REVIEW ARTICLE

Juvenile Idiopathic Arthritis

Christy I. Sandborg, M.D.,[1] Grant S. Schulert, M.D., Ph.D.,[2,3] and Yukiko Kimura, M.D.[4]

Author affiliations are listed at the end of the article. Dr. Sandborg can be contacted at sandborg@stanford.edu or at the Division of Pediatric Rheumatology, Department of Pediatrics, Stanford School of Medicine, 700 Welch Rd., Suite 301, Palo Alto, CA 94304.

N Engl J Med 2025;393:162-74.
DOI: 10.1056/NEJMra2402073

CME

Juvenile idiopathic arthritis (JIA) encompasses a group of pediatric inflammatory arthritides that includes oligoarticular JIA, polyarticular JIA, systemic JIA, psoriatic JIA, and enthesitis-related arthritis. Before the 2000s, 25 to 40% of children in whom JIA was diagnosed had moderate-to-severe disease, with lifelong complications.[1,2] Fortunately, since 1999, new antiinflammatory, biologic disease-modifying antirheumatic drugs (DMARDs) have transformed the therapeutic landscape, substantially mitigating the joint destruction, joint deformities, and disease-related disability previously seen in patients with JIA. This review focuses on our current understanding of the clinical features, biology, and genetics of each of the distinct JIA categories. We also review the major treatment advances that have improved disease outcomes for patients with JIA.

Classification and General Management of Childhood Arthritis

Although JIA is a common chronic childhood illness, its incidence and prevalence are unclear. Estimates vary, depending on research methods, geographic location, and the racial and ethnic compositions of study populations (Table 1).[3-6] The prevalence of JIA is approximately 30 cases per 100,000 children in Europe and North America but may be higher in other regions.[4,7]

The International League of Associations for Rheumatology (ILAR)[8] developed a classification system for JIA 20 years ago and grouped patients into distinct categories to facilitate trial enrollment. Recent pathobiologic insights have led to the development of revised classification systems, which remain to be finalized and validated.[9,10] Here we use the ILAR classification categories with key modifications from the proposed newer systems (Table 1).

The clinical manifestations of JIA depend on the patient's age and the JIA category (see Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) and reflect the effects of genetics, epigenetics, and environmental and infectious exposures.[11] Since definitive diagnostic tests for JIA are lacking, entities that mimic the disorder, including cancer, infections, and other autoimmune or autoinflammatory diseases, must be ruled out (Table 2).[3]

Nonsteroidal antiinflammatory drugs (NSAIDs) are commonly used to relieve musculoskeletal pain, but most patients require treatment with conventional synthetic DMARDs, biologic DMARDs, newer targeted synthetic DMARDs, or a combination of DMARDs for disease control. Systemic glucocorticoids are generally avoided except as bridging therapy during the initiation of DMARD therapy in patients with severe JIA.[12,13] On the basis of mechanistic studies, new treatment strategies aim to induce early control and sustained suppression of inflammation in order to prevent additional joint involvement, joint damage, nonarticular complications, and disease flares.[14] Tumor necrosis factor (TNF) inhibitors were the first biologic DMARDs shown to decrease disease activity in most JIA categories.[3] More

KEY POINTS

JUVENILE IDIOPATHIC ARTHRITIS

- Juvenile idiopathic arthritis (JIA) encompasses at least five clinically and biologically distinct categories of childhood-onset chronic arthritis.
- Most categories of JIA exist on a disease continuum that includes corresponding adult inflammatory arthritides.
- Asymptomatic chronic anterior uveitis and skeletal deformities (including deformity of the temporomandibular joint) are hallmarks of JIA.
- Systemic JIA differs from other JIA categories with respect to biologic and phenotypic features and is associated with a risk of life-threatening complications.
- New targeted treatments have profoundly improved outcomes for patients with JIA, but treatment-free remission is uncommon, and many patients require continued care in adulthood.
- Collaborative research networks have had a key role in advancing our knowledge of JIA and its treatment.

targeted therapies, such as interleukin-1 and interleukin-6 inhibitors for systemic JIA and interleukin-17 inhibitors for enthesitis-related arthritis, have been developed on the basis of the distinctive pathogenesis of each JIA category (Fig. 1).[15-18] Local intraarticular or intraocular glucocorticoid therapy may be appropriate as initial therapy for limited disease. Specific treatment approaches based on studies and consensus guidelines are described below and in Table S1.[12,13,19-21] Table 3 lists commonly used medications and their potential side effects.

OLIGOARTICULAR JIA

Oligoarticular JIA, the most common category of JIA, is characterized by the involvement of four or fewer joints in the first 6 months of disease[3] and predominantly affects girls between 1 and 5 years of age, who often have positive tests for antinuclear antibodies (ANA). Fifty percent of affected patients present with monoarthritis, most often of the knee.[3] Approximately half of patients with oligoarticular JIA have a persistent oligoarticular course, with four or fewer joints involved and a high likelihood of medication-free remission. The other 50% of patients have extended oligoarticular JIA (polyarthritis involving five or more joints) 6 months after disease onset and are less likely to have remission. Early involvement of the wrist or ankle and an elevated erythrocyte sedimentation rate are associated with an increased risk of extended oligoarticular JIA.[3] Chronic anterior uveitis, a cause of complications, develops in 30% of all patients with oligoarticular JIA (Fig. 2A and 2B), as discussed below.[22,23] In contrast to other JIA categories, there does not appear to be an adult-onset counterpart of persistent oligoarticular JIA (Table 1).[9,10]

First-line treatment of oligoarticular JIA usually involves intraarticular glucocorticoid injections, which may eliminate inflammation and prevent joint and bone damage. Conventional synthetic DMARDs (e.g., methotrexate), with or without biologic DMARDs (e.g., TNF inhibitors) are generally administered if glucocorticoid injections fail to control symptoms or prevent complications such as chronic anterior uveitis, temporomandibular joint arthritis, or extended oligoarticular JIA (Table 3).

RHEUMATOID FACTOR–NEGATIVE POLYARTICULAR JIA

Rheumatoid factor–negative polyarticular JIA accounts for 15 to 20% of JIA cases. The incidence peaks between 1 and 3 years of age and again after 8 years of age. Most patients are girls presenting with arthritis that involves more than four joints.[3] Like patients with oligoarticular JIA, those with rheumatoid factor–negative polyarticular JIA who are under the age of 6 years are at high risk for the development of chronic anterior uveitis.[23] A test for ANA is positive in up to 50% of patients, but a test for rheumatoid factor is by definition negative.[3] Many patients have a relapsing or chronic course. Newer classification proposals consider extended oligoarticular JIA, rheumatoid factor–negative polyarticular JIA, and adult seronegative rheumatoid arthritis as a continuum, given clinical, biologic, and genetic similarities (Table S2).[24] In oligoarticular and polyarticular JIA, activated type 1 and type 17 helper T lymphocytes drive inflammation at the synovium,

Table 1. Epidemiology and Clinical Classification of Juvenile Idiopathic Arthritis (JIA).*

Clinical Category	Most Common Age at Onset	Female:Male Ratio	Proportion of JIA Cases	Adult Correlate
Oligoarticular JIA	1–3 yr	3:1	40–50%; highest among patients of European ancestry[3,4]	None for early-onset, ANA-positive oligoarthritis with uveitis
Polyarticular JIA, RF-negative	Bimodal: 1–3 yr and >8 yr	2–4:1	15–20%	Seronegative rheumatoid arthritis
Polyarticular JIA, RF-positive	>8 yr	4–13:1	5% among White patients with European ancestry, higher in non-White cohorts[3]	Seropositive rheumatoid arthritis
Enthesitis-related arthritis, including juvenile spondyloarthritis and juvenile ankylosing spondylitis	>9 yr	Depends on cohort but approximately 1:1.4–9	9–19%; 33% in parts of eastern and southeastern Asia[3-6]	Spondyloarthritis, including ankylosing spondylitis
Psoriatic JIA	Bimodal: 2–4 yr and >9 yr	3:1 for onset at younger age, 1:1 for onset at older age	2–5%[3]	Psoriatic arthritis
Systemic JIA	Any age, but somewhat more frequent at 1–5 yr	1:1	10–20% in Europe, United States, and Canada; higher in Asia, Latin America, Africa, and the Middle East[3-5]	Adult-onset Still's disease

* Data are from Petty et al.,[8] with modifications based on reports by Martini et al. and Nigrovic et al.[9,10] ANA denotes antinuclear antibody, and RF rheumatoid factor.

activating macrophages and fibroblast-like synoviocytes to produce TNF and interleukin-6. The role of B cells and autoantibodies is less well characterized (Fig. 1).

Treatment with conventional synthetic DMARDs such as methotrexate should be initiated soon after the diagnosis of rheumatoid factor–negative polyarticular JIA. If the conventional synthetic DMARD is not effective within 2 to 3 months, a biologic DMARD (usually a TNF inhibitor) is added. If the biologic DMARD does not lead to disease control after 3 to 6 months, a targeted synthetic DMARD or a different biologic DMARD may be substituted for the original biologic DMARD with continued use of the conventional synthetic DMARD.

RHEUMATOID FACTOR–POSITIVE POLYARTICULAR JIA

Rheumatoid factor–positive polyarticular JIA accounts for only 5% of JIA cases and is uncommon in children under 9 years of age.[3] The diagnosis requires a positive test for rheumatoid factor. Anti–citrullinated protein antibodies (ACPAs) are often present, and a test for ANA may also be positive. Like adult rheumatoid factor–positive and ACPA-positive rheumatoid arthritis, rheumatoid factor–positive polyarticular JIA can be aggressive and destructive if left untreated. Extraarticular involvement (e.g., rheumatoid nodules) can be present. Rheumatoid factor–positive polyarticular JIA is genetically and clinically similar to, or even the same disease as, adult seropositive rheumatoid arthritis, given the prominent B-cell and plasma-cell activation, autoantibody generation, and immune complex formation (Fig. 1).[25,26] The therapeutic approach is similar to that for patients with rheumatoid factor–negative polyarticular JIA, although earlier treatment with conventional synthetic DMARDs and biologic DMARDs is more often initiated because of the poor prognosis.

ENTHESITIS-RELATED ARTHRITIS

The presence of enthesitis (inflammation at the entheses, where tendons and ligaments attach to bone) defines enthesitis-related arthritis.[3,27] Enthesitis and synovitis of peripheral joints (e.g., upper and lower extremities) often coexist,[28] with the peripatellar and calcaneal entheses most fre-

Table 2. Differential Diagnosis of JIA.

Diagnostic Category	Conditions
Infection	Bacterial endocarditis Septic arthritis (including kingella in young children) Bacterial osteomyelitis Viral infections (e.g., parvovirus, Epstein–Barr virus, hepatitis B virus, rubella virus, chikungunya virus) Lyme arthritis
Postinfectious disorder	Acute rheumatic fever Poststreptococcal reactive arthritis Other reactive arthritis (transient synovitis, postdysenteric reactive arthritis)
Oncologic or neoplastic disease	Acute leukemia Neuroblastoma Lymphoma Histiocytosis Benign and malignant bone and synovial tumors
Autoimmune disease	Systemic lupus erythematosus Mixed connective-tissue disease Sjögren's syndrome Juvenile dermatomyositis Vasculitis (including Kawasaki's disease and IgA vasculitis) Sarcoidosis Arthritis related to inflammatory bowel disease Celiac disease
Autoinflammatory disorder	Monogenic periodic fever syndromes Nonbacterial osteomyelitis (chronic, recurrent multifocal osteomyelitis)
Noninflammatory disorder	Trauma (accidental and nonaccidental) Overuse syndromes Osteochondrosis Hypermobility syndromes
Bone disease	Avascular necrosis Osteochondritis dissecans Skeletal dysplasias Vitamin C and other vitamin deficiencies
Primary immunodeficiency	Inborn errors of immunity
Pain amplification	Juvenile fibromyalgia Complex regional pain syndrome type 1

quently affected (Fig. 2C). Enthesitis-related arthritis is on a spectrum of diseases that includes juvenile spondyloarthritis and juvenile ankylosing spondylitis. The clinical manifestations depend on the patient's age at the onset of the disease. The disorder is more common in boys than in girls and is uncommon before the age of 6 years.[27] Symptomatic axial involvement (e.g., sacroiliitis, inflammatory spine disease, or both) develops in 40 to 60% of patients with enthesitis-related arthritis, usually during adolescence, although in one study, magnetic resonance imaging (MRI) identified asymptomatic sacroiliitis in 30% of patients at the time of disease onset.[29]

HLA-B27 positivity is associated with more severe disease, sacroiliitis, juvenile ankylosing spondylitis, and acute anterior uveitis.[27,30,31] The HLA-B27 molecule probably presents arthritogenic antigens to CD8+ T cells (Fig. 1).[32] In spondyloarthritis, local T cells and innate immune cells produce interleukin-17 and TNF-α, resulting in inflammation of tendons, entheseal fibrocartilage, subchondral bone marrow, and adjacent synovium.[28] Along with mechanical stress, these inflammatory processes lead to pathologic bone alterations.[26]

NSAIDs are usually helpful for relief of enthesitis-related arthritis symptoms, and sulfasalazine or a TNF inhibitor is an option for uncontrolled enthesitis. However, if sacroiliitis is present, treatment with a biologic DMARD (usually a TNF inhibitor) should be initiated.[33] Inhibitors of interleukin-17 may be used for disease that is refractory to treatment with a TNF inhibitor.[18]

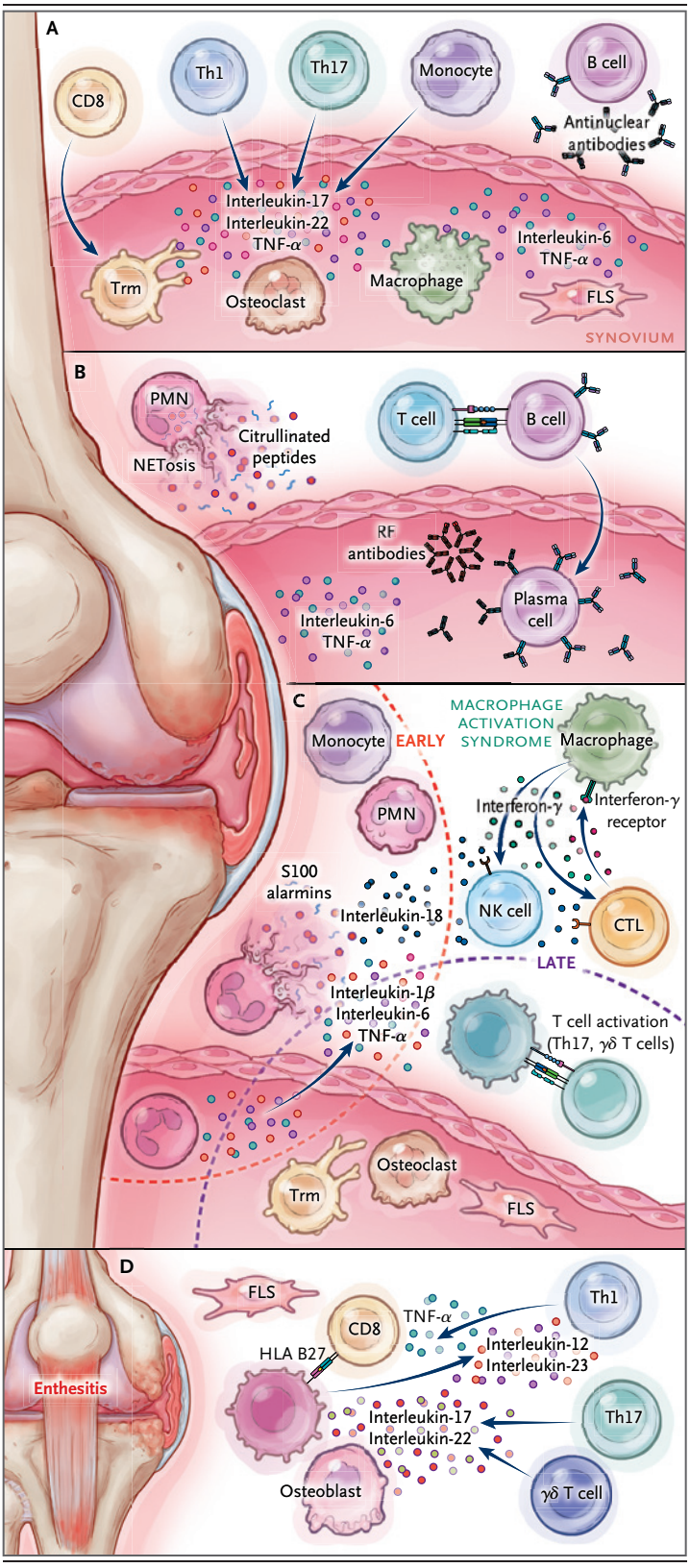

Figure 1. Shared and Divergent Pathogenesis of Arthritis in Juvenile Idiopathic Arthritis (JIA).

Panel A shows oligoarticular and rheumatoid factor (RF)–negative polyarticular JIA as a model, with activation and recruitment to the synovium of type 1 helper (Th1) and type 17 helper (T17) T lymphocytes and monocytes, leading to the production of inflammatory cytokines, including tumor necrosis factor (TNF) and interleukin-6. This process drives activation of fibroblast-like synoviocytes (FLS) toward an aggressive, proinflammatory phenotype with the production of matrix metalloproteinases, pannus formation, and osteoclast activation, leading ultimately to bone erosion. CD8 lymphocytes are also recruited and persist in the joint as tissue-resident memory lymphocytes (Trm), which drive joint-specific memory and flares that predominantly involve previously affected joints. Although many patients have antinuclear antibodies (ANA), the role of B cells and autoantibodies is unknown. The pathogenesis of RF-positive polyarticular JIA, shown in **Panel B**, is similar but more closely resembles that of seropositive rheumatoid arthritis. Activation of Th1 cells but also B cells leads to the development of plasma cells and production of autoantibodies, including anti–citrullinated protein antibodies (ACPA) and RF, with immune complex formation. The release of neutrophil extracellular traps (NETosis) serves to amplify these autoantibody responses. **Panel C** shows the pathogenesis of systemic JIA; this form of JIA is characterized by marked expansion and activation of neutrophils and monocytes, which is amplified by S100 alarmins and leads to inflammasome activation and the production of interleukin-1–related cytokines, including interleukin-1β and interleukin-18. Interleukin-18 is thought to be the key driver of interferon-γ production and macrophage activation syndrome. Late in the disease course, systemic JIA can be associated with more autoimmune features, including activation of Th17 and $\gamma\delta$ T cells. Enthesitis-related arthritis and juvenile spondyloarthritis, shown in **Panel D**, are associated with activation of Th1, Th17, and $\gamma\delta$ T cells and a cytokine environment dominated by interleukin-12, interleukin-23, and interleukin-17. Many patients carry the *HLA-B27* allele, which encodes a protein that presents arthritogenic antigens to CD8 cells and drives more innate immune inflammatory responses. Inflammation can occur at both entheses and the synovium. Psoriatic JIA has an overlapping pathogenesis that more closely resembles that of juvenile spondyloarthritis or early-onset, ANA-positive disease (Panel A).

PSORIATIC JIA

The incidence of psoriatic JIA peaks at 2 to 4 years of age and then again after the age of 10 years. In younger children, the disorder is clinically similar to early-onset oligoarticular and rheumatoid factor–negative polyarticular JIA, with

Table 3. Medications Commonly Used for JIA.*

Medication Category	Examples of Agents	Potential Safety Concerns
NSAID	Ibuprofen, naproxen, meloxicam, celecoxib, indomethacin	Gastritis and interstitial nephritis
Systemic glucocorticoids	Prednisone, prednisolone, methylprednisolone	Long-term therapy not recommended because of potential growth failure, osteoporosis, cushingoid features, weight gain, immunosuppression, hypertension, avascular necrosis, and diabetes mellitus
Topical glucocorticoids	Prednisolone eye drops	Increased intraocular pressure, glaucoma, and cataracts
Intraarticular glucocorticoids	Triamcinolone hexacetonide (preferred), triamcinolone acetonide	Repeated TMJ injections not recommended because of questionable efficacy and potential effects on bone growth[18]
Conventional synthetic DMARD	Methotrexate (most common), sulfasalazine, leflunomide	Methotrexate: nausea, aphthous ulcers, liver injury, and teratogenicity; leflunomide: liver injury and teratogenicity; sulfasalazine: gastrointestinal symptoms; methotrexate and leflunomide contraindicated in patients using alcohol
Biologic DMARD	Cytokine inhibitors: TNF, interleukin-6, interleukin-1, interleukin-17, interleukin-12 and -23, and interferon-γ inhibitors†; T- or B-cell–modulating agents: abatacept and rituximab	Opportunistic infections and demyelinating CNS lesions (specific to TNF inhibitors); increased risk of cancer not confirmed, events are very rare
Targeted specific DMARD	Janus kinase inhibitors: tofacitinib, upadacitinib (United States) and baricitinib (Europe)	Serious infections, major adverse cardiovascular events, thromboembolic disease, and increased cancer rates reported among adults with rheumatoid arthritis using these agents

* CNS denotes central nervous system, DMARD disease-modifying antirheumatic drug, NSAID nonsteroidal antiinflammatory drug, TMJ temporomandibular joint, and TNF tumor necrosis factor.
† Biologic DMARDs currently approved for JIA include the TNF inhibitors etanercept, adalimumab, golimumab, and certolizumab pegol; the interleukin-6 inhibitors tocilizumab and sarilumab; the interleukin-1 inhibitors canakinumab and anakinra (the latter approved in Europe but not in the United States); the interleukin-17 inhibitor secukinumab; the interleukin-12 and -23 inhibitor ustekinumab; and the interferon-γ inhibitor emapalumab (approved for children with primary hemophagocytic lymphohistiocytosis).

a female predominance, ANA positivity, and a risk of chronic anterior uveitis.[3] Psoriasis occurs in half of affected children but may not develop until later in the disease course. However, dactylitis, nail pits (Fig. 2D), or a family history of psoriasis can support an earlier diagnosis of psoriatic JIA. Manifestations of psoriatic JIA in older children and adolescents may be similar to those of psoriatic arthritis in adults, with enthesitis, peripheral polyarthritis, and sacroiliitis.[27] HLA-B27 is present in 10 to 12% of patients.

Treatment for early-onset oligoarticular or polyarticular psoriatic JIA is generally similar to treatment for oligoarticular and polyarticular JIA, and older children with enthesitis and sacroiliitis receive the same treatment administered in patients with enthesitis-related arthritis. Biologic medications targeting psoriasis and psoriatic arthritis, such as interleukin-17 inhibitors and inhibitors of interleukin-12 and -23, are approved for use in patients with psoriatic JIA.[18,34]

SYSTEMIC JIA

Unlike patients with other categories of JIA, those with systemic JIA present with markedly elevated levels of inflammatory markers, fevers, and rashes (Fig. 2E and 2F). Arthritis may not be present initially.[35] Lymphadenopathy, hepatosplenomegaly, and serositis may be present, along with life-threatening macrophage activation syndrome.[36] Infection and cancer must be considered and ruled out before treatment is initiated for systemic JIA, especially if arthritis is absent at presentation (Table 2). Early in the disease course, systemic JIA resembles monogenic autoinflammatory syndromes such as familial Mediterranean fever.[37] During this stage, activation of the innate immune system occurs, with high levels of proinflammatory cytokines; treatment with interleukin-1 and interleukin-6 inhibitors at this time may produce a remarkable clinical response and even remission.[15,21,38,39] However, chronic arthritis later in the course of

systemic JIA suggests the eventual involvement of adaptive immunity, with specific lymphocyte activation signatures, as well as a strong association with *HLA-DRB1*11*, a major histocompatibility complex (MHC) class II allele (Fig. 1).[38,40-42]

After the diagnosis of systemic JIA has been established, treatment with an interleukin-1 or interleukin-6 inhibitor is typically started, ideally during the early autoinflammatory phase.[15,21,43] Targeted synthetic DMARDs are emerging therapies for refractory systemic JIA.[21] Glucocorticoids are reserved for patients with severe systemic inflammation or macrophage activation syndrome, as discussed below.[21] DMARDs such as methotrexate and TNF inhibitors are generally not effective in early systemic JIA, although these and similar agents may be effective if chronic disease develops.[38] Systemic JIA and adult-onset Still's disease probably represent the same disease entity, and recent guidelines from an expert

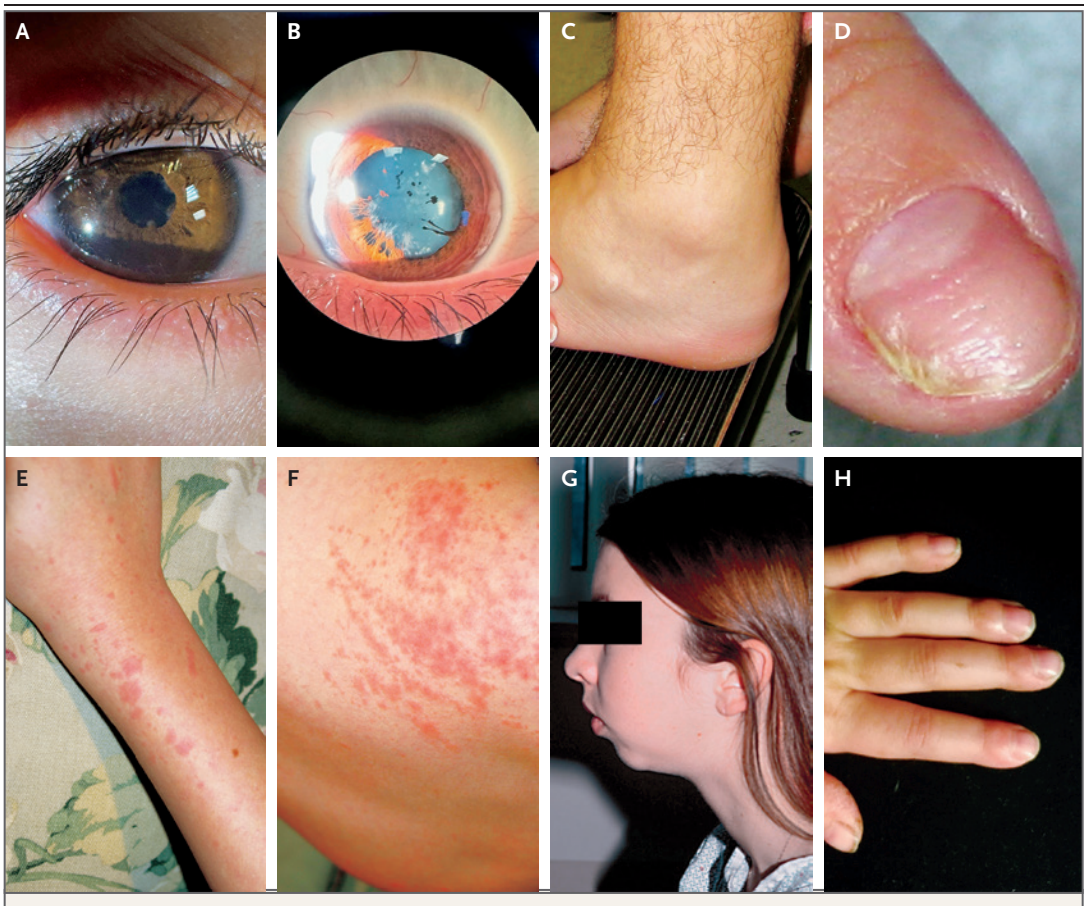

Figure 2. Common Clinical Manifestations of JIA.

Panel A shows synechiae (scarring resulting from adhesions of the iris to the lens) in a patient with oligoarticular JIA and chronic anterior uveitis. Extensive synechiae and early cataract formation, shown in Panel B, are the hallmarks of poorly controlled chronic anterior uveitis. Panel C shows calcaneal enthesitis in a patient with enthesitis-related arthritis. Panel D shows psoriatic nail pitting and onycholysis in a patient with psoriatic JIA. Skin psoriasis developed in this patient years later. The typical salmon-colored, evanescent, maculopapular rash of systemic JIA, shown in Panel E, often worsens during quotidian fevers and spares the face. This patient's rash was precipitated by scratching of the skin (Koebner's phenomenon). The rash is often subtle and can be missed in patients with dark skin tones. It may be more extensive and appear urticarial, as shown in Panel F, and is extremely pruritic in a minority of patients. Panel G shows micrognathia due in part to destruction of the mandibular condyle in a teenager with temporomandibular joint arthritis. Temporomandibular joint arthritis is often unrecognized until the damage has already occurred. Panel H shows clubbing of the fingers, a feature often associated with lung disease, in a young patient with systemic JIA.

joint task force of the European Alliance of Associations for Rheumatology and the Pediatric Rheumatology European Society propose using the term "Still's disease" to denote this apparent continuum.[21,35]

SPECIAL CONSIDERATIONS IN PATIENTS WITH JIA

UVEITIS

Chronic anterior uveitis (Fig. 2A and 2B), a distinctive complication of JIA that can lead to blindness, is seen most often in patients with oligoarticular, rheumatoid factor–negative polyarticular, or psoriatic JIA.[3,23] The prevalence ranges from 10 to 30%, depending on the JIA category, with girls under the age of 6 years who have ANA-positive disease at highest risk.[44] Chronic anterior uveitis is less common in older patients and is rare in those with systemic JIA, rheumatoid factor–positive polyarticular JIA, or enthesitis-related arthritis. Approximately 90% of cases of chronic anterior uveitis occur within 4 years after the onset of JIA, but JIA can precede the appearance of arthritis.[45] Because chronic anterior uveitis is typically asymptomatic initially, proactive ophthalmologic screening every 3 to 6 months is recommended for several years after the diagnosis of JIA, with specific screening intervals depending on risk factors.[19,20,23] Glucocorticoid eye drops can be used initially, but more than 40% of patients eventually require systemic therapy, usually with methotrexate, a TNF inhibitor, or both.[46]

Acute anterior uveitis, which occurs in 11 to 13% of patients with JIA and is usually seen in those with enthesitis-related arthritis, is characterized by a rapid onset of eye pain, conjunctival erythema, and photophobia. Patients are often positive for HLA-B27. However, since up to 40% of patients with enthesitis-related arthritis have asymptomatic uveitis,[47] regular ophthalmologic screening is recommended.[19,20] The response to topical glucocorticoids is prompt, but systemic DMARDs should be considered if a patient has more than two or three annual episodes of acute anterior uveitis.[48]

GROWTH ABNORMALITIES

Before the development of biologic DMARDs, many children with JIA had generalized growth failure in association with uncontrolled inflammation and prolonged glucocorticoid use. Poorly controlled JIA is also associated with limb length discrepancies, which are related to disproportionately rapid growth at epiphyseal growth plates due to inflammatory hyperemia,[49] as well as joint contractures, abnormal mandibular growth related to temporomandibular joint arthritis (Fig. 2G), and other deformities.[50] Early detection of temporomandibular joint arthritis with the use of contrast-enhanced MRI and timely treatment may prevent severe micrognathia, facial deformities, heterotopic calcification, and jaw dysfunction.[13,51]

MACROPHAGE ACTIVATION SYNDROME ASSOCIATED WITH SYSTEMIC JIA

Macrophage activation syndrome, a life-threatening acquired form of hemophagocytic lymphohistiocytosis (HLH), occurs in at least 10% of patients with systemic JIA.[36,52] Primary (e.g., familial) HLH is caused by rare defects in the perforin pathway, which leads to severe inflammation and death in early childhood.[53] Acquired HLH can be triggered by infection, cancer, or rheumatic disease flares. When HLH is associated with rheumatic disease, it is labeled macrophage activation syndrome.[54] This disorder can occur at any point in the progression of systemic JIA. Affected patients present with fever, coagulopathy, cytopenias, hyperferritinemia, liver injury, and central nervous system dysfunction.[21,55] Variants in HLH-related genes have been found in up to one third of patients with systemic JIA in whom macrophage activation syndrome developed.[56,57] Patients with systemic JIA and macrophage activation syndrome often have markedly elevated levels of interleukin-18.[58] Interferon-γ production induced by interleukin-18[59] is proposed to play a critical pathogenic role in macrophage activation syndrome, as indicated by the effectiveness of interferon-γ inhibitors in the treatment of macrophage activation syndrome (Fig. 1).[60] Advances in the recognition and treatment of macrophage activation syndrome, including the use of high-dose glucocorticoids, high-dose interleukin-1 inhibitors, and interferon-γ inhibitors, have greatly reduced mortality.[21,60]

LUNG DISEASE ASSOCIATED WITH SYSTEMIC JIA

A serious complication in patients with systemic JIA is lung disease, which can cause hypoxic respi-

ratory failure and even death.[61,62] The prevalence of lung disease among patients with systemic JIA is increasing and appears to be temporally associated with the increased use of interleukin-1 and interleukin-6 inhibitors. Children with systemic JIA and lung disease are generally younger at diagnosis and have more severe systemic disease (including macrophage activation syndrome) than children who have systemic JIA without lung disease. Other common features of systemic JIA–associated lung disease include adverse reactions to biologic DMARDs, atypical rashes, and acute finger clubbing (Fig. 2H). The cause of lung disease associated with systemic JIA is unclear, but these features[61-63] suggest a distinct systemic JIA subtype.[64] There may be an association with the *HLA-DRB1*15* allele.[65-68] Several hypotheses involving treatment with interleukin-1 and interleukin-6 inhibitors have been proposed, including cytokine-related lymphocyte plasticity and an unusual pulmonary complication of drug-induced hypersensitivity syndrome (also known as drug reaction with eosinophilia and systemic symptoms [DRESS]).[65,69] Studies are urgently needed to determine the pathogenesis of lung disease associated with systemic JIA, as well as effective approaches to identification, screening, and management.[21,64,67,68]

STRATEGIES FOR THE TREATMENT OF JIA

Advances in the treatment of JIA have resulted in meaningful disease control for up to 70% of patients. Clinicians have traditionally adopted a step-up treatment approach (i.e., the sequential addition of a conventional synthetic DMARD, followed by a biologic DMARD, to attain disease control). However, newer approaches that more rapidly control disease, such as initiating therapy with a biologic DMARD, with or without a conventional synthetic DMARD, are becoming more common. Two studies of these newer approaches for specific JIA categories showed improved outcomes and a reduction in disease burden in the short and long term.[15,70] In a single-group, single-center study involving patients with systemic JIA who received early treatment with an interleukin-1 inhibitor, more than 70% of the patients had medication-free remission at 5 years, indicating a possible window of opportunity early in the disease course for preventing the development of chronic systemic JIA.[15,38,39]

In STOP-JIA (Start Time Optimization of Biologics in Polyarticular JIA), a large, nonrandomized, prospective study involving 400 patients with polyarticular JIA,[70] patients treated early with a combination of conventional synthetic DMARDs and biologic DMARDs had better outcomes at 3 years than patients treated with traditional step-up therapy.[71] The patients in the combination DMARD group had significantly longer periods of inactive disease, on the basis of validated measures (e.g., the American College of Rheumatology criteria for clinically inactive disease, clinical remission during receipt of medications,[73] and the clinical Juvenile Arthritis Disease Activity Score 10).[72-74] In addition, patients who received a biologic DMARD within 2 months after diagnosis were almost 3 times more likely than those who did not receive biologic DMARDs within that time frame to have a rapid-improvement trajectory and sustained periods of disease inactivity.[75,76]

After disease activity has been reduced, ongoing disease control may be refined with the use of the treat-to-target strategy, in which therapy is modified at defined intervals to achieve clinical targets.[77] The randomized BeST-for-Kids trial compared three initial treatment combinations and a treat-to-target strategy in 90 children with JIA.[73,78] Most patients (70%) had clinical remission at 2 years, regardless of the initial treatment assignment. However, patients in the early combination group had the most rapid improvement and were most likely to have sustained responses, findings that are consistent with data from the STOP-JIA study.[71] The results of these trials suggest that initiating therapy early in the disease course with a biologic DMARD or with combination treatment, along with a treat-to-target strategy for ongoing disease control, may further improve outcomes. The STARS (Step-up and Step-down Therapeutic Strategies in Childhood Arthritis) trial is testing this approach by assessing step-up treatment intensification coupled with a treat-to-target framework as compared with early combination therapy without a treat-to-target framework in patients with oligoarticular or polyarticular JIA.[79]

Other important treatment components include physical and occupational therapy for patients at risk for functional limitations, shared decision making, and attention to the adverse effects of chronic disease, pain, and disability on a child's physical, emotional, and social development. As patients mature, facilitating the transition from pediatric to adult care is essential for favorable long-term health outcomes.[80] Limited global access to rheumatologic care and to advanced treatments are common barriers to disease control throughout the lifetime of a patient with JIA.[4,7]

CLINICAL RESEARCH IN PEDIATRIC RHEUMATOLOGY

Over the past decade, the development and approval of new targeted biologic DMARDs (e.g., inhibitors of interleukin-17, interleukin-12 and -23, and interferon-γ) and targeted synthetic DMARDs with new mechanisms of action (e.g., Janus kinase inhibitors) have advanced the treatment of JIA (Table 3). Networks of pediatric rheumatologists committed to performing robust clinical studies have been key to this progress. Through these networks, the long-term efficacy of early aggressive therapy, long-term safety of the medications, and personalization of treatment are being addressed. Quantification of the incidence of rare adverse events such as opportunistic infections and cancer is being performed through research registries.[81-83] These registries also provide data and matched controls for large, observational comparative-effectiveness trials.[84] The Childhood Arthritis and Rheumatology Research Alliance LIMIT-JIA trial is currently exploring whether early biologic DMARD treatment in patients with oligoarticular JIA can prevent extension to polyarthritis or uveitis (ClinicalTrials.gov number, NCT03841357).

Despite the availability of many new and effective treatments, questions about which treatment to choose and when it is safe to stop treatment in individual patients are critical and remain unanswered. A systematic review showed that 30 to 100% of patients with JIA have disease flares after their medication is discontinued,[85] and in 50% of patients with flares after stopping a DMARD, disease control cannot be regained.[14,86] Treatment personalization is being addressed by two international studies. The UCAN CAN-DU (Canada–Netherlands Personalized Medicine Network in Childhood Arthritis and Rheumatic Disease) study (NCT06560606) is designed to discover biologic predictors of treatment response, disease course, and remission. The randomized SMART-JIA trial (NCT06654882), a collaboration between the Pediatric Rheumatology European Society and the Childhood Arthritis and Rheumatology Research Alliance, will assess four medications with different mechanisms of action in patients with polyarticular JIA that is not responsive to initial TNF-inhibitor therapy. These studies represent critical global collaborations that will move the field forward.

SUMMARY

The effects of inflammatory arthritis in children and adolescents differ from those in adults because of the way the disease affects the growing musculoskeletal and immune systems in young persons. JIA consists of at least five biologically distinct phenotypes. New treatments and targeted therapies show promise for improving long-term outcomes of these disorders. The induction of rapid disease control with earlier initiation of biologic DMARDs and targeted synthetic DMARDs, as well as treat-to-target strategies to sustain inactive disease, may further reduce damage and the disease burden. Management of JIA includes recognizing and treating issues specific to childhood arthritis and ensuring an effective transition from pediatric to adult care as patients mature. More research is needed to identify specific predictors of treatment response, as well as biomarkers of true remission that may enable discontinuation of treatment.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Clement D. Lee, M.D., assisted with the editorial handling of this article for the *Journal*.

AUTHOR INFORMATION

[1]Stanford University School of Medicine, Stanford, CA; [2]Department of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati; [3]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati; [4]Joseph M. Sanzari Children's Hospital, Hackensack Meridian School of Medicine, Nutley, NJ.

REFERENCES

1. Packham JC, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. Rheumatology (Oxford) 2002;41:1428-35.
2. Oen K, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, Cheang M. Disease course and outcome of juvenile rheumatoid arthritis in a multicenter cohort. J Rheumatol 2002;29:1989-99.
3. Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, Mellins ED, Fuhlbrigge RC. Textbook of pediatric rheumatology. 8th ed. Philadelphia: Elsevier, 2021.
4. Consolaro A, Giancane G, Alongi A, et al. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study. Lancet Child Adolesc Health 2019;3:255-63.
5. Arkachaisri T, Tang S-P, Daengsuwan T, et al. Paediatric rheumatology clinic population in Southeast Asia: are we different? Rheumatology (Oxford) 2017;56:390-8.
6. Fujikawa S, Okuni M. Clinical analysis of 570 cases with juvenile rheumatoid arthritis: results of a nationwide retrospective survey in Japan. Acta Paediatr Jpn 1997;39:245-9.
7. Scott C, Chan M, Slamang W, et al. Juvenile arthritis management in less resourced countries (JAMLess): consensus recommendations from the Cradle of Humankind. Clin Rheumatol 2019;38:563-75.
8. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.
9. Martini A, Ravelli A, Avcin T, et al. Toward new classification criteria for juvenile idiopathic arthritis: first steps, Pediatric Rheumatology International Trials Organization international consensus. J Rheumatol 2019;46:190-7.
10. Nigrovic PA, Colbert RA, Holers VM, et al. Biological classification of childhood arthritis: roadmap to a molecular nomenclature. Nat Rev Rheumatol 2021;17:257-69.
11. Degboe Y, Vastert SJ, Prakken BJ, McInnes IB. How does age determine the development of human immune-mediated arthritis? Nat Rev Rheumatol 2022;18:501-12.
12. Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis. Arthritis Care Res (Hoboken) 2019;71:717-34.
13. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. Arthritis Rheumatol 2022;74:553-69.
14. Chang MH, Fuhlbrigge RC, Nigrovic PA. Joint-specific memory, resident memory T cells and the rolling window of opportunity in arthritis. Nat Rev Rheumatol 2024;20:258-71.
15. Ter Haar NM, van Dijkhuizen EHP, Swart JF, et al. Treatment to target using recombinant interleukin-1 receptor antagonist as first-line monotherapy in new-onset systemic juvenile idiopathic arthritis: results from a five-year follow-up study. Arthritis Rheumatol 2019;71:1163-73.
16. Ruperto N, Brunner HI, Quartier P, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367:2396-406.
17. De Benedetti F, Brunner HI, Ruperto N, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367:2385-95.
18. Brunner HI, Foeldvari I, Alexeeva E, et al. Secukinumab in enthesitis-related arthritis and juvenile psoriatic arthritis: a randomised, double-blind, placebo-controlled, treatment withdrawal, phase 3 trial. Ann Rheum Dis 2023;82:154-60.
19. Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the screening, monitoring, and treatment of juvenile idiopathic arthritis-associated uveitis. Arthritis Care Res (Hoboken) 2019;71:703-16.
20. Foeldvari I, Maccora I, Petrushkin H, et al. New and updated recommendations for the treatment of juvenile idiopathic arthritis-associated uveitis and idiopathic chronic anterior uveitis. Arthritis Care Res (Hoboken) 2023;75:975-82.
21. Fautrel B, Mitrovic S, De Matteis A, et al. EULAR/PReS recommendations for the diagnosis and management of Still's disease, comprising systemic juvenile idiopathic arthritis and adult-onset Still's disease. Ann Rheum Dis 2024;83:1614-27.
22. Chang MH, Shantha JG, Fondriest JJ, Lo MS, Angeles-Han ST. Uveitis in children and adolescents. Rheum Dis Clin North Am 2021;47:619-41.
23. Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. Clin Immunol 2020;211:108322.
24. Hinks A, Bowes J, Cobb J, et al. Fine-mapping the MHC locus in juvenile idiopathic arthritis (JIA) reveals genetic heterogeneity corresponding to distinct adult inflammatory arthritic diseases. Ann Rheum Dis 2017;76:765-72.
25. Hinks A, Marion MC, Cobb J, et al. The genetic profile of rheumatoid factor-positive polyarticular juvenile idiopathic arthritis resembles that of adult rheumatoid arthritis. Arthritis Rheumatol 2018;70:957-62.
26. Orsini F, Crotti C, Cincinelli G, et al. Bone involvement in rheumatoid arthritis and spondyloartritis: an updated review. Biology (Basel) 2023;12:1320.
27. Srinivasalu H, Sikora KA, Colbert RA. Recent updates in juvenile spondyloarthritis. Rheum Dis Clin North Am 2021;47:565-83.
28. Schett G, Lories RJ, D'Agostino M-A, et al. Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol 2017;13:731-41.
29. Lin C, MacKenzie JD, Courtier JL, Gu JT, Milojevic D. Magnetic resonance imaging findings in juvenile spondyloarthropathy and effects of treatment observed on subsequent imaging. Pediatr Rheumatol Online J 2014;12:25.
30. Gmuca S, Xiao R, Brandon TG, et al. Multicenter inception cohort of enthesitis-related arthritis: variation in disease characteristics and treatment approaches. Arthritis Res Ther 2017;19:84.
31. Angeles-Han ST, McCracken C, Yeh S, et al. HLA associations in a cohort of children with juvenile idiopathic arthritis with and without uveitis. Invest Ophthalmol Vis Sci 2015;56:6043-8.
32. Yang X, Garner LI, Zvyagin IV, et al. Autoimmunity-associated T cell receptors recognize HLA-B*27-bound peptides. Nature 2022;612:771-7.
33. Burgos-Vargas R, Loyola-Sanchez A, Ramiro S, et al. A randomized, double-blind, placebo-controlled 12-week trial of infliximab in patients with juvenile-onset spondyloarthritis. Arthritis Res Ther 2022;24:187.
34. Leu JH, Shiff NJ, Clark M, et al. Intravenous golimumab in patients with polyarticular juvenile idiopathic arthritis and juvenile psoriatic arthritis and subcutaneous ustekinumab in patients with juvenile psoriatic arthritis: extrapolation of data from studies in adults and adjacent pediatric populations. Paediatr Drugs 2022;24:699-714.
35. De Matteis A, Bindoli S, De Benedetti F, Carmona L, Fautrel B, Mitrovic S. Systemic juvenile idiopathic arthritis and adult-onset Still's disease are the same disease: evidence from systematic reviews and meta-analyses informing the 2023 EULAR/PReS recommendations for the diagnosis and management of Still's disease. Ann Rheum Dis 2024;83:1748-61.
36. Vastert SJ, Canny SP, Canna SW, Schneider R, Mellins ED. Cytokine storm syndrome associated with systemic juvenile idiopathic arthritis. Adv Exp Med Biol 2024;1448:323-53.
37. Zhang J, Lee PY, Aksentijevich I, Zhou Q. How to build a fire: the genetics of autoinflammatory diseases. Annu Rev Genet 2023;57:245-74.
38. Hinze CH, Foell D, Kessel C. Treatment

of systemic juvenile idiopathic arthritis. Nat Rev Rheumatol 2023;19:778-89.
39. Nigrovic PA. Is there a window of opportunity for treatment of systemic juvenile idiopathic arthritis? Arthritis Rheumatol 2014;66:1405-13.
40. Kuehn J, Schleifenbaum S, Hendling M, et al. Aberrant naïve CD4-positive T cell differentiation in systemic juvenile idiopathic arthritis committed to B cell help. Arthritis Rheumatol 2023;75:826-41.
41. Henderson LA, Hoyt KJ, Lee PY, et al. Th17 reprogramming of T cells in systemic juvenile idiopathic arthritis. JCI Insight 2020;5(6):e132508.
42. Ombrello MJ, Remmers EF, Tachmazidou I, et al. HLA-DRB1*11 and variants of the MHC class II locus are strong risk factors for systemic juvenile idiopathic arthritis. Proc Natl Acad Sci U S A 2015; 112:15970-5.
43. Nigrovic PA, Mannion M, Prince FHM, et al. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum 2011;63:545-55.
44. Wennink RAW, de Boer JH, Hiddingh S, et al. Next-generation HLA sequence analysis uncovers shared risk alleles between clinically distinct forms of childhood uveitis. Invest Ophthalmol Vis Sci 2021;62:19.
45. Nordal E, Rypdal V, Christoffersen T, et al. Incidence and predictors of uveitis in juvenile idiopathic arthritis in a Nordic long-term cohort study. Pediatr Rheumatol Online J 2017;15:66.
46. Heiligenhaus A, Minden K, Tappeiner C, et al. Update of the evidence based, interdisciplinary guideline for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Semin Arthritis Rheum 2019;49:43-55.
47. Walscheid K, Glandorf K, Rothaus K, et al. Enthesitis-related arthritis: prevalence and complications of associated uveitis in children and adolescents from a population-based nationwide study in Germany. J Rheumatol 2021;48:262-9.
48. Jacquot R, Kodjikian L, Chapurlat R, Sève P. Targeted therapies for uveitis in spondyloarthritis: a narrative review. Joint Bone Spine 2024;91:105697.
49. Vostrejs M, Hollister JR. Muscle atrophy and leg length discrepancies in pauciarticular juvenile rheumatoid arthritis. Am J Dis Child 1988;142:343-5.
50. Stoll ML, Sharpe T, Beukelman T, Good J, Young D, Cron RQ. Risk factors for temporomandibular joint arthritis in children with juvenile idiopathic arthritis. J Rheumatol 2012;39:1880-7.
51. Stoustrup P, Resnick CM, Abramowicz S, et al. Management of orofacial manifestations of juvenile idiopathic arthritis: interdisciplinary consensus-based recommendations. Arthritis Rheumatol 2023; 75:4-14.
52. Minoia F, Davì S, Horne A, et al. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. Arthritis Rheumatol 2014; 66:3160-9.
53. Filipovich AH. Hemophagocytic lymphohistiocytosis and related disorders. Curr Opin Allergy Clin Immunol 2006;6: 410-5.
54. Grom AA, Horne A, De Benedetti F. Macrophage activation syndrome in the era of biologic therapy. Nat Rev Rheumatol 2016;12:259-68.
55. Ravelli A, Minoia F, Davì S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation collaborative initiative. Ann Rheum Dis 2016;75:481-9.
56. Kaufman KM, Linghu B, Szustakowski JD, et al. Whole-exome sequencing reveals overlap between macrophage activation syndrome in systemic juvenile idiopathic arthritis and familial hemophagocytic lymphohistiocytosis. Arthritis Rheumatol 2014;66:3486-95.
57. Correia Marques M, Rubin D, Shuldiner EG, et al. Enrichment of rare variants of hemophagocytic lymphohistiocytosis genes in systemic juvenile idiopathic arthritis. Arthritis Rheumatol 2024;76: 1566-72.
58. Yasin S, Solomon K, Canna SW, et al. IL-18 as therapeutic target in a patient with resistant systemic juvenile idiopathic arthritis and recurrent macrophage activation syndrome. Rheumatology (Oxford) 2020;59:442-5.
59. Landy E, Carol H, Ring A, Canna S. Biological and clinical roles of IL-18 in inflammatory diseases. Nat Rev Rheumatol 2024;20:33-47.
60. De Benedetti F, Grom AA, Brogan PA, et al. Efficacy and safety of emapalumab in macrophage activation syndrome. Ann Rheum Dis 2023;82:857-65.
61. Schulert GS, Yasin S, Carey B, et al. Systemic juvenile idiopathic arthritis-associated lung disease: characterization and risk factors. Arthritis Rheumatol 2019; 71:1943-54.
62. Saper VE, Chen G, Deutsch GH, et al. Emergent high fatality lung disease in systemic juvenile arthritis. Ann Rheum Dis 2019;78:1722-31.
63. Huang Y, Sompii-Montgomery L, Patti J, et al. Disease course, treatments, and outcomes of children with systemic juvenile idiopathic arthritis associated lung disease (SJIA-LD). Arthritis Care Res (Hoboken) 2024;76:328-39.
64. Towe C, Grom AA, Schulert GS. Diagnosis and management of the systemic juvenile idiopathic arthritis patient with emerging lung disease. Paediatr Drugs 2023;25:649-58.
65. Saper VE, Ombrello MJ, Tremoulet AH, et al. Severe delayed hypersensitivity reactions to IL-1 and IL-6 inhibitors link to common HLA-DRB1*15 alleles. Ann Rheum Dis 2022;81:406-15.
66. Lerman AM, Mahmud SA, Alfath Z, et al. HLA-DRB1*15 and eosinophilia are common among patients with systemic juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2023;75:2082-7.
67. Wobma H, Arvila SR, Taylor ML, et al. Incidence and risk factors for eosinophilia and lung disease in biologic-exposed children with systemic juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2023;75:2063-72.
68. Saper VE, Tian L, Verstegen RHJ, et al. Interleukin (IL)-1/IL-6-inhibitor-associated drug reaction with eosinophilia and systemic symptoms (DReSS) in systemic inflammatory illnesses. J Allergy Clin Immunol Pract 2024;12(11):2996-3013.e7.
69. Binstadt BA, Nigrovic PA. The conundrum of lung disease and drug hypersensitivity-like reactions in systemic juvenile idiopathic arthritis. Arthritis Rheumatol 2022;74:1122-31.
70. Kimura Y, Schanberg LE, Tomlinson GA, et al. Optimizing the start time of biologics in polyarticular juvenile idiopathic arthritis: a comparative effectiveness study of Childhood Arthritis and Rheumatology Research Alliance Consensus treatment plans. Arthritis Rheumatol 2021;73:1898-909.
71. Ringold S, Tomlinson G, Schanberg L, et al. Two- and three-year outcomes from the childhood arthritis and rheumatology research alliance start time optimization of biologic therapy in polyarticular JIA (STOP-JIA) study. Arthritis Rheumatol 2023;75:Suppl 9:0831. abstract (https://acrabstracts.org/abstract/two-and-three-year-outcomes-from-the-childhood-arthritis-and-rheumatology-research-alliance-start-time-optimization-of-biologic-therapy-in-polyarticular-jia-stop-jia-study/).
72. Wallace CA, Giannini EH, Huang B, et al. American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2011;63:929-36.
73. Wallace CA, Ruperto N, Giannini E, Childhood Arthritis and Rheumatology Research Alliance, Pediatric Rheumatology International Trials Organization, Pediatric Rheumatology Collaborative Study Group. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol 2004;31: 2290-4.
74. Trincianti C, Van Dijkhuizen EHP, Alongi A, et al. Definition and validation of the American College of Rheumatology 2021 juvenile arthritis disease activity

score cutoffs for disease activity states in juvenile idiopathic arthritis. Arthritis Rheumatol 2021;73:1966-75.
75. Ong MS, Ringold S, Kimura Y, et al. Improved disease course associated with early initiation of biologics in polyarticular juvenile idiopathic arthritis: trajectory analysis of a Childhood Arthritis and Rheumatology Research Alliance consensus treatment plans study. Arthritis Rheumatol 2021;73:1910-20.
76. Ringold S, Ong MS, Tomlinson G, et al. Three-year outcomes and latent class trajectory analysis of the Childhood Arthritis and Rheumatology Research Alliance Polyarticular JIA Consensus Treatment Plans study. Arthritis Rheumatol 2025 May 8 (Epub ahead of print).
77. Ravelli A, Consolaro A, Horneff G, et al. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. Ann Rheum Dis 2018; 77:819-28.
78. Hissink Muller P, Brinkman DMC, Schonenberg-Meinema D, et al. Treat to target (drug-free) inactive disease in DMARD-naive juvenile idiopathic arthritis: 24-month clinical outcomes of a three-armed randomised trial. Ann Rheum Dis 2019;78: 51-9.
79. Burrone M, Mazzoni M, Naddei R, et al. Looking for the best strategy to treat children with new onset juvenile idiopathic arthritis: presentation of the "comparison of STep-up and step-down therapeutic strategies in childhood ARthritiS" (STARS) trial. Pediatr Rheumatol Online J 2022;20:80.
80. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: recommendations for nonpharmacologic therapies, medication monitoring, immunizations, and imaging. Arthritis Rheumatol 2022;74:570-85.
81. Lionetti G, Kimura Y, Schanberg LE, et al. Using registries to identify adverse events in rheumatic diseases. Pediatrics 2013;132(5):e1384-1394.
82. Armaroli G, Klein A, Ganser G, et al. Long-term safety and effectiveness of etanercept in JIA: an 18-year experience from the BiKeR registry. Arthritis Res Ther 2020;22:258.
83. Swart J, Giancane G, Horneff G, et al. Pharmacovigilance in juvenile idiopathic arthritis patients treated with biologic or synthetic drugs: combined data of more than 15,000 patients from Pharmachild and national registries. Arthritis Res Ther 2018;20:285.
84. Ringold S, Nigrovic PA, Feldman BM, et al. The Childhood Arthritis and Rheumatology Research Alliance consensus treatment plans: toward comparative effectiveness in the pediatric rheumatic diseases. Arthritis Rheumatol 2018;70:669-78.
85. Halyabar O, Mehta J, Ringold S, Rumsey DG, Horton DB. Treatment withdrawal following remission in juvenile idiopathic arthritis: a systematic review of the literature. Paediatr Drugs 2019;21:469-92.
86. Ringold S, Dennos AC, Kimura Y, et al. Disease recapture rates after medication discontinuation and flare in juvenile idiopathic arthritis: an observational study within the Childhood Arthritis and Rheumatology Research Alliance registry. Arthritis Care Res (Hoboken) 2023;75:715-23.