

Juvenile Idiopathic Arthritis

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Juvenile idiopathic arthritis (JIA) is an umbrella term referring to a group of disorders characterized by chronic arthritis. JIA is the most common chronic rheumatic illness in children and is a significant cause of short- and long-term disability. It is a clinical diagnosis made in a child less than 16 years of age with arthritis (defined as swelling or limitation of motion of the joint accompanied by heat, pain, or tenderness) for at least 6 weeks' duration with other identifiable causes of arthritis excluded. The incidence of JIA ranges from 1 to 22 per 100,000 with a prevalence of 8 to 150 per 100,000 [1–3].

Three separate systems are used currently to classify patients under 16 years of age with chronic arthritis: the American College of Rheumatology (ACR) [4], the European League Against Rheumatism (EULAR) [5], and the International League of Associations for Rheumatology (ILAR) systems [6] classification systems. Duffy et al [7] have written an excellent review of the history and relative advantages, disadvantages, and controversies surrounding the classification of chronic arthritis in children. None of the classification systems is perfect: some patients fulfill criteria for more than one subtype, whereas others are difficult to classify into any specific subgroup. (In the ILAR system, these patients are classified as “other.”) Additionally, there is difficulty in characterizing juvenile spondyloarthropathies including juvenile ankylosing spondylitis and

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Table 1
Summary of classification of chronic arthritis in children

ACR (1977) JRA	EULAR (1978) JCA	ILAR (1997) JIA
Systemic	Systemic	Systemic
Polyarticular	Polyarticular	Polyarticular RF-negative
	JRA	Polyarticular RF-positive
Pauciarticular	Pauciarticular	Oligoarticular
		persistent
		extended
	Juvenile psoriatic	Psoriatic
		Enthesitis-related
		Other

juvenile psoriatic arthritis (JPsA). All three schemata are shown in [Tables 1 and 2](#). This article uses the ILAR system when applicable.

Etiology and pathophysiology

Although the causes of JIA remain unclear, JIA seems to be a complex genetic trait involving the effects of multiple genes related to immunity and inflammation. Some hypothesize that arthritis may be triggered in a genetically predisposed individual by psychologic stress, abnormal hormone levels, trauma to a joint, or bacterial or viral infection. Several studies have implicated rubella and parvovirus B19 as possible causes of JIA because rubella virus persists in lymphocytes and establishes a focus of persistent infection in the synovium resulting in chronic inflammation [8]. These data have been difficult to replicate in other laboratories, however. Highly conserved bacterial heat shock proteins may be potential disease triggers [9]. Results of studies investigating whether breastfeeding decreases the risk of developing JIA are inconclusive.

Table 2
Summary of the differences among the schemata

	ACR	EULAR	ILAR
Onset types	3	6	7
Age of onset	< 16 years	< 16 years	< 16 years
Duration of arthritis	> 6 weeks	> 3 months	> 6 weeks
Includes JAS, JpsA	No	Yes	Yes
Includes IBD	No	Yes	Yes
Includes course	No	No	Yes

Abbreviations: IBD, inflammatory bowel disease; JAS, juvenile ankylsosing spondylitis; JpsA, juvenile psoriatic arthritis.

Certain HLA class I and class II alleles are associated with an increased risk of JIA. The class I antigen HLA-A2 is associated with early-onset oligoarticular arthritis in girls [10]. The class II antigens HLA-DRB1*08 and *11, DQA1*04 and *05, and DQB1*04 are associated with persistent oligoarticular and extended oligoarticular JIA. HLA-DRB1*08 confers an increased risk of rheumatoid factor (RF)-negative polyarthritis, and HLA-DRB1*11 confers an increased risk of systemic-onset JIA (SOJIA). HLAB1*04, which is associated with adult rheumatoid arthritis, is associated with an increased risk of RF-positive polyarticular arthritis. The class I antigen HLA-B27 and class II antigens HLA-DRB1*01 and DQA1*0101 are associated with enthesitis-related arthritis (ERA) and JPsA [11]. Other genes conferring risk include cytokine production-regulating genes [12–14]. Data using genome-wide scanning techniques in affected sib-pair families provide further evidence that multiple genes influence susceptibility to JIA [15].

There is evidence of immunodysregulation in JIA. Complement activation and consumption promote inflammation, and increasing serum levels of circulating immune complexes are found with active disease. Anti-nuclear antibodies (ANA) are found in approximately 40% of patient's with JIA, especially in young girls with pauciarticular disease [16]. Approximately 5% to 10% of patients with JIA are RF positive [8].

The T-lymphocyte-mediated immune response is involved in chronic inflammation, and T cells are the predominant mononuclear cells in synovial fluid [17]. Patients with JIA have elevated serum levels of interleukin (IL)-1, -2, -6, and IL-2 receptor (R) and elevated synovial fluid levels of IL-1 β , IL-6, and IL-2R, suggesting a Th1 profile [18]. Elevated serum levels of IL-6, IL2R, and soluble tumor necrosis factor (TNF) receptor correlate with inflammatory parameters, such as C-reactive protein, in JIA patients with active disease. Serum levels of IL-6 are increased in SOJIA and rise before each fever spike, correlating with active disease and elevation of acute-phase reactants. [19].

Classification of JIA

The ILAR classification of JIA includes seven subtypes: SOJIA, oligoarticular, polyarticular RF-positive and RF-negative, ERA, JpsA, and "other." This classification system was developed to identify clinically homogenous JIA subtypes to facilitate communication regarding epidemiology, therapeutics, and outcomes among physicians globally [6].

In order of frequency, the disease subtypes are oligoarticular JIA (50%–60%), polyarticular JIA (30%–35%), SOJIA (10%–20%), JPsA (2%–15%), and ERA (1%–7%). The subtypes are recognized based on the clinical features during the first 6 months of disease. Important clinical features that assist in classifying patients include the presence of enthesitis (inflammation at the sites of attachment of ligament, tendon, or fascia to bone), dactylitis, inflammatory lumbosacral pain, nail pitting, sacroiliitis, psoriasis, fever, rash, and serositis.

Oligoarticular JIA

Oligoarticular JIA is diagnosed in patients with arthritis in fewer than five joints during the first 6 months of disease. These patients tend to have involvement of the large joints of the lower extremities such as knees and ankles. Monoarticular onset affecting only the knee (Fig. 1) is common, seen in half of all patients [20,21]. These patients tend to function remarkably well and often do not complain of pain. Oligoarticular patients, especially ANA-positive girls, are at high risk for developing uveitis, usually their most serious clinical problem. Arthritis that remains confined to four or fewer joints is designated persistent oligoarticular JIA.



Fig. 1. Swollen left knee in a patient with oligoarticular JIA. Note the quadriceps atrophy.

A child who develops active arthritis of five or more joints after the first 6 months of disease is considered to have extended oligoarticular JIA. Up to 50% of oligoarticular patients may develop extended disease, and 30% will do so in the first 2 years after diagnosis. Risk factors for extended disease include ankle or wrist arthritis, hand disease, symmetric arthritis, arthritis of two to four joints, and an elevated erythrocyte sedimentation rate (ESR) and ANA titer [22]. Extended disease confers a worse prognosis. One study retrospectively evaluated JIA patients into adulthood with a median of 16.5 years of follow-up and found an overall remission rate of 12% in patients with extended oligoarticular JIA, compared with 75% in patients with persistent oligoarticular JIA [23].

Polyarticular JIA

Patients with arthritis in five or more joints within the first 6 months of disease are diagnosed as having polyarticular JIA. This subtype includes children with RF-negative disease (20% to 30% of JIA patients) and RF-positive disease (5% to 10% of JIA patients) [8]. Both types affect girls more frequently than boys.

RF-seronegative patients often develop polyarthritis in early childhood, in contrast to RF-seropositive patients, who develop arthritis during late childhood and adolescence. The seronegative patients have a variable prognosis. This subtype has no strong HLA association and may represent a group of disorders that can be further subtyped.

The seropositive patients are primarily adolescent girls with symmetric small joint involvement, and severe erosive disease. They may develop subcutaneous nodules (nontender, firm lesions over pressure points and tendon sheaths). The HLA associations in these patients are the same as in adult seropositive rheumatoid arthritis patients and probably represent the early expression of adult rheumatoid arthritis. The arthritis usually involves the large and small joints of the hands and feet, although the axial skeleton, including cervical spine and temporomandibular joints, may be affected. Boutonnière deformities (proximal interphalangeal joint flexion and distal interphalangeal joint hyperextension) and swan-neck deformities (proximal interphalangeal joint hyperextension and distal interphalangeal joint flexion) are common. Chronic uveitis develops less frequently than in oligoarticular disease.

Systemic onset juvenile idiopathic arthritis

SOJIA is the only subtype of JIA without a strong age, gender, or HLA association. At onset, extra-articular manifestations including rash, fever, lymphadenopathy, hepatosplenomegaly, and serositis predominate. Ten percent of patients may present with extra-articular manifestations only and may not develop arthritis for many months. In the right clinical setting, with characteristic fever and classic rash, the diagnosis of probable systemic onset disease may be made, with confirmation of the diagnosis when persistent arthritis develops [24].

Children with SOJIA typically have 2 weeks of high-spiking fever, classically with two peaks daily (double quotidian). During episodes of fever, chills are common, and the child appears ill, but when the fever breaks, the child appears well [25].

The classic rash is evanescent (usually coming and going with the fever spikes) and consists of discrete, circumscribed, salmon-pink macules 2 to 10 mm in size that may be surrounded by a ring of pallor or may develop central clearing. Lesions are more common on the trunk and proximal extremities, including the axilla and inguinal areas. Stress or a warm bath may exacerbate the rash. A linear streak on the skin, known as the Koebner phenomenon, may be elicited by scratching the skin. The rash is rarely pruritic and is never purpuric [25].

The arthritis associated with SOJIA is usually polyarticular and usually manifests within 6 months of systemic features. Both large and small joints are affected [24]. Asymmetric, oligoarticular arthritis is less common.

Laboratory findings in a patient with active SO JIA include anemia (which may be severe), leukocytosis, thrombocytosis, elevated liver enzymes, and elevated acute-phase reactants. The ANA titer is rarely positive [24].

SOJIA patients have a variable course, with 60% to 85% of patients going into remission or quiescence and up to 37% developing a chronic, destructive polyarthritis. It is usual for systemic systems to resolve over months to years; the mean period of disease activity is approximately 6 years [26]. Predictors of a poor prognosis include an age less than 6 years at diagnosis, disease duration longer than 5 years, IgA levels, and persistent systemic symptoms (defined by prolonged fever or sustained treatment with corticosteroids) or the presence of thrombocytosis (platelet count $\geq 600 \times 10^9/L$) 6 months into the disease course [27–29]. Radiographic changes consistent with disease progression are associated with a poor prognosis but not necessarily with poor functional status [26]. Patients with severe SOJIA who are inadequately treated have an increased incidence of amyloidosis (1.4%–9%) [23,26]. The mortality rate of patients with JIA is less than 0.3% in North America, where most deaths in SOJIA patients are secondary to macrophage activation syndrome, infection resulting from immunosuppression, or cardiac complications [30].

Macrophage activation syndrome is a rare but life-threatening complication of SOJIA characterized by increased activation and demonstration of histiophagocytosis in bone marrow. This complication is sometimes referred to as secondary or acquired hemophagocytic syndrome or hemophagocytic lymphohistiocytosis. Triggers include a preceding viral illness and the addition of or a change in medications, especially nonsteroidal anti-inflammatory drugs (NSAIDs), intramuscular gold injections, sulfasalazine, and more recently, etanercept [31]. Patients are acutely ill with hepatosplenomegaly, lymphadenopathy, purpura, and mucosal bleeding and may develop multiorgan failure. Pancytopenia, prolongation of the prothrombin time and partial thromboplastin time, elevated fibrin split products, hyperferritinemia, and hypertriglyceridemia are common. The sedimentation rate is often low (a clue to the diagnosis of macrophage activation syndrome versus exacerbation of SOJIA) because of hypofi-

brinogenemia secondary to consumptive coagulopathy and hepatic dysfunction [32–34]. Impaired cytotoxic activity of nuclear killer and CD8-positive T lymphocytes, low perforin levels, and endothelial activation may be involved in the pathogenesis [35]. Treatment includes pulse methylprednisolone (30 mg/kg with a maximum of 1 g), to which some patients do not respond, and cyclosporine A (2–5 mg/kg/day) [33]. Refractory patients may respond to dexamethasone and etoposide [36,37].

Enthesitis-related arthritis

Patients with juvenile ankylosing spondylitis and arthritis associated with inflammatory bowel disease are included in the ERA subtype (Table 2). ERA has a prevalence of 12 to 33 per 100,000 [38] and is most common in boys older than 8 years of age. It has a strong genetic predisposition as evidenced by a positive family history and the high frequency of the presence of HLA-B27 in affected patients. The hallmarks of the disease are pain, stiffness, and eventual loss of mobility of the back. ERA should be suspected in any child with chronic arthritis of the axial and peripheral skeleton, enthesitis (inflammation at points where tendons insert to bone), and RF and ANA seronegativity. Peripheral arthritis, usually affecting few joints of the lower extremity, precedes axial involvement, and arthritis of the sacroiliac joints may take years to develop. Radiographic changes of the sacroiliac joint include joint space narrowing, erosions, sclerosis, osteoporosis of the pelvis, and fusion (a late finding) [39].

The arthropathy of inflammatory bowel disease may present a diagnostic dilemma, because the arthritis may be the first manifestation of the disease. Clues to the diagnosis include gastrointestinal symptoms, weight loss or growth failure, and mucocutaneous abnormalities such as erythema nodosum, aphthous stomatitis, and pyoderma gangrenosum. There are two distinct forms of inflammatory disease-related arthritis. The first, an acute polyarticular form, generally mirrors the activity of the bowel disease; as a rule, the arthritis improves when the gastrointestinal disease is quiescent. In the second form, which is much more typical of ERA, the course of arthritis is independent of the course of the bowel disease.

Extra-articular manifestations include anterior uveitis, aortic insufficiency, aortitis, muscle weakness, and low-grade fever. Acute uveitis (distinguished from the chronic form common in oligo- and polyarticular disease) may develop in up to 27% of patients, is often unilateral and recurrent, and presents as a red, painful, photophobic eye, often without sequelae [40]. Laboratory data may show mild anemia, a normal to moderately elevated white blood cell count, and a thrombocytosis and elevated sedimentation rate [38,39].

Psoriatic arthritis

JPsA is chronic inflammatory arthritis with a peak age of onset in mid-childhood. JPsA is a difficult diagnosis to make, because the arthritis may



Fig. 2. Dactylitis involving the right thumb and fourth right finger.

develop many years before the rash. JPsA is an asymmetric arthritis that often affects the knees and ankles and the small joints of the hands and feet. Proximal interphalangeal joints, distal interphalangeal joints, and the tendon sheath are often inflamed, resulting in the diffuse swelling of the digit known as “sausage digit” (Fig. 2) [41].

Extra-articular manifestations include rash, nail changes (including pitting, onycholysis, oil-drop sign) and uveitis. One third of patients with JPsA develop the rash by 15 years of age [42]. All children with JPsA should have a slit-lamp examination every 6 months, because asymptomatic anterior uveitis may be found in up to 17% of patients [43].

Laboratory data show elevated acute-phase reactants, anemia of chronic disease, and thrombocytosis. ANA may be positive.

Extra-articular manifestations

Uveitis

Chronic, anterior, nongranulomatous uveitis (iridocyclitis) develops in up to 21% of patients with oligoarticular JIA and 10% of patients with polyarticular JIA [44]. Uveitis is most common in young girls with oligoarticular disease and a positive ANA titer [16]. The uveitis is usually asymptomatic, although patients may present with conjunctivitis, unequal pupils, eye pain, and headache. The uveitis may be present at diagnosis, develop during the course of JIA, or be an initial manifestation of the JIA. Patients with JIA should be screened routinely (Table 3) to prevent delay in diagnosis of uveitis. Complications of uveitis include posterior synechiae, cataracts, band keratopathy, glaucoma, and visual impairment (in up to 30%) (Fig. 3) [45]. A study of 703 JIA patients, followed for a period of 1 to 5 years, found that of the 13% of oligoarticular patients with

Table 3
Frequency of ophthalmologic examinations in patients with JIA

Sub-type at onset	Age at onset	
	<7 years	≥ 7 years
Oligoarticular		
+ANA	H	M
-ANA	M	M
Polyarticular		
+ANA	H	M
-ANA	M	M
Systemic	L	L

Abbreviations: H, high risk (indicates ophthalmologic exam every 3–4 months); L, low risk (indicates ophthalmologic exam every 12 months); M, medium risk (indicates ophthalmologic exam every 6 months).

Data from Anonymous. Guidelines for ophthalmologic examinations in children with juvenile rheumatoid arthritis. *Pediatrics* 1993;92(2):295–6; with permission.

uveitis, 4% had loss of vision in 1 eye, and 17% had some loss of vision in both eyes. Of the 5% of polyarticular patients with uveitis, 17% had vision loss. None of the SOJIA patients was diagnosed as having uveitis [46].

Treatment of uveitis includes topical steroids and mydriatics to decrease inflammation and prevent posterior synechiae. Glucocorticoid ophthalmic drops may need to be given as often as hourly while the child is awake. Oral corticosteroids at a dose of 2 to 4 mg/kg/day with a maximum of 1 gram may be needed in patients who do not respond to topical therapy, and in some instances pulse intravenous methylprednisolone (30 mg/kg) has been used with benefit. Methotrexate, cyclosporine A, and a sub-tenon injection of steroids may benefit patients unresponsive to glucocorticoids. Preliminary case reports have shown infliximab and etanercept to be beneficial in treating refractory uveitis in children and adults [47,48].



Fig. 3. Posterior synechiae and cataract formation in a JIA patient with iritis.

Nutrition

Nutritional impairment is common in children with rheumatic disease. The daily caloric requirement for a healthy child is approximately 80 to 120 kcal/kg/day for the first year of life with a decrease of approximately 10 kcal/kg for each succeeding 3-year period [49]. In a random sample of 33 JIA patients, all had a total caloric intake of less than 50% of their estimated needs [50].

Children with JIA have a decrease in lean muscle mass and an increase in fat mass [51,52]. Increased resting energy expenditure was also found, especially in SOJIA patients, who had significantly elevated resting energy expenditure when compared with healthy controls [53]. These effects may be attributed to elevated levels of IL-1 and TNF- α [54].

It is important that the pediatrician use dietary guidelines on for healthy children based on sex and age instead of actual weight [53] and that a dietician or nutritionist be part of the treatment team, especially when significant malnutrition exists.

Growth disturbance

Generalized growth retardation and delayed puberty are common in patients with JIA. The causes are multifactorial (Box 1) [55–57].

Children with SOJIA and polyarticular disease of long duration are at greatest risk for diminished linear growth. It is important that diminished linear growth

Box 1. Causes of generalized growth delay

Metabolic

Increased catabolic demands secondary to active disease [51,52]

Endocrinologic

Decreased levels of insulin-like growth factor 1 (IGF-1) in children secondary to elevated levels of IL-6 [53] and corticosteroids [52]

Suppressive effect of corticosteroids on osteoblasts [52]

Malnutrition

Cachexia secondary to increased levels of TNF- α and IL-1
 Mechanical (temporomandibular joint dysfunction, retrognathia)
 Anorexia secondary to nausea/vomiting and oral ulcers (methotrexate) and gastritis (corticosteroids and NSAIDs)

be recognized, because it is an undesirable and permanent disease outcome [52,53,55]. During periods of remission, patients may catch up if epiphyses have not closed prematurely. Alternate-day corticosteroid treatment or a daily dose of less than 0.5 mg/m^2 may lessen the adverse effects of corticosteroids on growth [58].

Growth hormone has been shown to be effective for severe growth retardation in select patients [59]. One study of prepubertal systemic and nonsystemic JIA patients treated with growth hormone found that patients had a net height gain of 1 SD over a period of 4 years, greater than the 0.7 SD height loss of the control group. This net gain of 1.7 SD may result in a greater final height [55].

Localized growth disturbance can result from destruction of a growth center, as in micrognathia (Fig. 4), accelerated bone maturation (Fig. 5), or premature



Fig. 4. Micrognathia in a patient with JIA, an example of localized growth retardation.



Fig. 5. Accelerated maturation of the right carpal bones in a patient with oligoarticular JIA secondary to active right wrist arthritis.

closure of the physis, as in brachydactyly of the digits. Overgrowth of a lower limb may develop in a patient with chronic inflammation of the knee secondary to hyperemia of inflammation [21]. Intra-articular steroid injections in the knee are helpful, because they control local inflammation and thereby reduce the incidence of leg-length discrepancy [60].

Osteopenia/osteoporosis

As a consequence of the disease and of corticosteroid treatment, children with JIA are at increased risk for osteopenia and osteoporosis, putting them at increased risk of fracture. Osteoporosis is defined as the parallel loss of bone mineral and matrix, resulting in a bone mineral density (BMD) more than 2.5 SD below the mean for age and sex. Osteopenia is a low bone mass for age with a BMD between 1 and 2.5 SD below the mean for age and sex. In interpreting results of dual energy X-ray photon absorptiometry scans, it is important to use pediatric, not adult, controls as normative data.

Low BMD in children with JIA has been associated with severe disease, younger age, lower body mass index, lower lean body mass, decreased intake of calcium and vitamin D, and decreased physical activity. Reduced levels of physical activity have been shown to correlate with osteopenia [61], and up to 5.6% of postpubertal female JIA patients have been found to be osteopenic based on lumbar spine BMD [62]. It is uncertain whether diminished BMD is secondary to increased bone resorption or decreased formation. Il-1, which is elevated

during periods of active disease, stimulates osteoclast activity [63], and one study concluded that the insufficient skeletal growth results from depressed formation rather than increased bone resorption [52]. Roth et al [64] concluded that an important musculoskeletal abnormality in JIA is diminished muscle mass and force, resulting in abnormal bone geometry that may predispose a patient to fractures.

In most children with JIA, BMD and bone mineral content are below the norms for pre- and postpubertal children [52,62,64]. Total BMD and regional measurements, especially in postpubertal females with JIA, were significantly different from controls [52,65]. Patients with active JIA are at increased risk during their pubertal growth spurt because they may fail to achieve the normal increase in bone mass [66,67].

The best way to prevent these complications is to control disease activity, encourage appropriate caloric and calcium intake, and promote physical activity. Supplementation for any patient receiving oral corticosteroid treatment should start at 1200 to 1500 mg of calcium and 400 units of vitamin D [66,67]. The use of bisphosphonates should be considered in patients who develop osteoporosis, although there are concerns regarding the safety of these agents in children.

Special considerations

Psychosocial considerations/pain

Huygen et al [68] found children with JIA do not differ from healthy controls in regard to self-esteem, motivation for achievement and fear of failure, and physical appearance. Almost none of the JIA patients showed signs of depression. This finding is contrary to a study by Schanberg et al [69], which found depression in approximately 5% of JIA patients. Schanberg et al also found psychosocial anxiety, correlated with increased frequency and intensity of pain and fatigue, in approximately 10% of patients.

Pain is a major factor affecting the ability of JIA patients to perform activities of daily living, attend school, and participate in recreational activities. Children with polyarticular JIA report mild to moderate pain on most days, and pain and stiffness result in increased school absenteeism and less participation in social activities [68]. Up to 27% of polyarticular patients had limitation of school function, primarily in physical education [46]. A more recent study by Sällfors et al [70] confirmed that children with JIA missed an average of 3.7 days of school over a 2-month period, and more than half of the patients reported never or only sometimes attending physical education class. Seventy-four percent of patients had either 1 or no days free of pain during the 2-month study period, and they scored their pain at a level that interfered with their ability to concentrate and limited their activities. Reduced pain and attending physical education classes were found to be predictors of well being in patients with JIA [70].

Compared with healthy controls, mild to moderately active prepubertal JIA patients had significantly less physical activity and significantly more sleep [62,71]. These findings are in contrast to a study by Malleson et al [72], who found no association between physical fitness, functional ability, and joint pain. One study found mild to moderate pain in JIA patients, but their findings did not show that disease status, social support, or hopelessness and depressed mood account for the differences in patients' pain [73]. Because the degree of pain does not necessarily correspond with the degree of inflammation, treatment of the two should be separated. Cognitive behavioral pain management has been shown to be effective treatment for pain [74,75].

Disability

The Childhood Health Assessment Questionnaire (CHAQ) has been shown to be a reliable, valid, and sensitive tool for measuring functional status in JIA [76]. Median cut-off values corresponding to no, mild to moderate, and moderate disability and changes in CHAQ scores corresponding to a minimal clinically important improvement and deterioration have been quantified [77]. Based on the CHAQ score, polyarticular JIA patients have been shown to have mild to moderate functional limitations, and increased functional disability correlates with increased daily pain and stiffness [69]. Another study demonstrated that JIA patients had the most difficulty with gripping, activity, and getting up [70].

The Steinbrocker [78] classification has been used to assess functional outcome in JIA. Girls have a 2.5 times greater risk (95% confidence interval [CI], 1.1–5.4) and polyarticular JIA patients have a 5.5 times greater risk (95% CI, 1.6–9.8) of being classified as Steinbrocker class II–IV [79]. Based on this classification, no oligoarticular JIA patient had significant functional limitation outside of school. Twelve percent of the polyarticular patients and 30% of the SOJIA patients were in class III or class IV [46].

Outcome of adults with JIA

Studies have shown that 9% to 83% of JIA patients followed for up to 37 years have disease that persists into adulthood, and 14% to 48% of patients (31% overall) have a poor functional outcome as evidenced by a Steinbrocker class III or class IV [30,80–84]. Disease duration, polyarticular disease, and systemic corticosteroid treatment are important factors in determining disease outcome [80]. RF-positive polyarticular patients fared worst. They were predominantly females with onset in adolescence. They required significant assistance with hygiene, dressing, and domestic duties [81]. Foster et al [85] found that of 82 adult patients who had been diagnosed with JIA, 39% continued to have active disease. Compared with controls, JIA patients had a lower Medical Outcomes Study 36-item Short Form score indicating worse general health and quality of life.

In a study of JIA patients with a disease duration greater than 10 years, 28% of patients had depression (7% mild, 21% moderate-severe). Depression correlates with disability and persistently active disease [81]. Concerning education, 30% of patients did not graduate from high school, and 21% went on for higher education. Thirty percent of patients were unemployed, and they believed their unemployment was a result of their illness [81]. Foster [85] also reported that academic achievement in adults with a history of JIA was comparable to that of local controls, but the unemployment rate was threefold greater.

Up to 72% of patients, primarily extended oligoarticular, polyarticular, or SOJIA patients, had JIA-related surgery [80,81]. RF-positive patients had the greatest number of joint replacement surgeries and revisions [81].

The mortality rate, based on reports from the United States and Canada, is reported at 0.29/100 patients. Most deaths were patients with SOJIA [30].

Differential diagnosis

The diagnosis of JIA is a clinical one made after other identifiable causes of arthritis have been excluded by a careful history and examination in conjunction with appropriate radiographs and laboratory tests. Important clinical signs such as systemic illness, preceding infection, duration of fever, rash, and character of the arthritis help differentiate JIA from other causes of arthritis. The differential diagnosis of acute arthritis includes entities in the broad categories of reactive arthritis, inflammatory disease, infection, systemic disease, malignancy, and trauma (Box 2).

It may be difficult to differentiate SOJIA and polyarticular JIA from other causes of systemic disease with polyarthritis, such as acute rheumatic fever and other vasculitic and systemic rheumatic diseases. Acute rheumatic fever classically causes migratory arthritis, unlike the additive arthritis in JIA. The fever of SOJIA is more spiking in character and longer in duration. JIA patients never have overlying erythema, which is quite common in acute rheumatic fever. Endocardial disease strongly suggests acute rheumatic fever, but pericarditis can occur in both.

Sarcoidosis is a chronic noncaseating granulomatous disease, uncommon in children, manifesting as fever, arthritis, uveitis, rash, and pulmonary disease. The arthritis is characterized by substantial synovial hypertrophy and associated synovial cysts, especially in the ankles and wrists. The uveitis, either anterior or posterior, is granulomatous and nodular with formation of coarse keratic precipitates. The fixed macular eruption is unlike the evanescent rash of SOJIA [86].

Other multisystem rheumatic diseases can be distinguished from JIA by diagnostic clinical features and supporting laboratory data. Systemic lupus erythematosus (SLE) commonly presents in adolescence with fever and a painful, nonerosive polyarthritis affecting large and small joints [87]. The ANA titer can be positive in SLE and in polyarticular and oligoarticular JIA, and both SLE and SOJIA can manifest as polyserositis with fever, but hepatosplenomegaly and

Box 2. Differential diagnosis of arthritis*Reactive*

Postenteric
Reiter's syndrome
Rheumatic fever
Poststreptococcal

Inflammatory

Juvenile idiopathic arthritis
Inflammatory bowel disease
Sarcoidosis

Infection

Septic
Osteomyelitis
Lyme disease
Viral
Bacterial sacroiliitis
Discitis

Systemic

Kawasaki disease
Behcet's disease
Henoch-Schönlein purpura
Serum sickness
Systemic lupus erythematosus
Dermatomyositis
Progressive systemic sclerosis

Malignancy

Leukemia
Neuroblastoma
Malignant bone tumors:
Osteosarcoma
Ewing's sarcoma
Rhabdosarcoma

Benign bone tumors:

Osteoid osteoma

Osteoblastoma

Trauma

Accidental

Nonaccidental

lymphadenopathy; malar erythema, nephritis, autoimmune pancytopenia, hypocomplementemia, and the presence of anti-double-stranded DNA and other autoantibodies are unique to SLE. Patients with systemic sclerosis and dermatomyositis may have a mild, symmetric polyarthritis early on, but the proper diagnosis becomes apparent as symptoms progress. Patients with systemic sclerosis may have limited range of motion secondary to sclerotic changes of the skin that should be distinguished from inflammatory arthritis.

Numerous causes of oligoarthritis need to be excluded before the diagnosis of oligoarticular JIA is made. In most cases, the distinction can be made based on the history of an antecedent infection and arthritis less than 6 weeks' duration. Septic arthritis must be excluded in any patient with acute onset of fever, severe joint pain, and an erythematous, hot, swollen joint with elevated acute-phase reactants. Synovial fluid should be examined and cultured, and treatment with antibiotics should be started immediately, because septic arthritis can rapidly lead to joint destruction. Bacterial sacroiliitis and discitis are more indolent in nature. Patients with gonococcal arthritis may present with systemic manifestations (fever, chills) and rash in addition to arthritis and tenosynovitis, especially of the wrist and ankles. It is important that the physician obtain a thorough sexual history, preferably without the parents present.

Reactive arthritis is an acute, sterile autoinflammatory arthritis that may be caused by T-cell- or B-cell-mediated cross-reactivity to similar antigens (molecular mimicry). Postenteric reactive arthritis (ReA) should be considered in any child with gastroenteritis and arthritis of the large joints of the lower extremity. The term Reiter's syndrome refers to the clinical syndrome of ReA that presents with the extra-articular manifestations of conjunctivitis and urethritis completing the classic triad. (It has been proposed that Reiter's name be removed from the medical lexicon because he was declared a Nazi war criminal [88].) HLA-B27 is strongly associated with ReA and with this syndrome [42]. Patients with sustained fever, arthritis, and a preceding streptococcal infection who do not fulfill Jones' criteria of acute rheumatic fever may be diagnosed as having poststreptococcal ReA.

Lyme disease, caused by *Borrelia burgdorferi*, is a major health problem in endemic areas [89]. Arthritis is a late manifestation of the disease but may be the presenting complaint, because the tick bite and initial rash may go unnoticed. The

arthritis is episodic, with each episode being relatively short lived. The diagnosis should be confirmed with Lyme serology (ELISA and immunoblot assays). There are numerous viruses that cause arthritis including parvovirus B19, hepatitis B virus, rubella, varicella, herpesvirus, smallpox, and HIV. Identifiable infections should always be considered.

Arthritis of Kawasaki disease usually presents during the subacute phase of the illness and is commonly found in the knees and ankles, although the small joints of the hands may be involved. The arthritis of Kawasaki disease may be accompanied by desquamation and subcutaneous edema of the hands and feet, distinguishing it from SOJIA. Occasionally these distinctions are blurred. Behçet's disease (although rare) should be suspected in patients with recurrent oral and genital mucosal ulceration. When the arthritis of Henoch-Schönlein purpura precedes purpura, nephritis, or abdominal involvement, the diagnosis may be difficult. In Henoch-Schönlein purpura, arthritis rarely manifests with synovial effusions, and the inflammation is more likely to be periarticular.

Numerous conditions characterized by arthralgia or myalgia may be misdiagnosed as JIA. The presence of bone pain and bone tenderness should heighten suspicion for an underlying malignancy. A discrepancy between the blood counts and sedimentation rate (eg, relative thrombocytopenia) may be a clue to the diagnosis [90]. Night pain and low-grade fever should also lead to the suspicion of malignancy. Young children with generalized hypermobility complain predominantly of joint pain that occurs in the evening, often waking them from sleep, without associated swelling or morning stiffness, contrary to JIA. Overuse syndromes such as patellofemoral syndrome and Osgood-Schlatter's disease, are common in adolescents complaining of knee pain exacerbated by exercise. Fibromyalgia and reflex sympathetic dystrophy are chronic pain syndromes with onset in late childhood and adolescence. Musculoskeletal pain, without arthritis, is the predominant feature. These disorders are not inflammatory, and the diagnosis is suspect if the patient has evidence of synovitis.

Treatment

Objectives of the treatment of JIA include controlling pain and inflammation, preserving function, and promoting normal growth, overall development, and well being. During the past few years, remarkable advances in the treatment of JIA have been made with the advent of new disease-modifying antirheumatic agents (DMARDS), and biologic therapy.

Therapeutic modalities

Physical and occupational therapy are important adjuncts to medication because they help maintain and improve range of motion, muscle strength, and skills for activities of daily living. Splints may be used to prevent contractures

or work to improve range of motion. Arthroplasty may be needed for patients with severe deformities.

Nonsteroidal anti-inflammatory medications

Initial treatment for most patients with JIA includes intra-articular long-acting corticosteroid injections and NSAIDs (Fig. 6). NSAIDs control pain and inflammation and are usually given for 4 to 8 weeks before starting treatment with a second-line agent. Naproxen (15–20 mg/kg divided into twice-daily doses; maximum dose of 500 mg BID), tolmetin (20–30 mg/kg divided into thrice-daily doses; maximum dose of 600 mg TID), diclofenac (2–3 mg/kg divided into thrice-daily doses; maximum dose; maximum dose of 50 mg TID), and ibuprofen (40 mg/kg/divided into thrice-daily doses; maximum dose of 800 mg TID) are commonly used and are usually well tolerated with little gastrointestinal discomfort. The choice of NSAID may be based on the taste of the medication and the convenience of the dosing regimen. Naproxen is prescribed most frequently but should be used with caution in fair-skinned children, because they may develop pseudoporphyria cutanea tarda, a scarring photosensitive rash [91]. Indomethacin (1–2 mg/kg/day; maximum dose of 200 mg/day) is a potent anti-inflammatory medication commonly used to treat ERA and SOJIA. When indomethacin is prescribed, patients should be warned about the possibility of headaches, difficulty in concentrating, and gastrointestinal upset [92].

The cyclo-oxygenase (COX)-2 inhibitors (ie, celecoxib) selectively inhibit the COX-2 enzyme allowing continued production of COX-1 and resulting in a decreased incidence of gastrointestinal side effects in adults. Although serious gastrointestinal complications are rare in children treated with conventional

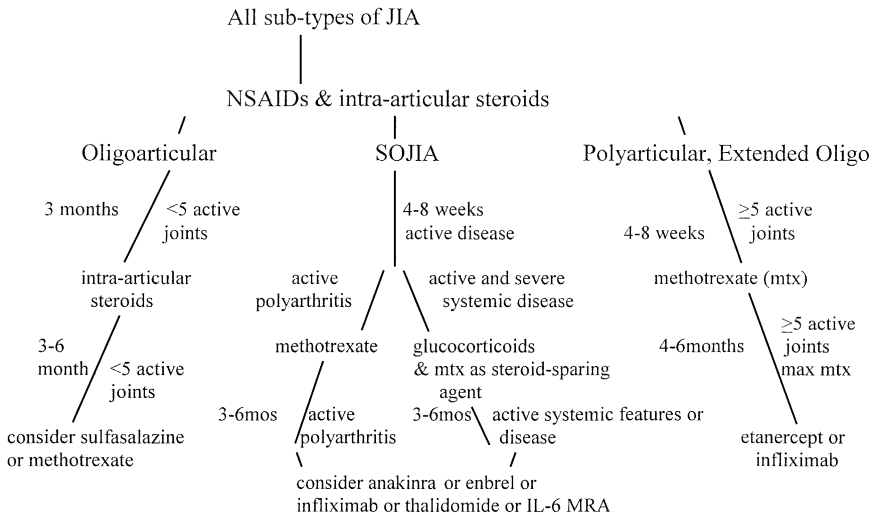


Fig. 6. Suggested treatment algorithm for JIA.

NSAIDS, COX-2 inhibitors may be useful in selected populations, especially children who have developed significant gastrointestinal symptoms [93–95]. Studies are now ongoing to assess the efficacy and pharmacokinetics of COX-2 inhibitors in children. An increased incidence of cardiovascular events, especially congestive heart failure, has been found in patients taking rofecoxib, more recently, celecoxib [96]. The mechanism by which COX-2 inhibitors increase cardiovascular risk may be, in part, the absence of inhibition of prostaglandin production in platelets, which would otherwise inhibit their function and thus promote thrombosis. The increased risk also may be related to sodium and water retention and blood pressure elevation [97]. These findings resulted in rofecoxib's being removed from the market shortly after being approved for use in children by the Food and Drug Administration. There is some evidence that naproxen sodium and celecoxib may be relatively cardioprotective [97,98], but some recent data suggest that in certain populations naproxen may actually demonstrate cardiovascular toxicity. Further studies are needed to determine whether cardiovascular toxicity is a class effect of all COX-2 inhibitors or all NSAIDs.

Glucocorticoids

Glucocorticoids are potent anti-inflammatory medications that should be used judiciously in patients with arthritis because the side-effect profile includes cushingoid appearance, hyperglycemia, immunosuppression, cataracts and glaucoma, adrenal suppression, peptic ulcer, dyslipoproteinemia, hypertension, avascular necrosis of bone, and central nervous system disturbance. Although glucocorticoids are the mainstay of treatment for controlling serious systemic manifestations of SOJIA, use in polyarticular patients should be limited to patients with extreme pain and functional limitation while waiting for a second-line agent to show some effect [99]. In rare instances pulse methylprednisolone (30 mg/kg; maximum of 1 gm) has been used to treat SOJIA patients who have not responded to oral glucocorticoids. Once disease improvement is noted, steroids should be tapered as quickly as possible (or used at the lowest dose that controls symptoms).

Treatment of a few joints with intra-articular long-acting corticosteroid injections is an effective method to treat arthritis while minimizing systemic side effects from oral medications. Triamcinolone hexacetonide (10–40 mg/joint or 1–2 mg/kg/joint) is commonly used and has been shown to result in improvement of signs and symptoms of arthritis, growth abnormalities, and gait disturbances that may last for many months [100–102]. Side effects may include infection, atrophic skin changes at the injection site, and asymptomatic calcifications on radiographs [99]. Injections can be given safely as often as every 3 months, but the same joint should not be injected more than three times in any year.

Disease-modifying antirheumatic agents

DMARDs that have been shown to be effective in JIA include sulfasalazine, methotrexate, and etanercept. Other DMARDs such as hydroxychloro-

quine, D-penicillamine, and auranofin have failed to show efficacy in double-blind, placebo-controlled trials [99]. Intramuscular or oral gold is rarely used for JIA currently because of poorer response rates and higher incidence of toxicity when compared with methotrexate and other DMARDs. SOJIA patients have shown improvement with monthly treatment with intravenous cyclophosphamide and intravenous immunoglobulin.

Sulfasalazine

Sulfasalazine was more effective than placebo in controlling arthritis and improving laboratory parameters in a double-blind, placebo-controlled trial [103]. Sulfasalazine is used commonly to treat oligoarticular JIA and HLA-B27 spondyloarthropathies, although a recent trial did not document efficacy [104]. Its use, however, is limited by side effects such as headache, rash, gastrointestinal toxicity, myelosuppression, and hypoinnoglobulinemia. A complete blood count and liver transaminases must be obtained before the beginning of treatment and monitored every other week for the first 3 months, monthly for the next 3 months, and every 3 months thereafter [99].

Methotrexate

Methotrexate, a folate antagonist, is the most frequently used second-line agent for patients with JIA [105], particularly polyarticular and SOJIA. Up to 80% of JIA patients have some clinical response on methotrexate, and studies suggest it retards radiographic progression. Extended oligoarticular patients respond best to methotrexate; SOJIA patients may not do as well on this agent [92]. Methotrexate is also helpful in controlling the rash and arthritis of JPSA.

Methotrexate is tolerated quite well in children with doses starting at 0.3 mg/kg/week and increased to a maximum of 1 mg/kg/dose (no more than 25 mg/wk orally or 15 mg/m² subcutaneously to a maximum of 50). Subcutaneous methotrexate may be more effective than oral administration, but there seems to be a plateau in efficacy at about 15 mg/m² [106,107]. Gastrointestinal toxicity is the most common adverse event, occurring in 13% of the patients. Additional side effects include hepatotoxicity, oral mucosal ulcerations, teratogenicity, immunosuppression, pulmonary disease, pancytopenia, and an increased risk of lymphoproliferative malignancies [108]. Pulmonary disease is rare in the pediatric population, and there have not been convincing reports of lymphoma caused by methotrexate in JIA patients. These risks, therefore, may be theoretical in pediatric patients. Supplementation with folic acid has been shown to lessen the gastrointestinal and mucocutaneous side effects without altering the therapeutic effect of methotrexate [109]. Liver enzymes and a complete blood cell count should be monitored every 1 to 2 months, although serious, irreversible liver disease is rare in children [110]. The medication should be withheld if liver enzymes approach three times normal. Patients are advised not receive live virus vaccines because of the possible immunosuppressive effects of the medication.

It is the practice of some physicians, before the start of treatment to check varicella titers and to vaccinate patients if they are susceptible to varicella. Patients in remission for 1 year can gradually discontinue methotrexate to reduce potential long-term toxicity [92].

Leflunomide

Leflunomide, an immunosuppressive agent that reversibly inhibits de novo pyrimidine synthesis, is approved for the treatment of adult rheumatoid arthritis and is currently being studied for use in JIA. Preliminary results published in abstract form show efficacy similar to that of methotrexate [111]. Side effects include diarrhea, elevated liver enzymes, mucocutaneous abnormalities, and teratogenicity [92].

Biologic agents

The biologic agents, including the TNF inhibitors etanercept, infliximab, adalimumab, the IL-1 inhibitor anakinra, and the B-cell depleter rituximab, have improved the armamentarium for the treatment of patients with rheumatoid arthritis and JIA. All carry a risk of immunosuppression, and live virus vaccines are relatively contraindicated. Cases of reactivated tuberculosis have been reported in patients using the TNF inhibitors; tuberculin (PPD) nonreactivity should be demonstrated at the start of therapy. If the PPD is positive, the patient should be treated with isoniazid for at least 1 month before starting the biologic agent.

Etanercept

Elevated levels of TNF- α and soluble TNF receptor are found in serum of JIA patients. In addition, these patients also have elevated levels of TNF- α in the synovial fluid [112]. Etanercept, a soluble TNF receptor, is a fusion protein made up of two recombinant p75-soluble receptors fused with the Fc fragment from human IgG. It binds and inhibits TNF- α and lymphotoxin- α (TNF- β). In a double-blind, placebo-controlled study of polyarticular-course JRA patients who had not responded to or were intolerant of methotrexate, etanercept was proven effective in controlling pain and swelling and in improving laboratory parameters [113]. There is also evidence that it retards radiographic progression of disease. Approximately three fourths of patients who do not respond adequately to methotrexate will have a good response to etanercept. After 2 years of follow-up, patients in the initial clinical trial continue to have an excellent response [114]. Preliminary findings on etanercept in combination with a DMARD have shown it to be well tolerated [115].

Etanercept, 0.4 mg/kg (maximum 25 mg) given subcutaneously twice weekly has a dramatic response and is highly recommended for patients with extended

oligoarticular and polyarticular JIA who have not responded to NSAIDs and methotrexate. The parents and possibly the adolescent patient are trained in reconstitution of the etanercept and administration of the injection using aseptic technique.

In placebo-controlled clinical trials, etanercept was well tolerated, and no increased incidence of infection was found. The most common adverse events were injection-site reactions (39%) and upper respiratory tract infection (35%). Less frequently, patients experienced headache, rhinitis, gastrointestinal symptoms, and rash [113]. Three cases of varicella zoster infection were reported, one resulting in aseptic meningitis [114]. It is recommended that varicella-susceptible children be immunized 3 months before the start of the drug, if possible. Any susceptible patient exposed to varicella should be treated with varicella-zoster immune globulin and acyclovir at the first sign of infection [114]. Pediatric patients with significant exposure to varicella should temporarily discontinue the etanercept [92].

Although etanercept is not currently approved for JPsA, a double-blind, placebo-controlled study of etanercept (25 mg subcutaneously two times per week) in adults with PsA showed remarkable improvement of arthritis and skin manifestations [116]. Etanercept has also shown promise in adults with spondyloarthropathy.

Infliximab

Infliximab is a chimeric monoclonal anti-TNF- α antibody. The variable region of a mouse monoclonal anti-TNF- α antibody is coupled to the constant region of human IgG1. Adult patients with rheumatoid arthritis are treated with infliximab, 3 to 10 mg/kg, at time 0, 2 weeks, 6 weeks, and then every 6 to 8 weeks. There are preliminary data on dosing, efficacy, and pharmacokinetics in pediatric patients. In a recent small, nonrandomized, open-label study, etanercept and infliximab (in combination with a DMARD) were found to be equally efficacious in treating patients with JPsA, polyarticular arthritis, and SOJIA. The incidence of adverse effects was higher and more serious in the infliximab group than in the etanercept group [117]. Results from a double-blind, placebo-controlled trial have recently been presented, demonstrating efficacy at a 3-mg/kg dose and a 6-mg/kg dose, with improved safety at the 6-mg/kg dose. Further studies are needed to evaluate the benefits and risks of infliximab in patients with JIA and JPsA [118].

Adalimumab

Adalimumab is a completely humanized monoclonal antibody to TNF given by subcutaneous injection every 2 weeks. The results of a recent open-label phase of a planned double-blind, placebo-controlled, randomized withdrawal study have recently been presented and suggest efficacy in polyarticular JRA [119].

Anakinra

Anakinra, a recombinant IL-1 receptor antagonist, has been studied in a manner similar to the seminal etanercept study in JIA in a randomized, placebo-controlled withdrawal design, but only the first, open-label portion of the study has been presented. Response was documented in 58% of subjects after 4 months of therapy but was highest (79%) in the systemic-onset patients. There have been a few reports of either isolated cases or small series of recalcitrant systemic-onset JIA patients responding dramatically in both rapidity of response and degree of response [120–123]. This agent may prove to be very effective in this subtype of JIA.

Humanized anti-interleukin-6 receptor antibody

There is evidence that SOJIA is in part an IL-6–mediated disease. In a dose-escalation study, SOJIA patients treated with humanized anti-interleukin-6 receptor antibody (MRA) at a dose of 8 mg/kg had significant improvement in the ACR improvement criteria and disease activity indices, in addition to a decrease in acute-phase reactants. No child withdrew from the trial because of disease flare or adverse effects [124]. MRA may be useful in patients with intractable disease who are receiving high-dose corticosteroids [125,126], but further randomized, placebo-controlled efficacy and long-term safety studies are needed.

Autologous stem cell transplantation

Autologous stem cell transplantation has been considered in recalcitrant cases of SOJIA. Drug-free remissions of disease have been reported, but the procedure carries a significant mortality risk, usually from macrophage activation syndrome [127]. Stem cell transplantation should be performed only in experienced centers after all other treatment options have failed [92].

In summary, all patients diagnosed with JIA should be given a trial of NSAIDs, and intra-articular corticosteroid injections should be considered. Patients with persistent oligoarticular JIA usually have a good response and need no further intervention. Patients with polyarticular disease benefit from aggressive therapy with methotrexate to improve function and prevent permanent damage. Intra-articular corticosteroids are a good adjunct to treatment. Extended oligoarticular JIA patients and JPsA patients who do not respond to first-line treatment should be treated like polyarticular patients. SOJIA patients with active systemic disease may require oral glucocorticoids for rapid relief of serious systemic manifestations including pericarditis, progressive anemia, malnutrition, and persistent fever. Methotrexate should be considered for articular disease treatment as well as a steroid-sparing agent. Sulfasalazine may be particularly effective in patients with ERA and extended oligoarticular patients who do not

respond to NSAIDs. Presently, the only biologic agent that has been proved to be effective in JIA is etanercept, which should be used in patients with polyarticular disease who do not respond to methotrexate.

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