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## REVIEW ARTICLE

### Overview of Juvenile Idiopathic Arthritis

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**Abstract:** Joint pain is a common symptom in children and adolescents. While there are many causes of joint pain in children, most of these are acute or not related to underlying joint inflammation. Chronic arthritis, however, can be one of the reasons behind the joint pain. The most common causes of chronic arthritis in children are categorized under juvenile idiopathic arthritis (JIA). The purpose of this review is to highlight the most important clinical features, work-up, and medical management of the different subtypes of JIA.

**Keywords:** Juvenile idiopathic arthritis, Pediatrics, Medical management, Pediatric arthritis, Joint pain, Joint inflammation.

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## 1. INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is the most common cause of arthritis in childhood. It is difficult to assess the true incidence rates as nomenclature and disease criteria have changed over time, but it is estimated that about 300,000 children in North America have JIA [1]. JIA is an umbrella term that captures several subtypes of chronic arthritis that have varying clinical features. Each of these subtypes has a different prognosis, complications, and treatments. The precise etiology of JIA is unknown, and is likely the result of a complex interaction between genetics and the environment.

To help better understand JIA for research purposes, generally accepted classification criteria are used. Although these are not diagnostic, they can help guide physicians when treating a child with arthritis. One of the most widely used classification criteria was proposed by the International League of Associations for Rheumatology (ILAR) in 1995 through expert consensus, and has undergone subsequent revisions [2].

Under the ILAR criteria, a child's arthritis must begin before the age of 16 years and be of at least 6 weeks' duration [2]. To diagnose arthritis, two characteristics of inflammation should be present, which may include swelling, redness, warmth, or limited range of motion. Importantly, to make the diagnosis of JIA, mimickers of arthritis, including infections, malignancy, myositis, and other forms of chronic arthritis must be excluded.

The ILAR classification criteria divide JIA into seven subtypes. Their definitions, as well as exclusion criteria, are de-

scribed in Table 1. The remainder of this review describes the epidemiology, pathogenesis, clinical features, and medical management of JIA.

## 2. DEFINITIONS AND EPIDEMIOLOGY

Oligoarticular JIA is the most common subtype of JIA [4]. Oligoarticular JIA is defined as arthritis affecting four or fewer joints during the first 6 months of disease [2]. There are two further subcategories depending on the number of joints involved after 6 months. Persistent oligoarthritis is defined as arthritis in four or fewer joints for the entire disease course. If at any time after the initial 6 months of disease, five or more joints become affected, the disease is classified as extended oligoarthritis. A systemic review of 26 studies found the pooled incidence rate to be 3.7 per 100,000 children, and the prevalence to be 16.8 per 100,000 from 19 studies [4]. Oligoarthritis has a peak incidence between the ages of 1 and 3 years, and predominantly occurs in girls [5].

Polyarticular JIA accounts for about 20% of all JIA patients [7]. It is defined as arthritis in five or more joints within the first 6 months of disease onset. Rheumatoid Factor (RF) positivity helps to further classify this category. Approximately 85% of children with polyarthritis are RF negative [7]. A systematic review of 12 studies in RF negative arthritis found an incidence of 1 per 100,000 and a prevalence of 5.1 per 100,000 [4]. If a child has two or more tests for RF that are positive at least 3 months apart during the first 6 months of disease, they are considered to have RF-positive polyarticular JIA. Those who are RF positive tend to mirror adult rheumatoid arthritis and have more severe disease. A systematic review of 14 studies found the incidence rate of RF positive arthritis to be 0.4 per 100,000, and a prevalence of 1

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per 100,000 from 12 studies [4]. RF positive arthritis tends to occur in early adolescence, while RF negative arthritis has a peak in the toddler years and in late childhood/adolescence [8]. Again, girls are affected more often than boys.

Juvenile psoriatic arthritis (jPsA) accounts for 5% of all JIA patients [9]. As defined by the ILAR criteria, jPsA is arthritis and psoriasis, or arthritis with at least two of the following: dactylitis; nail pitting or onycholysis; or psoriasis in a first-degree relative [2]. The incidence and prevalence of jPsA are unknown and have not been reliably published upon. It can occur in all ethnic groups. It has a female predominance [10]. The average age of symptom onset in a North American cohort was 4-12 years [9, 11, 12].

The ILAR classification criteria define Enthesitis-Related Arthritis (ERA) as arthritis and enthesitis, or arthritis or enthesitis with two or more of the following: sacroiliac joint tenderness and/or inflammatory lumbosacral pain; the presence of HLA-B27; family history of HLA-B27 associated disease (ankylosing spondylitis, ERA, sacroiliitis with inflammatory bowel disease, reactive arthritis, acute anterior uveitis) in a first-degree relative; acute symptomatic anterior uveitis; or onset of arthritis in a boy after 6 years of age [2]. Current studies have reported a range of 8.6 to 18.9% of children with ERA amongst children with JIA [7, 13 - 15]. The age at diagnosis has been reported to be around 10 to 13 years, and there is a male predominance [15].

Systemic juvenile idiopathic arthritis (sJIA) is distinct from the other forms of JIA with a much different presentation, prognosis, and management. Many propose that it may be a different disease entity entirely. It has more extraarticular manifestations than the other types of JIA and these are often more dominant than arthritis. sJIA is similar to Adult-onset Still's disease (AOSD). Systemic JIA accounts for 5 to 15% of JIA in North America and Europe [16, 17]. Studies are limited, so the exact prevalence and incidence are unknown. sJIA may occur at any time during childhood. Boys and girls are affected with equal frequency.

Undifferentiated arthritis is defined as arthritis that does not fulfill sufficient inclusion criteria for any category, or is excluded by fulfilling criteria for more than one category [2]. There are multiple different types of JIA in this category with overlapping features.

### 3. PATHOGENESIS

There is likely a complex interplay of genetic susceptibility, environmental triggers, and a disordered immune response that leads to the development of JIA. However, the exact pathogenesis is unknown, and it is likely that the pathogenesis of each subtype differs. Most obviously different is the pathophysiology of systemic JIA. It has distinct clinical manifestations and an inflammatory immune response with elevations of cytokines, such as IL-1 and IL-18. Systemic JIA more closely resembles an autoinflammatory disease [18 - 21].

It is hypothesized that an environmental exposure in a genetically susceptible child leads to an altered immune response. The genetics of JIA have been extensively studied,

and it is likely a polygenic disease [22 - 27]. In 2000, 13 pairs of twins were identified as concordant for onset and course of disease [24]. Furthermore, multiple studies have described an association between HLA alleles and both oligoarticular and polyarticular JIA [23]. Genome-wide association studies have identified multiple single nucleotide polymorphisms that are associated with oligoarticular and RF negative polyarticular JIA, likely uniquely contributing to their pathogenesis [26, 27]. A possible theory for an environmental trigger is an infection as heat shock proteins are found to be elevated in JIA patients [28,29]. However, no specific infection has yet been confirmed. Further studies are needed to describe the role of genetics and the environment in the pathogenesis of JIA.

## 4. CLINICAL MANIFESTATIONS

### 4.1. Joint Disease

Oligoarticular JIA typically affects large joints in the lower extremities in an asymmetric pattern. Since oligoarthritis tends to affect toddlers, the first symptoms that may be noticed by the parent are a limp or a swollen joint. The knees and ankles are the most commonly involved joints. Joints may be warm. They are not typically red or very painful. Surrounding muscles may become atrophic as the child becomes more immobile. Leg length discrepancies can occur, with the leg on the affected side becoming longer.

The onset of arthritis in RF-negative polyarthritis is most variable. It can be acute or progressive. Large and small joints are affected in a symmetric or asymmetric pattern. Commonly involved joints are the knees, ankles, elbows, wrists, cervical spine, temporomandibular joint (TMJ) and small joints of the hands and feet [30, 31].

Children who are RF-positive tend to have more aggressive arthritis. Both large and small joints can be affected and it typically occurs in a symmetrical pattern. The hips, cervical spine and TMJ may also be involved [30, 31]. Rheumatoid nodules can be seen, but are rare in other forms of JIA. The classic child with RF-positive polyarticular JIA is a teenage girl with symmetric arthritis in her wrists, metacarpophalangeal (MCP) joints, and metatarsophalangeal (MTP) joints.

The arthritis in jPsA tends to begin as a monoarthritis and can progress to a polyarthritis. The knees, ankles, and small joints of the hand and feet are most commonly affected. The distribution of polyarthritis is often asymmetric. Hip arthritis is not infrequent. Additionally, sacroiliitis can be seen [12]. Older children with jPsA tend to have more enthesitis (diagnosed by specific tenderness and occasional swelling) and axial disease. Some patients will have dactylitis without joint involvement. Their digits will appear uniformly swollen and "sausage-like". On radiographs, flexor synovitis is a common finding [32].

ERA is characterized by enthesitis and/or arthritis. Enthesitis refers to inflammation at the sites of attachment of ligaments and tendons to bone. In ERA, enthesitis typically occurs in the lower limbs. Children may report knee, foot, or heel pain. On examination, children will have tenderness or swelling at the enthesial insertion into the bone. Peripheral arthritis may occur and is often asymmetrical and generally involves the lower extremities. Hip arthritis is common. Axial

disease and sacroiliitis develop over time [33]. On examination, pain may be elicited by direct pressure over one or both of the sacroiliac joints. The modified Schober test may show limited forward flexion of the lumbar spine.

**4.2. Extraarticular Manifestations**

Uveitis is an extraarticular manifestation seen in all types of JIA, albeit at different rates. The prevalence of uveitis is about 20% in oligoarticular JIA, 12 to 20% in polyarticular JIA, and 10-15% in jPsA [34 - 36]. In all subtypes of JIA, with the exception of ERA, uveitis tends to be asymptomatic.

Uveitis in ERA is characterized by an acutely red, painful, photophobic eye. A recent analysis of a German database found a uveitis prevalence of 7.4% in children with ERA [37]. In 63% of these children, uveitis was acutely symptomatic. A majority had unilateral disease (83%) and anterior uveitis (88%) [37]. Regular ophthalmological screening is recommended for all children with JIA [38]. Children with risk factors for uveitis, including female gender, oligoarthritis, younger age of JIA onset and Anti-Nuclear Antibody (ANA) positivity, should undergo more frequent ophthalmological screening [35, 36, 39].

**Table 1. 2001 ILAR JIA Definitions and Exclusion Criteria <sup>2</sup>**

JIA Categories	Definition	ILAR Exclusion Criteria
1. Oligoarticular JIA, Persistent and Extended	Arthritis affecting four or fewer joints during the first 6 months of disease Persistent oligoarthritis: Arthritis in four or fewer joints for the entire disease course Extended oligoarthritis: Arthritis in five or more joints after the initial 6 months of disease	(1) Psoriasis in the patient or a history of psoriasis in a first-degree relative; OR (2) Arthritis in an HLA-B27 male beginning after his sixth birthday; OR (3) Two positive tests for RF obtained at least three months apart; OR (4) HLA-Associated disease* in a first-degree relative; OR (5) Systemic arthritis
2. RF-negative polyarticular JIA	Arthritis affecting 5 or more joints during the first 6 months of disease, with an RF negative test	(1) Psoriasis in the patient or a history of psoriasis in a first-degree relative; OR (2) Arthritis in an HLA-B27 male beginning after his sixth birthday; OR (3) Two positive tests for RF obtained at least three months apart; OR (4) HLA-Associated disease* in a first-degree relative; OR (5) Systemic arthritis
3. RF-positive polyarticular JIA	Arthritis affecting 5 or more joints during the first 6 months of disease, with 2 or more positive tests for RF at least 3 months apart during the first 6 months of disease	(1) Psoriasis in the patient or a history of psoriasis in a first-degree relative; OR (2) Arthritis in an HLA-B27 male beginning after his sixth birthday; OR (3) HLA-Associated disease* in a first-degree relative; OR (4) Systemic arthritis
4. Systemic arthritis	Arthritis in one or more joints with or preceded by fever of at least 2 weeks duration that is documented to be daily for at least 3 days, AND Accompanied by one or more of the following: 1. Evanescent erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly and/or splenomegaly 4. Serositis	(1) Psoriasis in the patient or a history of psoriasis in a first-degree relative; OR (2) Arthritis in an HLA-B27 male beginning after his sixth birthday; OR (3) Two positive tests for RF obtained at least three months apart; OR (4) HLA-Associated disease* in a first-degree relative
5. Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: 1. Dactylitis 2. Nail pitting or onycholysis 3. Psoriasis in a first-degree relative	(1) Arthritis in an HLA-B27 male beginning after his sixth birthday; OR (2) Two positive tests for RF obtained at least three months apart; OR (3) HLA-associated disease* in a first-degree relative; OR (4) Systemic arthritis.
6. Enthesitis-related arthritis	Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: 1. Presence or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain 2. The presence of HLA-B27 antigen 3. Onset of arthritis in a male over 6 years of age 4. Acute anterior uveitis 5. History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative	(1) Psoriasis in the patient or a history of psoriasis in a first-degree relative; OR (2) Arthritis in an HLA-B27 male beginning after his sixth birthday; OR (3) Two positive tests for RF obtained at least three months apart; OR (4) Arthritis that fits 2 or more categories

*(Table 1) contd...*

JIA Categories	Definition	ILAR Exclusion Criteria
7. Undifferentiated arthritis	Arthritis that fulfills criteria in no category or in 2 or more of the above categories	

Legend: ILAR = International League of Associations for Rheumatology

RF = Rheumatoid Factor

HLA = Human Leukocyte Allele

ERA = Enthesitis-Related Arthritis

\*HLA-associated disease includes ankylosing spondylitis, ERA, sacroiliitis with inflammatory bowel disease, reactive arthritis, or acute anterior uveitis

Beyond arthritis and uveitis, psoriatic arthritis can also present with psoriasis, as its name suggests. Psoriasis occurs in 34 to 68% of patients with jPsA [12]. Skin findings lag behind arthritis in up to half of children with jPsA arthritis, sometimes by a decade or more [40]. For this reason, the diagnosis relies heavily on dactylitis and/or a family history of psoriasis. Of note, if a child is being treated for psoriasis with methotrexate or a Tumor Necrosis Factor (TNF) blocker, this can mask arthritis. Children with jPsA can also have nail changes, including pits, horizontal ridging, and discoloration [41].

As previously mentioned, systemic JIA has a different clinical picture and pathogenesis from the other subtypes of JIA. Systemic JIA includes a triad of fever, rash, and arthritis [42]. The fever is typically described as prolonged (at least two weeks duration). Characteristically, these children look ill with a fever, and well between fever episodes. The rash with sJIA is commonly described as evanescent, salmon-colored macules that appear with the fevers and disappear when the fevers resolve. In some children, the rash may be pruritic and mimic atopic dermatitis. It is not uncommon for the fever and rash to precede arthritis by years, making the diagnosis challenging. Other manifestations of sJIA include organomegaly, lymphadenopathy, and serositis [42].

## 5. WORK-UP

### 5.1. Laboratory Work-Up

Juvenile idiopathic arthritis, regardless of subtype, is largely a clinical diagnosis. There are no specific diagnostic tests. Mild inflammation may be reflected by an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). However, a substantial part of the work-up is to rule out other childhood mimickers of arthritis. Synovial fluid analysis is useful to rule out many conditions, such as Lyme arthritis and septic arthritis. Late-stage Lyme disease can mimic oligoarticular JIA as these children present typically with one warm, swollen erythematous joint. The knee is most commonly affected [43]. Lyme serologies with ELISA followed by Western blot IgG and IgM if positive, and synovial fluid analysis with Lyme PCR can assist in making this diagnosis [43]. A child with a septic joint may present similarly. Synovial fluid analysis for white blood cell count with differential, gram stain, and culture are all useful. In septic arthritis, higher synovial white blood counts are associated with a higher risk of having an infection even before the gram stain and culture result. The white blood count may be more than 50,000 per mm<sup>3</sup> [44].

Inflammatory bowel disease should be considered in a child with gastrointestinal complaints or slow growth velocity. Beyond the elevation of inflammatory markers and anemia, a fecal calprotectin and hemocult are useful tests [45, 46].

Leukemia is another mimicker of childhood arthritis. A clue is arthritis with nocturnal pain and without morning stiffness [47]. Lab work-up may reveal anemia, thrombocytopenia, leukocytosis or leukopenia, an elevated LDH and uric acid, and blasts on the peripheral smear [47].

In regards to risk stratification of JIA, autoantibodies are useful. A positive ANA has clinical implications as it is a risk factor for the development of uveitis [35,36,39]. As previously mentioned, frequent ophthalmologic screening is needed to detect asymptomatic uveitis [38]. With respect to polyarticular JIA, RF and Cyclic Citrullinated Peptide (CCP) autoantibodies, generally indicate a worse prognosis [48, 49]. These children have a disease course that parallels adult rheumatoid arthritis and require more aggressive therapy [50]. The HLA-B27 gene is present in 60 to 80% of children with ERA, but is also found in about 7% of the overall healthy population [51 - 53]. Although it is not a diagnostic test, it can be used to indicate the risk of ERA.

Systemic JIA is challenging to diagnose because children may look very ill and symptoms overlap with other disease entities. Basic blood tests are nonspecific and may be of little value. Tests generally show elevation in inflammatory markers and anemia. Since sJIA can mimic leukemia, and in early cases of leukemia blasts may not be present on the peripheral smear, a bone marrow biopsy may be needed. Appropriate work-up for infectious etiologies should also be considered. One important complication associated with systemic JIA is Macrophage Activation Syndrome (MAS). Children with MAS can have pancytopenia, an inappropriately low or normal ESR, elevated liver enzymes, a prolonged coagulation profile, and elevated triglycerides [54]. It is important to promptly recognize MAS as it can quickly lead to clinical deterioration and death.

### 5.2. Imaging

If the diagnosis of JIA is unclear, imaging can help confirm the presence of arthritis. Radiographic changes such as joint space narrowing, bone erosions, and bone overgrowth can be seen, although generally late in the course of the disease if not well treated [55]. Synovitis and joint effusions can be seen on ultrasound and magnetic resonance imaging. Since children may have TMJ and cervical spine arthritis that is difficult to detect on examination, there should be a low threshold for imaging if there is pain, retrognathia, or upcoming surgery to evaluate for cervical spine instability. Evidence of enthesitis is most commonly seen at the plantar fascia insertion to the calcaneus or the insertion of the Achilles tendon to the calcaneus [56].

## 6. PROGNOSIS

Prognosis in JIA depends on multiple factors, including subtype, age at disease onset, and the presence of autoantibodies [57 - 61]. Children with persistent oligoarticular JIA achieve clinically inactive disease more frequently than the other subtypes [59, 62]. In the Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh-Out) inception cohort, they identified clinically inactive disease for 6 months within the first year of diagnosis in 54% of patients with oligoarthritis, 38% with RF negative polyarthritis, 39% with ERA, 47% with sJIA, 52% with psoriatic arthritis, 15% with RF positive polyarthritis, and 32% with undifferentiated arthritis [59]. In the Nordic JIA cohort, the remission rate of children overall (excluding those with sJIA) was about 40% at 8 years after disease onset [63]. Remission off medication is estimated to be from 39% at 3 years to 66% at a median of 9 years for oligoarthritis [64, 65]. Conversely, children with RF negative polyarthritis and ERA have remission rates of 48% and 33% at 9 years, respectively [65]. A systematic review found 2 out of 5 studies and 3 out of 8 studies that reported no disease remission in RF positive polyarticular JIA and ERA, respectively [65]. The Nordic JIA database found that anti-CCP and RF detected early in the disease course predicted joint damage eight years after disease [66]. The long-term prognosis for children with jPsA is not completely known. A study that followed patients for at least 15 years showed that children with jPsA have worse functional outcomes than children with oligoarticular or polyarticular JIA, and 33% still required DMARD therapy [68].

The disease course in sJIA typically follows one of the three patterns [69]. About 11% of children have a monocyclic disease course. They are able to achieve complete remission without a relapse in disease. About 34% of children have a polycyclic course. This is characterized by relapses and remissions of varying length. Unfortunately, about 55% of children with sJIA have an unremitting course and never achieve remission [69]. Treating these patients remains a challenge, as described further below.

The ability to predict disease course and long-term outcome would be beneficial in providing information to families and tailoring individual treatment courses. The Canadian prediction model based off of the ReACCh-Out inception cohort and the Nordic prediction model are two such models that are addressing this concern [57 - 61]. They factor predictors such as subtype of arthritis, cumulative active joint count, ESR, CRP, morning stiffness, physician's global assessment of disease activity, the presence of ANA, the presence of HLA-B27, and arthritis in different locations [57]. Most recently, both models have been found to predict severe disease course [57]. Additionally, the Nordic model was able to predict non-remission and severe disease in Canadian children with JIA [58]. Further testing of these models can help us better understand the factors that relate to long-term outcomes.

## 7. MEDICAL MANAGEMENT

The ideal approach to treating a child with JIA is to use an individualized, multidisciplinary team. Untreated arthritis can lead to severe disfigurement and disability, therefore, prompt

treatment is needed. The overall goal is to achieve remission, prevent joint damage and improve quality of life. The medical therapies for JIA include NSAIDs, intraarticular corticosteroids, conventional Disease Modifying Anti-Rheumatic Drugs (DMARDs) and biologic DMARD therapies [70 - 72]. The initial choice of therapy and the rapidity of escalation to more aggressive medications depend on the clinical presentation and classification of JIA.

A basic treatment algorithm can be applied to oligoarthritis, RF-negative and RF-positive polyarthritis, ERA and psoriatic arthritis [71]. While the diagnosis is being established, or if the arthritis is mild, NSAIDs are typically first used. If only one or a few joints are affected, or if NSAIDs are ineffective, intraarticular corticosteroids can be given. Oftentimes, it is easiest to administer steroids to large joints such as the wrists, knees, and ankles. Younger children or those with small joint involvement may require ultrasound-guided injections or injections under sedation.

NSAIDs are generally not sufficient to treat arthritis and do not target the underlying disease. Usually progression to a disease-modifying antirheumatic drug is needed. If NSAIDs are ineffective after an 8-week trial, then escalation to either a conventional or biologic DMARD is indicated. Methotrexate is a commonly chosen DMARD that has been shown to be effective in clinical trials [70, 72, 73]. Other considerations are sulfasalazine and leflunomide [74,75]. Sulfasalazine is effective for peripheral joint arthritis in ERA [71]. The choice may depend on route of administration and side effect profile. If there is an inadequate response to one DMARD, it is reasonable to try another one. After 3 months of a methotrexate trial, most providers will move on to a biologic, usually an anti-TNF agent.

With the advent of anti-TNF therapy in the late 1990s/early 2000s, more providers have a low threshold to progress to this therapy earlier in the disease course for children with moderate or severe disease activity, or for children with poor prognostic factors such as hip arthritis, the presence of RF or anti-CCP antibodies, or radiographic evidence of joint damage [71]. Adalimumab (Humira®) and etanercept (Enbrel®) are two commonly used anti-TNF therapies that have proven effective for JIA [76, 77]. While no specific anti-TNF has been shown to be superior for arthritis, adalimumab is also effective for patients with uveitis or GI involvement [78]. Some children respond better to adalimumab than etanercept, and vice versa. It is not possible to predict which medication a child will respond to, so it is also reasonable to switch between anti-TNF therapies. In severe cases, DMARDs and anti-TNF therapies are used in combination [79 - 81]. Newer therapies, such as tocilizumab (Actemra®) (humanized anti-IL6 antibody) and abatacept (Orencia®) (a fusion protein that blocks T cell activation) are being increasingly used for refractory JIA [82 - 85]. Further randomized clinical trials are needed amongst the different JIA subtypes for more efficacy data.

The main orthopedic complications of JIA are the development of leg-length discrepancies and joint contractures. Surgical treatment is rarely needed since the advent of more effective medical therapy. However, surgery may be needed in severe cases resistant to treatment to fuse joints or for joint

replacements, such as the hip. Guidelines for the perioperative management of antirheumatic medications for children with JIA are not extensively published. However, we can extrapolate from the 2017 American College of Rheumatology and the American Association of Hip and Knee Surgeon guidelines [86]. They recommend continuing methotrexate for JIA and psoriatic arthritis patients who are undergoing an elective total hip or total knee arthroplasty [86]. For those on biologics, they recommend holding the biologic and scheduling the surgery near the end of the dosing cycle, and then restarting once there is wound healing about 2 weeks after surgery [86].

Systemic JIA can be difficult to treat since there are extraarticular manifestations that are not always responsive to therapies. Even with prompt treatment, the disease can progress. Children may look acutely ill and require hospitalization. If the child does not have severe disease, NSAIDs alone may be a reasonable initial therapy. If features of systemic inflammation are present or features of MAS that were described previously are present, steroids can be used. The route, IV pulses followed by oral prednisone or oral prednisone alone, depends on the severity of disease at onset. Beyond steroids, biological agents can be used to treat sJIA. These include drugs that inhibit interleukin-1, such as anakinra and canakinumab, and IL-6 inhibitors, such as tocilizumab [21, 87 - 89].

The treatment of uveitis includes topical corticosteroids and DMARDs. Choice of DMARD therapy is typically provider dependent. Consensus-based recommendations for the treatment of uveitis in JIA recommend methotrexate as the first choice for systemic immunosuppression, but had class D evidence [90]. In resistant cases, anti-TNF treatments are typically used next. Refractory cases may benefit from tocilizumab, rituximab, abatacept, or JAK inhibitors [90, 91].

JIA requires a multidisciplinary team. Beyond medical therapy, aggressive physical and occupational therapy are integral to the management of JIA. Continued assessments can help prevent contractures and leg-length discrepancies. These therapies are most effective when they are continued daily at home. The major goal is to maintain strength and range of motion. In certain cases of severe arthritis, splinting of joints, especially the wrists, overnight may be helpful to prevent flexion contractures. Fortunately, with the use of biologics, we rarely see children who are wheelchair dependent. A nurse specialist and social worker are also integral members of the team to provide support, education, and facilitate long-term medication adherence.

## CONCLUSION

Juvenile idiopathic arthritis is the most common form of chronic arthritis in children. It encompasses many subtypes of arthritis that can range from mild to severe disease. Multiple factors contribute to the overall prognosis, including subtype and presence of autoantibodies. Children with oligoarticular JIA have higher rates of remission, and those with RF positive polyarticular JIA are more likely to have severe arthritis years after disease onset. Prompt recognition and treatment of arthritis are essential in preventing associated morbidity and mortality. With the use of conventional and biologic DMARDs

therapies, the quality of life has substantially improved for these children.

## CONFLICT OF INTEREST

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