops in a previously healthy individual and as secondary when it is associated with an underlying rheumatic disease.

The pathogenesis of Sjögren syndrome primarily involves organ-specific autoantibodies-antibodies to cellular antigens of salivary ducts, the thyroid gland, the gastric mucosa, erythrocytes, the pancreas, the prostate, and nerve cells. In addition, non-organ-specific autoantibodies are found in approximately 60% of individuals with the disease [67].

EPIDEMIOLOGY

The incidence of primary Sjögren syndrome has been estimated to range from 0.5% to 1% of the total population [56; 67; 270; 354]. On the basis of prevalence and population estimates, researchers suggest that 0.4 to 3.1 million people in the United States have primary Sjögren syndrome; but experts note that approximately half of all cases are undiagnosed [56; 67; 271; 354].

Sjögren syndrome occurs predominantly in women, at a ratio of more than 9:1, and primarily occurs during the fourth to sixth decades of life [67; 354]. The age at the time of symptom occurrence has been reported to be between 45 and 55 years of age [272]. Differences in prevalence according to race/ethnicity are unknown.

POTENTIAL ENVIRONMENTAL RISK FACTORS

Data on potential environmental risk factors for Sjögren syndrome are lacking. Viral triggers, such as Epstein-Barr virus, hepatitis C virus, and human T-cell leukemia virus-1, have been suggested, but their roles have not been definitively determined [45].

ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

Approximately 60% of cases of Sjögren syndrome are secondary to another autoimmune rheumatic disorder, such as systemic lupus, rheumatoid arthritis, or scleroderma [67]. In addition, autoimmune thyroiditis (and/or thyroid dysfunction) was found in 45% of individuals with Sjögren syndrome in one study, and fibromyalgia was found in 22% [67].

CLINICAL MANIFESTATIONS

The typical clinical features of Sjögren syndrome are dry eyes (xerophthalmia or keratoconjunctivitis sicca) and dry mouth (xerostomia), which have been reported to occur in 93% and 98% of cases, respectively [272]. In addition to dryness, symptoms related to xerophthalmia include grittiness, itchiness, and sensation of a foreign body in the eye. Symptoms related to xerostomia include difficulty eating, swallowing, and speaking and the premature and accelerated loss of teeth. As with other autoimmune diseases, nearly half of individuals report debilitating fatigue [67].

Individuals with Sjögren syndrome may also have extraglandular involvement; among the most common manifestations are joint pain and/or swelling (37% to 75%), gastrointestinal symptoms (54%), pulmonary disease (e.g., chronic cough, recurrent bronchitis, fibrosis) (29%), and Raynaud phenomenon (16% to 28%) [272; 273]. Occurring less frequently are cutaneous vasculitis, lymphadenopathy, and renal involvement (e.g., proteinuria, interstitial nephritis, glomerulonephritis) [272; 273]. Peripheral neuropathies are often associated with Sjögren syndrome, and the reported prevalence of this complication has ranged widely, from 10% to more than 60% [226; 274]. Cognitive dysfunction has been reported in about half of individuals [226].

DIAGNOSTIC EVALUATION

Diagnosing primary Sjögren syndrome is challenged by its slow, insidious onset, its variable course, its wide range of clinical features, and its symptoms, which are nonspecific and not always concurrent [67; 271]. These factors have led to delays in diagnosis, often over several years [67].

Early diagnosis is essential, however, to prevent complications and to allow for surveillance to detect serious systemic manifestations.

There is no single diagnostic characteristic of Sjögren syndrome. Although xerophthalmia and xerostomia are found in nearly all individuals with the syndrome, they may be symptoms of other conditions. As a result, the diagnosis should be based on a combination of characteristic symptoms, the history and physical examination, diagnostic testing, and the distinguishing of Sjögren syndrome from other conditions with similar signs and symptoms. Differentiating Sjögren syndrome from other autoimmune diseases with similar clinical features, such as systemic lupus, rheumatoid arthritis, and scleroderma, is important to ensure appropriate treatment [67]. Healthcare professionals should remember that if another rheumatic condition is diagnosed, Sjögren syndrome may still be present, given the high rate of secondary disease [67].

In 2016, the ACR/EULAR published classification criteria for primary Sjögren syndrome as part of a collaborative expert consensus (***Table 17***) [78; 275]. According to these criteria, a diagnosis of Sjögren syndrome is made when a score of ≥4 of five weighted classification criteria is achieved. Subjective measures used in older criteria, including daily dry eyes or dry mouth, have been eliminated in the ACR classification because they were shown to have poor specificity for Sjögren syndrome [78; 275]. The objective measures chosen by the panel were strongly associated with the disorder, with final validation reports showing 96% sensitivity and 95% specificity [78].

The physical examination should focus on evaluation of the eye, mouth, and parotid glands. In examining the eye, the clinician should look for signs of corneal ulceration and superficial erosions of the corneal epithelium, conjunctival injection, and clouding or irregularity of the cornea [67; 276]. The mucous membranes of the mouth may appear dry, with a decreased salivary pool. In more severe cases, there may be erythema, fissuring, and ulceration of the mucous membranes [277]. There may also be evidence of dental caries as a result of reduced salivary flow. The parotid glands may be swollen or tender. Objective tests to assess oral and ocular symptoms are included in the 2012 criteria, and most of these tests are performed by specialists rather than primary care providers.

The non-organ-specific autoantibodies commonly found in serologic testing include ANA, rheumatoid factor, or antibodies to the anti-SSA (Ro) and anti-SSB (La) antigens [67]. Testing for ANA has been reported to be positive in 55% to 97% and rheumatoid factor is positive in 32% to 95% [67; 160]. Anti-SSA and anti-SSB antigens have been found in 16% to 70% and 7% to 50%, respectively [270; 271; 272; 277]. The presence of anti-SSA and anti-SSB antibodies is usually associated with extraglandular manifestations [160]. The ACR classification panel strongly agreed that positive anti-SSA is the most specific serologic marker for Sjögren syndrome, but that a positive rheumatoid factor and an ANA titer of 1:320 or greater is also a strong indicator in instances when anti-SSA/B serology is negative [275].

Tests to obtain the Sjögren's International Collaborative Clinical Alliance ocular staining score (OSS) use two different vital dyes to grade different areas of the ocular surface: fluorescein to grade the cornea and lissamine green to grade the bulbar conjunctiva [275; 337]. In the Corneal Fluorescein Staining Pattern test, fluorescein is instilled into the cornea, and four to eight minutes after, punctate epithelial erosions that stain with fluorescein are counted and scored using a slit lamp. Additional points are added if one or more patches of confluent staining, including linear stains, are found anywhere on the cornea, punctate epithelial erosions occur in the central 4-mm diameter portion of the cornea, or one or more filaments is seen anywhere on the cornea [337]. The punctate epithelial erosions are graded according to the form, and any additional points are added to the grade for a total of 6 points for each cornea. In the Conjunctival Lissamine Green Staining Pattern test, stained dots on the conjunctivae are counted and scored with the slit lamp at 10 times magnification immediately after lissamine green dye is applied

ACR/EULAR CLASSIFICATION CRITERIA FOR SJÖGREN SYNDROME[a]

Inclusion Criteria

Patients meet inclusion criteria if there is a positive response to at least one of the following ocular or oral dryness symptoms:

- Have you had daily, persistent, troublesome dry eyes for more than three months?
- Do you have a recurrent sensation of sand or gravel in the eyes?
- Do you use tear substitutes more than three times per day?
- Have you had a daily feeling of dry mouth for more than three months?
- Do you frequently drink liquids to aid in swallowing dry food?)

Exclusion Criteria

Patients with a prior diagnosis of any of the following conditions are excluded a diagnosis of Sjögren syndrome:

- History of head and neck radiation treatment
- Active hepatitis C infection (with positive PCR)
- Acquired immune deficiency syndrome (AIDS)
- Sarcoidosis
- Amyloidosis
- Graft versus host disease
- IgG4-related disease

Additional Criteria After Meeting Both Inclusion and Exclusion Criteria

Criteria	Weight
Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥1 focus/4 mm	3
Positive serum anti-SSA (Ro)	3
Ocular staining score ≥5 (or van Bijsterfeld score ≥4) on at least one eye	1
Schirmer ≤5 mm/5min on at least one eye	1
Unstimulated whole saliva flow rate ≤0.1 ml/min	1

[a]The classification of Sjögren syndrome, which applies to individuals with signs/symptoms that may be suggestive of the disease, will be met in patients who have at least a score of >4 of the five weighted objective features

Source: [78; 275] *Table 17*

to the eyes [337]. Temporal and nasal areas of the conjunctiva are counted separately, with a maximum grade of 3 for each area or a total maximum grade of 6 for each eye. The fluorescein score for the cornea and the lissamine green scores for the conjunctiva (nasal and temporal) are added to give the total OSS for each eye. The maximum possible score for each eye is 12. Unlike previously recommended dyes used for other ocular tests, these dyes are nontoxic and nonirritating [337]. The OSS provides a simplified, non-irritating, quantitative grading system that is easily applicable to clinical practice without the need for specialized equipment other than a slit lamp.

After the Corneal Fluorescein Staining Pattern test and before the Conjunctival Lissamine Green Staining Pattern test, an external eye exam should be performed using the slit lamp, noting the presence or absence of [337]:

- Abnormalities of the conjunctiva, cornea, and lids
- Specific diseases that might affect the OSS, such as entropion, lagophthalmos, pinguecula, and pterygium
- Clinical signs of blepharitis (e.g., ulceration around the base of the lashes, collarettes, misdirected lashes, absent lashes, poliosis, tylosis)

- Evidence of meibomitis (e.g., expression of thick material from the glands, inflammation of the meibomian glands, plugging of the orifices with inspissated secretions, lid telangiectasia)
- Signs of rosacea

Labial salivary gland (LSG) biopsy and histopathology is the third component of diagnosing Sjögren syndrome in the ACR classification [275; 336]. The biopsy is recommended for establishing a diagnosis of primary Sjögren syndrome in the absence of anti-SSA antibodies [305]. LSG biopsy has demonstrated much more specificity for Sjögren syndrome than testing unstimulated salivary flow rate and/or self-reported dry mouth (or dry eyes). A biopsy sample of 4 mm^2 (preferably 10–20 mm^2) is required for histopathologic exam [336]. Samples are stained with hematoxylin and eosin, and lymphocytic aggregate and infiltrate foci are counted. A score of 12 foci/4 mm^2 is typically the highest that can be counted; above that number of foci, infiltrates appear confluent [336]. Distinguishing focal lymphocytic sialadenitis from non-specific or sclerosing chronic sialadenitis is important for accurate diagnosis. Focal lymphocytic sialadenitis with a score of 1 focus/4 mm^2 or more is strongly associated with ocular and serologic indications of Sjögren syndrome [336].

TREATMENT OPTIONS

In 2016, the first ever guidelines for the treatment of Sjögren syndrome were published by the Sjögren's Syndrome Foundation (SSF). However, it was noted that there are many unmet clinical needs in regard to treatment, and there is no cure or remittive agent for Sjögren syndrome. Treatment goals are symptom palliation, prevention of complications, and proper selection of patients for immunosuppressive therapy [58]. Treatment of dry eye involves patient education regarding the nature of the problem and aggravating factors. Artificial tears have been found effective to replace moisture, and a topical anti-inflammatory agent should be used for moderate-to-severe symptoms. Preservative-free artificial tears have been better tolerated than tear solutions with preservatives because of the irritation that can be caused by frequent use of the latter type [58; 67]. Randomized controlled trials have shown that topical ocular cyclosporine (0.05%) significantly improves objective measures of dry eye, blurred vision, and use of artificial tears in patients with moderate or severe dry eye [278]. In its guidelines for dry eye, the AAO includes topical cyclosporine as a level IA recommendation for moderate dry eye [279].

If symptoms are not relieved by artificial tears or anti-inflammatory agents, a muscarinic agonist can increase tear production by stimulating muscarinic receptors. These receptors are a type of cholinergic receptor and are present on exocrine glands as well as on heart muscle and smooth muscle [276]. The two muscarinic agonists shown to be effective for dry eye are pilocarpine (a nonselective agonist) and cevimeline (a selective muscarinic agonist). According to a review of the literature, placebo-controlled trials have provided evidence of improvement with these agents. In three trials, pilocarpine was associated with subjective and objective improvement of dry eye in 42% to 53% of patients (compared with 26% for the control), and in two trials, cevimeline was associated with improvement in 39% to 72% (compared with 24% to 30% for the control) [278]. Systemic cholinergic agents, such as pilocarpine and cevimeline, are a level IA recommendation for severe dry eye in the AAO guidelines [279].

Treatment of dry mouth involves stimulating production of saliva and using saliva substitutes; muscarinic agonists can be used for severe dry mouth. Saliva production can be stimulated with the use of sugar-free chewing gum and sour lozenges [276]. Saliva substitutes are available as over-the-counter and prescription products and are manufactured as lozenges, rinses, sprays, and swabs [67]. As with dry eye, muscarinic agonists can improve subjective symptoms of dry mouth.

Three placebo-controlled trials showed improvement with pilocarpine in 61% to 70% of patients (compared with 24% to 31% in the placebo group), and two placebo-controlled trials showed improvement with cevimeline in 66% to 76% (compared with 35% to 37% in the placebo group) [78; 278].

A systematic review published in 2010 demonstrated a low level of evidence for most of the systemic drugs that are used to treat Sjögren syndrome [278]. Systemic immunomodulatory agents, such as glucocorticoids and hydroxychloroquine, have not offered significant benefit in terms of improvement in sicca symptoms, parotid enlargement, or fatigue, myalgia, and arthralgia [278]. Similarly, immunosuppressant therapy with azathioprine or oral cyclosporine has not provided significantly improved outcomes, and methotrexate, leflunomide, and mycophenolic mofetil have led to limited improvements in sicca symptoms only [278]. Furthermore, these systemic agents have all been associated with a high rate of adverse events [278]. The off-label use of biologic agents, such as infliximab and etanercept, has also not improved outcome [278]. Rituximab has been found to have limited benefit in improving some extraglandular features (i.e., vasculitis, neuropathy, glomerulonephritis, and arthritis), but the trials have been small and primarily uncontrolled [278]. On the basis of these findings, glucocorticoid, immunosuppressive, and biologic agents are not recommended for the treatment of Sjögren syndrome. Rituximab may be considered as a rescue therapy for individuals who have not had a response to standard treatment [278].

The SSF guidelines recommend hydroxychloroquine as first-line treatment (moderate strength of recommendation). If hydroxychloroquine is not effective, methotrexate may be used. If methotrexate is ineffective, then a combination of the two should be used (moderate strength of recommendation). The next option for treatment would be a short-term corticosteroid of less than 15 mg per day for less than one month (moderate strength of recommendation). If corticosteroids are needed for more than one month (long-term treatment), efforts should be made to find a steroid-sparing agent as soon as possible [58].

FOLLOW-UP AND PROGNOSIS

In general, the prognosis for patients with established Sjögren syndrome is good, and studies have shown no increase in the rate of all-cause mortality [264; 280; 281]. However, close follow-up is needed for the prevention and/or early recognition of complications [276]. Among the complications reported to be associated with Sjögren syndrome are oral infections, infection or a tumor of the parotid gland, and lymphoproliferative diseases [67].

Lymphoma, primarily non-Hodgkin lymphoma, is the most serious complication of Sjögren syndrome, with a risk that has been reported to be 40 times greater than that for the general population [276]. Among the possible indicators of lymphoma are low levels of complement protein C3 or C4 at the time that Sjögren syndrome is diagnosed, persistently enlarged parotid glands, lymphadenopathy (regional or general), splenomegaly, pulmonary infiltrates, vasculitis, and hypergammaglobulinemia [67; 276]. The average time from the diagnosis of Sjögren syndrome to the development of non-Hodgkin lymphoma has been six to seven years [276].

PATIENT EDUCATION

Patient education should focus on the importance of careful eye and oral care. Oral care should include frequent dental examinations, use of fluoride, and daily rinsing with an antimicrobial solution [67; 282]. Healthcare professionals should emphasize the importance of maintaining general health, reporting any changes in symptoms, following the prescribed use of medications, and keeping appointments for follow-up visits.

CELIAC DISEASE

Celiac disease, also known as celiac sprue, is inflammation of the small intestine caused by gluten proteins, which are found in foods containing rye, wheat, and barley. Gluten proteins are not digested well by digestive enzymes in the upper gastrointestinal tract, and in individuals with a genetic predisposition, the undigested gluten proteins cause an inflammatory reaction in the mucosa of the small intestine.

EPIDEMIOLOGY

The prevalence of celiac disease is approximately 0.5% to 0.8% [338; 339]. The true prevalence is thought to be higher than has previously been reported, and the number of so-called silent cases (with few or no symptoms) of the disease has increased [340]. In addition, the incidence pattern has changed, with more cases being diagnosed in adulthood [340]. A 2009 Mayo Clinic study compared stored blood samples taken from male Air Force recruits in 1950 with samples from similarly aged men around the time of the study [312]. The modern samples showed a 4.5-fold increase in the celiac antibody, which correlates with a rate of celiac disease of approximately 1%. This study underscores the fact that the incidence is truly rising, rather than the notion that increased awareness of the disease has led to a spike in its diagnosis [311; 312].

Most U.S. studies have involved predominantly white populations, leaving unclear the prevalence among racial/ethnic groups. European studies (conducted in the United Kingdom, Sweden, the Netherlands, Ireland, and Finland) have indicated that the prevalence may be slightly higher in those countries [22]. Individuals with a family history of celiac disease (first-degree relative) have a higher risk for the disease, with a prevalence of 16% [22].

Serum samples or a self-reported diagnosis from a representative U.S. cohort (7,798 individuals) as part of the National Health and Nutrition Examination Survey 2009–2010 confirmed a prevalence of 1% in the non-Hispanic white population; overall, the prevalence was 0.71%, reflecting the rarity of celiac disease in non-white individuals [313].

POTENTIAL ENVIRONMENTAL RISK FACTORS

It is not clear how gluten sensitivity begins or how sensitivity is increased by early exposure. The results of studies have suggested that first exposure to dietary gluten before the age of 3 months or after the age of 6 months is a risk factor for disease [68]. Other environmental factors may be a high number of gastrointestinal infections before 6 months of age and frequent rotavirus infections in children younger than 4 years of age [68]. Alternately, the "hygiene hypothesis" posits that an increasingly sterile environment has left the immune system of many individuals unchallenged and, therefore, unfortified by the bacteria, viruses, and parasites that their ancestors faced, causing increased susceptibility to allergic and immune disorders [311].

Some researchers believe that changes in grain itself, rather than increased levels of consumption, are at least partially responsible for the increase in celiac cases [311]. Despite increasing wheat consumption in the last several decades, consumption is still significantly less than it was 100 years ago. In that time, wheat has undergone extensive hybridization as a crop (i.e., modified wheat genetics), and drastic changes during processing, which involves oxidizers, new methods of yeasting, and other chemical processes (e.g., enzymatic modification of wheat prolamins), have occurred in the past 40 years [311; 312]. The effect these changes have had on the immune system is presently unknown; however, human genetic modifications in response to environmental challenges are extremely slow [312].

ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

Autoimmune diseases are 3 to 10 times more likely in individuals with celiac disease than in the general population [341]. The strongest associations have been found between celiac disease and Sjögren syndrome (4.5% to 14.7%), type 1 diabetes (1% to 12%), Addison disease (1.2% to 8%), primary biliary cirrhosis (1.3 to 7%), autoimmune hepatitis (4% to 6%), and autoimmune thyroid disease (up to 5.8%) [22; 68].

CLINICAL MANIFESTATIONS

The classic symptoms of celiac disease were once diarrhea and malabsorption, but this presentation is now rare [342]. Although diarrhea, borborygmus (intestinal rumbling), abdominal pain, weight loss, and nutritional deficiencies are the most common gastrointestinal symptoms, many other nonspecific and extraintestinal symptoms often occur [342]. Fatigue is present in nearly 80% of patients, and signs of iron-deficient anemia and osteoporosis are also common [22; 37; 68; 342]. As many as 38% of individuals have silent celiac disease [68; 339].

Dermatitis herpetiformis, a skin disease characterized by blistering lesions that are intensely itchy and often painful, is found in up to 25% of individuals with celiac disease. These lesions are typically located on the extensor surfaces of the elbows, knees, buttocks, and back [343]. Neurologic manifestations develop in about 10% to 12% of individuals with celiac disease, including cerebellar ataxia, peripheral neuropathy, seizures, and myelopathy [68].

DIAGNOSTIC EVALUATION

The American College of Gastroenterology (ACG) recommends celiac disease diagnostic testing for patients with symptoms, signs, or laboratory evidence suggestive of malabsorption (e.g., chronic diarrhea with weight loss, steatorrhea, postprandial abdominal pain and bloating). The ACG also recommends [344]:

- Patients with a first-degree family member who has a confirmed diagnosis of celiac disease should also be tested if they show possible signs/symptoms or laboratory evidence of celiac disease.
- Patients with type 1 diabetes should be tested if they have any digestive symptoms/signs/laboratory evidence suggestive of celiac disease.
- Testing for celiac disease is warranted if the patient has elevated serum aminotransferase levels when no other etiology is found.

All of these are strong recommendations with a high level of evidence [344].

The differential diagnosis of celiac disease involves the exclusion of several conditions with similar characteristics, including anorexia nervosa, bacterial overgrowth, Crohn disease, and intestinal lymphoma [340]. Irritable bowel syndrome has been diagnosed before the detection of celiac disease in as many as 36% of individuals [340].

The diagnosis of celiac disease should be made on the basis of several factors, including the findings of the history and physical examination, serologic testing, and biopsy of the small intestine [37; 344]. The preferred single test for detection of celiac disease in patients older than 2 years of age is the immunoglobulin A (IgA) anti-tissue transglutaminase (TTG) antibody [344]. Diagnostic testing should be done while the patient's diet includes foods that contain gluten. Children younger than 2 years of age should be screened using the IgA TTG test combined with immunoglobulin G (IgG) based testing (e.g., IgG-deamidated gliadin peptides [DGPs]) [344]. IgG-based testing (IgG DGPs and IgG TTG) should also be used in adult patients in whom low IgA or selective IgA deficiency is identified. Serum IgA endomysial antibodies (EMA) have also been used but are not recommended in the ACG guidelines [22; 37; 344].

SUGGESTED CRITERIA FOR DIAGNOSIS OF CELIAC DISEASE[a]	
Criteria	**Description**
Typical symptoms	Chronic diarrhea, iron-deficient anemia, weight loss (adults), deficient growth (children)
High titers of serum autoantibodies	Both IgA class tTG and EMA in IgA-sufficient patients or IgG class tTG and EMA in IgA-deficient patients
HLA-DQ2 or DQ8 genotypes	Found in almost all persons with celiac disease
Biopsy findings of celiac enteropathy	Total to partial villous atrophy and crypt lengthening with an increase in lamina propria and intraepithelial lymphocytes
Response to gluten-free diet	Positive response to restricted diet
[a]Four of these five criteria are needed for diagnosis.	
Source: [346]	*Table 18*

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Gastroenterological Association recommends that all diagnostic serologic testing should be done with patients on a gluten-containing diet. (https://journals.lww.com/ajg/pages/articleviewer.aspx?year=2013&issue=05000&article=00007&type=Fulltext. Last accessed July 23, 2020.)

Level of Evidence: High (Further research is unlikely to change our confidence in the estimate of effect)

There is no one universally accepted diagnostic standard, and the diagnosis of celiac disease should be made on the basis of several factors, including the findings of the history and physical examination, serologic testing, and biopsy of the small intestine [37].

Although the sensitivity of IgA TTG antibodies has been good (greater than 95%), the degree depends on the extent of mucosal involvement. The risk of a false-positive result is high; false-negative results may also occur in patients who have celiac disease and IgA deficiency [37]. In general, no further diagnostic testing is needed if serologic testing is negative in a patient at low risk (and without IgA deficiency); further testing (i.e., intestinal biopsy) should be done to confirm the diagnosis when serologic testing is positive [37; 344]. Intestinal biopsy should also be pursued if the suspicion of celiac disease is high, even if serologies are negative [344].

Upper endoscopy with biopsy of the small intestine has been considered the criterion standard for confirmation of diagnosis of celiac disease [344]. Evaluation of a biopsy specimen will demonstrate celiac enteropathy in almost 100% of patients who have typical symptoms in combination with high titers of IgA TTG [345]. However, there is a spectrum of characteristic histologic changes in the small intestinal mucosa; villous atrophy may vary from partial to total, and other mucosal changes may include subtle crypt lengthening or increased epithelial lymphocytes. Lymphocytic infiltration of the intestinal epithelium in the absence of villous atrophy is not specific for celiac disease, and other causes should be considered [344]. Because changes may be intermittent along the mucosa, it is recommended that at least four tissue samples be obtained for evaluation from the distal duodenum and one or two from the bulb [37; 344]. Findings on biopsy are not 100% sensitive or specific, as evidence of celiac disease may be similar to that of infection, enteritis, lymphoma, or bacterial overgrowth.

Given the potential difficulty in confirming the diagnosis of celiac disease with use of serologic testing and biopsy, some authors have suggested that a diagnosis can be made when four of five criteria are present (***Table 18***) [346]. It should be noted that these criteria are different from the ACG clinical guidelines for the diagnosis and management of celiac disease.

The ACG guidelines state that HLA-DQ2/DQ8 genotyping testing should not be routinely used in the initial diagnosis of celiac disease, but it is recommended to effectively rule out the disease in selected clinical situations [344]. These include, but are not limited to, patients with Down syndrome, patients on a gluten-free diet in whom no celiac disease testing was done before the diet, patients with discrepant celiac-specific serology and histology, and patients with suspicion of refractory celiac disease where the original diagnosis of celiac remains in question [344]. HLA-DQ2/DQ8 genotyping testing should be used in an attempt to rule out celiac disease in patients already on a gluten-free diet before a formal gluten challenge, but a formal gluten challenge should be considered in order to obtain an accurate diagnosis.

TREATMENT OPTIONS

Celiac disease is treated with a lifetime gluten-free diet, as avoidance of gluten proteins from wheat, barley, and rye can help mucosal lesions to heal and reverse the effects of the disease. In addition to alleviating gastrointestinal symptoms, long-term compliance with a gluten-free diet can also improve outcomes related to bone density, iron-deficiency anemia, and dermatitis herpetiformis [347; 348]. For example, anemia and iron-deficiency generally improve in six months and one year, respectively [347]. Some neurologic manifestations may remain despite adherence to a gluten-free diet [349].

A multidisciplinary approach to treatment is needed and may involve gastroenterologists, endocrinologists, allergists, dermatologists, hepatologists, pharmacists, and social workers. Central to the team is a registered dietician. In addition to assessing the food/nutrition-related history, the results of diagnostic testing, factors affecting quality of life, gastrointestinal symptoms, and other diseases, the dietician provides medical nutrition therapy and is responsible for educating the patient about how to adhere to a gluten-free diet [344; 347]. Testing and treatment for micronutrient deficiencies (particularly folic acid, iron, vitamin D, and vitamin B12) may be warranted in newly diagnosed patients. Treatment with medication and aggressive nutritional support (including parenteral nutrition) is indicated for patients with refractory celiac disease [344].

According to the American Gastroenterological Association, people with newly diagnosed celiac disease should undergo testing and treatment for micronutrient deficiencies. Deficiencies to be considered for testing should include, but not be limited to, iron, folic acid, vitamin D, and vitamin B12.

(https://journals.lww.com/ajg/pages/articleviewer.aspx?year=2013&issue=05000&article=00007&type=Fulltext. Last accessed July 23, 2020.)

Strength of Recommendation/Level of Evidence: Conditional recommendation, low level of evidence

The treatment of celiac disease also includes the management of complications. Dapsone can be used to treat dermatitis herpetiformis until the gluten-free diet has had effect; the drug typically relieves symptoms within one to three days [343]. Because of the potential for dapsone to cause hemolysis in some individuals, a baseline CBC and periodic follow-up testing are recommended [343]. Calcium and vitamin D supplements may also be necessary to ensure bone health [37]. The use of bisphosphonates for osteoporosis may be appropriate, although their use for osteoporosis related to celiac disease has not been studied extensively [37].

FOLLOW-UP AND PROGNOSIS

Follow-up for individuals with celiac disease should focus on four components [22; 350]:

- Monitoring adherence to a gluten-free diet
- Treatment of nutritional deficiencies
- Assessment of bone mineral density
- Evaluation for signs of lymphoma

Healthcare professionals should ensure that patients and their families have the resources, education, motivation, and support to comply with a gluten-free diet. Serologic testing should be done to monitor compliance with a gluten-free diet; strict adherence usually leads to antibody levels becoming normal within 3 to 12 months after starting the diet [37]. A lack of response according to serologic testing may indicate continued exposure to gluten; if the patient has been adhering to the gluten-free diet, the clinician should explore other diagnoses. Among other diseases that appear similar to celiac disease are microscopic colitis, pancreatic insufficiency, inflammatory bowel disease, ulcerative jejunoileitis, collagenous sprue, and T-cell lymphoma [37].

Follow-up should also include monitoring of nutritional deficiencies to ensure adequate levels of iron, folate, and vitamin B12. Low bone mineral density usually resolves in children who adhere to a gluten-free diet, but it may not resolve in adults. Thus, bone density testing may be appropriate to determine whether treatment for osteopenia or osteoporosis is needed [37]. Children should be monitored for normal growth and development [344].

Celiac disease is associated with a risk of non-Hodgkin lymphoma that is three to six times higher than that for the general population, and the risk for lymphoma is higher for individuals in whom celiac disease is diagnosed later in adulthood [351; 352]. Data have suggested that the risk of lymphoma decreases over time on a strict gluten-free diet [22]. New gastrointestinal symptoms or other signs of lymphoma should prompt further evaluation. Studies have indicated that the risk of other gastrointestinal malignancies, such as esophageal, gastric, and colorectal cancer, are not increased among individuals with celiac disease [306; 351; 353].

COMMERCIAL AND PROCESSED FOOD THAT MAY CONTAIN GLUTEN

Baked beans (canned)
Bouillon cubes
Candy
Canned meats
Coffee (flavored instant)
Cold cuts, hot dogs, salami, sausage
Communion wafers
French fries
Fruit pie fillings
Gravy, sauces
Herbal teas
Hot cocoa mixes
Imitation fish
Matzo
Nondairy cream substitutes
Rice mixes
Potato chips
Prepared salad dressings
Seasoned tortilla chips
Self-basting turkey
Soups (canned)
Soy sauce
Vegetables in sauce
Yogurt (flavored or frozen)

Source: [37; 307] *Table 19*

PATIENT EDUCATION

Patient education is key to the success of treatment and must focus on strict adherence to a gluten-free diet. A registered dietician should talk to patients and family members on ways to be compliant, noting the importance of addressing potential nutritional deficiencies through eating whole/enriched gluten-free grains and taking a multivitamin or mineral supplement [347]. Especially important is education about possible cross-contamination in food manufacturers and restaurants as well as at home and the careful reading of food labels to identify foods containing gluten (***Table 19***) [37; 307; 347].

CASE STUDY

Patient A is a woman, 25 years of age, who recently gave birth to her second child. She visits her primary care provider because of the gradual onset of fatigue, anxiety, and a feeling of her "heart pounding." The physician finds nothing remarkable on physical examination; a CBC indicates slight anemia. The physician tells her he believes the symptoms are related to slight anemia and the stress of giving birth in addition to caring for a toddler. The physician recommends that Patient A try to rest more, take a daily multivitamin with iron, and obtain some help caring for her two small children.

Over the next year, Patient A's symptoms wax and wane. Her family is supportive as she tries to reduce the stress in her life, but her symptoms do not resolve completely. At a routine physician office visit, she describes continued extreme fatigue as well as muscle weakness. On physical examination, her skin feels warm and moist and her pulse is slightly elevated (80 beats per minute). During the history-taking, the physician learns that Patient A's mother has Graves disease. On further physical examination, the physician notes that the thyroid gland feels normal, that her eyes and eyelids appear normal, and that she has no fine finger tremor. However, based on the family history and Patient A's desire to have another child in the near future, the physician orders thyroid function studies. The TSH level is normal, as are the T3 and T4 levels. The physician reiterates the need for lifestyle modifications, including enhanced nutrition, exercise, better sleep, and over-the-counter analgesics as needed.

Rationale and comments: *Several factors indicate the possibility of Graves disease, although some do not. Patient A is younger than the typical woman in whom Graves disease first occurs (40 to 60 years). But in individuals with genetic susceptibility, stress and recent childbirth have been identified as potential environmental triggers for the disease. Her symptoms of fatigue, anxiety, and palpitations are among the common symptoms of Graves disease, as is her warm, moist skin. However, the lack of thyroid enlargement, a pulse of less than 90 beats per minute, and the absence of finger tremor are findings with the most significance in ruling out hyperthyroidism.*

It seems appropriate to rule out a diagnosis of Graves disease given that Patient A wants to have another child. The American Association of Clinical Endocrinologists recommends TSH with measurement of total T4 or a free T4 index testing for women of childbearing age before or during pregnancy. Laboratory testing confirmed that she did not have Graves disease, as a low TSH level with increased T4 levels indicates hyperthyroidism.

Patient A's symptoms continue, and she becomes increasingly frustrated by the lack of symptomatic relief. Among the new symptoms that have developed are dry eyes, intermittent headaches, and pain in the finger joints of both hands, all of which she attributes to too much time working on the computer at her job. The pain in her fingers resolves with rest. She also begins to have occasional pain and stiffness in both hips, especially in the morning. She starts to take large doses of over-the-counter analgesics as well as nutritional supplements. She continues to feel fatigue so overwhelming that she must call in sick to work at least once or twice every month. She wants to have another child but does not feel as though she would be able to physically handle a pregnancy and the care of a third child. She begins to have mood swings, and she feels depressed "sometimes." She makes an appointment with her primary care provider to discuss her increasing symptoms. Based on her description of new symptoms, the physician orders a rheumatoid factor test, and the result is a low positive. He refers her to a rheumatologist for possible rheumatoid arthritis.

On examining Patient A, the rheumatologist finds normal vital signs, except for a low-grade fever. There is slight limitation in the range of motion of both hips, with some decreased muscle strength in the left leg. In taking the history, the rheumatologist learns that Patient A's joint pain has been present for about one month and that her pain/stiffness in the hip lasts for about 30 to 60 minutes each morning. The physician orders a CBC, platelet count, ACPA, ESR, and CRP; the results of all are normal, except for continued slight anemia. Radiographs of the hips show slight degeneration in the left hip. The rheumatologist tells Patient A that her pain may be related to early osteoarthritis, and he prescribes a COX-2 inhibitor for pain relief, prescribes an antidepressant, and recommends regular exercise, more rest, and counseling for stress reduction. Patient A interprets the suggestion of counseling and an antidepressant as meaning that her physical symptoms are "in her head," and she becomes even more frustrated.

Rationale and comments: *Again, some of the details of Patient A's case fit with a diagnosis of rheumatoid arthritis and others do not. The proximal interphalangeal and metacarpophalangeal joints are among the most commonly involved joints, and they are not usually painful at rest. Joint symptoms are usually bilateral. As is the case for most individuals, the symptoms of rheumatoid arthritis develop over a long period of time (weeks to months). Her other symptoms–fatigue, weakness, and generalized muscular aches–are also suggestive of rheumatoid arthritis. Approximately 46% of individuals with rheumatoid arthritis have extra-articular manifestations, and among the most common are dry eye syndrome and anemia of chronic disease. Depression is also common, occurring in about one-third of individuals. In addition, the findings of a low-grade fever, limitation in the range of motion of the hip, and decreased muscle strength near an affected joint are consistent with rheumatoid arthritis. The positive rheumatoid factor would also seem to suggest rheumatoid arthritis, as this finding has long been known as an indicator of rheumatoid arthritis, and studies have shown that it is positive in approximately 69% to 90% of people with the disease. However, the test may be positive in healthy individuals as well as in individuals with other rheumatic diseases (e.g., Sjögren syndrome, systemic sclerosis, systemic lupus), with chronic infections, or with pulmonary disease. The 2010 ACR/EULAR classification criteria for rheumatoid arthritis call for a rheumatoid factor as well as an ACPA, which has a higher specificity. The negative ACPA and normal ESR and CRP level, along with her other signs and symptoms, yield a score of 5 on the diagnostic criteria, one point lower than the 6 needed for a diagnosis of "definite" rheumatoid arthritis. The radiographic evidence of degeneration in the left hip and the morning stiffness that lasts less than one hour suggest osteoarthritis.*

The rheumatologist's treatment plan is appropriate. There is good evidence that nonselective NSAIDs and COX-2 inhibitors have comparable efficacy, and a COX-2 inhibitor has been associated with lower risks of gastrointestinal adverse events than a nonselective NSAID plus a proton-pump inhibitor. The recommendations for nonpharmacologic treatment are also in line with established recommendations.

Patient A adheres to her medication treatment, and the pain in her hips is somewhat relieved. However, more new symptoms appear over the course of the next year. During the winter, she becomes intolerant to cold weather, with her hands and feet becoming painful and discolored when she is exposed to cold. When she sees her primary care provider, he tells her that she may have Raynaud phenomenon. Her other symptoms continue, and he reiterates the need for her to continue with the rheumatologist's treatment plan. The following summer, she has a strange red, raised rash on her cheeks after being out in the sun. In addition, small, raised sores begin to develop on her legs and arms.

The joint pain, swelling, and fatigue continue. She returns to her primary care provider who is himself frustrated by Patient A's continuing symptoms. He suggests that she return to the rheumatologist, but she says she did not have a good experience with him and wants to see a different rheumatologist. He refers her to another local rheumatologist and notes in her chart that she has been a "chronic complainer."

At the first visit, the new rheumatologist elicits Patient A's long medical history and description of her numerous symptoms. On physical examination, the vital signs are normal, except for a low-grade fever. The physician notices small ulcers in her mouth, pain and swelling in both hips, and a slight pleural rub. He orders a CBC and platelet count, an ANA titer, an anti-double-stranded DNA titer, and antiphospholipid antibodies. He also obtains biopsy samples from the lesions on her legs. The results of the lab work show a normal white blood cell count, a low platelet count (<100,000/mm^3), and positive ANA titer, anti-double-stranded DNA titer, and antiphospholipid antibodies. The findings of the skin biopsy indicate small vessel vasculitis. The rheumatologist diagnoses systemic lupus erythematosus, explaining to Patient A that all of her symptoms over the past four years can be attributed to the disease.

Rationale and comments: *Patient A's constellation of symptoms indicates systemic lupus. The classic sign of a butterfly-shaped rash in the malar area of the face is present in up to 90% of cases. Other common symptoms include the discoid rash elsewhere on the body, photosensitivity, Raynaud phenomenon, joint pain (especially in proximal joints of the fingers), fatigue, dry eye syndrome, low-grade fever, small oral ulcers, pain and swelling in both hips, and slight pleural rub. The ANA titer is highly sensitive for systemic lupus, with a positive result in approximately 93% to 100% of individuals with the disease. An anti-double-stranded DNA test can help confirm a diagnosis of systemic lupus, as it has greater specificity than the ANA titer. About 20% to 30% of people with systemic lupus have antiphospholipid antibodies, which increases the risk for thromboembolism and pregnancy loss. The clinical findings, coupled with the results of laboratory testing, fulfill nine of the 11 criteria for the diagnosis of systemic lupus; four criteria are needed for a definite diagnosis.*

The rheumatologist emphasizes the need for both pharmacologic and nonpharmacologic measures. He begins treatment with hydroxychloroquine (200 mg PO) twice daily and 5 mg of prednisone daily, after obtaining baseline dual x-ray absorptiometry, measuring her height, and determining the serum 25-hydroxyvitamin D level. The rheumatologist also makes several recommendations:

- Use artificial tear drops.
- Take supplemental calcium and vitamin D.
- Engage in regular exercise.
- Schedule a comprehensive eye examination.
- Schedule routine gynecologic examinations.
- Modify lifestyle factors to reduce the risk of cardiovascular disease.
- Protect skin against exposure to ultraviolet rays.
- Maintain follow-up visits at six-month intervals.

He also warns her of the risk of pregnancy loss related to the presence of antiphospholipid antibodies and encourages her to learn all she can about the disease, providing her with educational materials, a list of reliable websites, and a list of local support groups.

Rationale and comments: *The rheumatologist's treatment and follow-up plan meet all the recommendations in established guidelines. The preferred first-line treatment of systemic lupus without major organ involvement is an antimalarial drug and a low-dose glucocorticoid (usually prednisone), two of only three drugs approved by the FDA for use in systemic lupus. Antimalarial agents offer many benefits. They can alleviate joint-related, cutaneous, constitutional, and serosal manifestations of systemic lupus; they can prevent disease flares; they are well tolerated; they have been associated with a lower risk of infection than other*

treatment approaches; and they have a protective effect on survival. Artificial tear drops are recommended for the treatment of mild dry eye syndrome related to systemic lupus. Glucocorticoid-induced osteoporosis occurs in 4% to 24% of individuals with systemic lupus, and the ACR recommends a daily calcium intake of 1,200 to 1,500 mg and supplemental vitamin D, as well as a baseline dual x-ray absorptiometry, height, and serum 25-hydroxyvitamin D level. Hydroxychloroquine increases the risk for retinopathy, although this side effect is rare at Patient A's dose. Still, ophthalmologic follow-up is important, and the American Academy of Ophthalmology recommends a complete ophthalmologic examination within the first year after treatment. Systemic lupus is associated with an increased risk for HPV infection and cervical dysplasia, making it necessary to have regular gynecologic evaluations. In addition, the risk of cardiovascular disease is increased, and steps should be taken to reduce the risk. Lastly, systemic lupus is associated with an increased risk for other autoimmune diseases, and healthcare professionals should carefully consider the possibility of these diseases during follow-up. Providing educational resources in a variety of formats helps to ensure that patients better understand their disease and its management, which is an essential component in the treatment of a chronic disorder.

Over the next month, Patient A's rash gradually resolves, and her pain and fatigue improve. She feels well enough to comply better with an exercise program, and her symptoms further improve. Her rheumatologist sees her for follow-up every six months. One year after the initiation of treatment, she continues to feel much better than she "has in a long time" and has made several new friends in her local support group.

Rationale and comments: *This case reflects the challenges in diagnosing an autoimmune disease because of vague, overlapping symptoms. The absence of characteristic features on physical examination does not necessarily rule out an autoimmune disease, because signs and symptoms tend to wax and wane. As was the situation for Patient A, most individuals consult many healthcare providers, often over the course of several years, before a diagnosis is made. In addition, the attitudes of Patient A's physicians represent a common reaction. More than 45% of individuals with an autoimmune disease have reported that they had been labeled as a chronic complainer in the early stages of their disease because no cause for their symptoms could be determined.*

ONLINE PATIENT EDUCATION RESOURCES

American Association of Clinical Endocrinologists
https://www.aace.com

American Autoimmune Related Diseases Association, Inc.
https://www.aarda.org

American College of Rheumatology
https://www.rheumatology.org

Academy of Nutrition and Dietetics
http://www.eatright.org

American Fibromyalgia Syndrome Association, Inc.
http://www.afsafund.org

American Gastroenterological Association
https://www.gastro.org

American Thyroid Association
https://www.thyroid.org

Arthritis Foundation
https://www.arthritis.org

Celiac Disease Foundation
https://celiac.org

National Celiac Association
https://nationalceliac.org

Graves' Disease and Thyroid Foundation
https://www.gdatf.org

Lupus Foundation of America, Inc.
https://www.lupus.org

Lupus Research Alliance
https://www.lupusresearch.org

National Fibromyalgia Association
https://fmaware.net

National Institute of Arthritis and Musculoskeletal and Skin Diseases
https://www.niams.nih.gov

National Institute of Diabetes and Digestive and Kidney Diseases
https://www.niddk.nih.gov

Office on Women's Health
https://www.womenshealth.gov

Sjögren's Syndrome Foundation
https://www.sjogrens.org

CONCLUSION

When considered collectively, autoimmune diseases affect more individuals than heart disease and cancer combined. However, because these diseases have been studied separately, their health burden has been underappreciated. As chronic illnesses with no cure, autoimmune diseases and fibromyalgia require lifelong treatment and many are associated with substantial morbidity, disability, and mortality. Healthcare professionals, especially primary care providers, face many challenges in diagnosing and treating autoimmune diseases. First, because the prevalence of each autoimmune disease is low, a typical primary care provider will not have experience with the diagnosis and care recommended for every disease. Second, many autoimmune diseases (as well as fibromyalgia) lack objective testing to confirm the diagnosis. Third, the initial symptoms of most autoimmune diseases are vague and are common across many autoimmune diseases and/or fibromyalgia. Lastly, few guidelines are available for diagnosis and management, especially guidelines with up-to-date evidence bases. As a result, it often takes several years before a definitive diagnosis is made. Even after diagnosis, the most effective treatments are not always used. Most individuals with autoimmune diseases or fibromyalgia need close follow-up to assess response to treatment, to monitor side effects of treatment, and to prevent comorbidities. At every follow-up visit, healthcare professionals should encourage their patients to participate actively in decision making and self-management. Although a variety of specialists are often involved in the care of individuals with an autoimmune disease or fibromyalgia, the primary care team has a pivotal role in the overall management of these patients.

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