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ONLINE EXCLUSIVE

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Juvenile idiopathic arthritis: Old disease, new tactics

Beyond NSAIDs and disease-modifying antirheumatic drugs are now biologic agents and anti-interleukin drugs that can augment therapy.

PRACTICE RECOMMENDATIONS

› *Pair the findings of your clinical exam with the results of imaging and laboratory testing to make the diagnosis of juvenile idiopathic arthritis (JIA), as it is a diagnosis of exclusion.* (B)

› *Individualize treatment based on where the patient falls in the JIA disease spectrum to increase the likelihood that medical therapy will be effective.* (A)

› *Consider treating diagnosed JIA with an available biologic agent, which can provide a long asymptomatic period.* (B)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Juvenile idiopathic arthritis (JIA) is a clinically heterogeneous group of arthritides that are characterized by onset before 16 years of age and defined in part as lasting ≥6 weeks.[1] Significantly, the etiology of JIA is unknown, making it a diagnosis of exclusion.[2]

The most common autoimmune condition of childhood, JIA has a prevalence of 3.8 to 400 affected children for every 100,000 people.[3,4] As the leading cause of musculoskeletal disability in children,[5] and comprising 7 categories of disease, JIA must be managed with appropriate initial and ongoing intervention.

The amalgam of care that a JIA patient requires—medical, social, physical, psychological—calls for a primary care physician's expert ability to collaborate and coordinate with medical specialists and subspecialists, including rheumatology, ophthalmology, social work, physical and occupational therapy, and psychology. The goal? As this article describes, the goal is to provide prompt diagnosis, suitable and effective intervention, and continuity of care. (JIA is a lifelong disease, in many cases.)

How JIA is classified for diagnosis and treatment

JIA comprises 7 categories, or classes.[6] The scheme devised by the International League of Associations for Rheumatology (ILAR), now widely accepted, classifies JIA on the basis of clinical and biochemical markers that aid detection and treatment of the disorder, as well as research. (See "How efforts to classify JIA have caused confusion,"[7-10] page E10.) The ILAR classes (**TABLE**[11]) are:

- enthesitis-related arthritis (ERA)
- extended oligo-articular JIA (eoJIA), which involves ≤4 joints
- juvenile psoriatic arthritis (jPsA)
- rheumatoid factor (RF)-positive polyarticular JIA (RF+ pJIA)

TABLE

Key characteristics of JIA subtypes: Frequency, age of onset, gender distribution[11]

Subtype	% of all cases of JIA[a]	Age of onset	Gender distribution
Enthesitis-related arthritis	3-11	Late childhood and adolescence	Highly predominant in females
Extended oligo-articular arthritis	27-56	Early childhood (peaks at 2-4 y)	Exceedingly predominant in females
Psoriatic arthritis	2-11	Biphasic distribution (early peak at 2-4 y, later peak at 9-11 y)	Predominant in females
Rheumatoid factor-positive polyarthritis	2-7	Late childhood and adolescence	Highly predominant in females
Rheumatoid-factor-negative polyarthritis	11-28	Biphasic distribution (early peak at 2-4 y, later peak at 6-12 y)	Highly predominant in females
Systemic arthritis	4-17	Throughout childhood	Equal
Undifferentiated	11-21	—	—

JIA, juvenile idiopathic arthritis.

[a] As variously reported in the literature.

Source: Adapted from Basra HAS, et al. *Br J Radiol.* 2017.[11]

- RF-negative polyarticular JIA (RF– pJIA)
- systemic-onset JIA (sJIA)
- undifferentiated JIA, which, generally, involves ≥4 joints.

Updated guidelines regarding the 7 ILAR classes of JIA emphasize heterogeneity among disease subtypes, with overlapping and exclusive features noted from class to class.[11]

Extended oligo-articular JIA (27%-56%), pJIA (13%-35%), sJIA (4%-17%), and ERA, (3%-11%) are the most common JIA subtypes,[12] with age of onset and sex predilection differing according to JIA class.[11] The disease occurs more often in girls than in boys,[11] and the predisposition is higher among Whites and Asians. The incidence of JIA (all classes taken together, for every 100,000 people) is: in Japan, 10 to 15 cases[13]; in Turkey, 64 cases[14]; in Norway, 65 cases[15]; and in the United States and Canada, taken together, 10 to 15 cases.[16]

What causes JIA?

The etiology of JIA remains unclear. It is known that the disease involves inflammation of the synovium and destruction of hard and soft tissues in joints.[17] It has been postulated, therefore, that a combination of genetic, environmental, and immunogenic mechanisms might be responsible for JIA.

For example, there is an increased frequency of autoimmune diseases among JIA patients.[18] There are also reports documenting an increased rate of infection, including with enteric pathogens, parvovirus B,[19] rubella, mumps, hepatitis B, Epstein-Barr virus, mycoplasma, and chlamydia.[19] Stress and trauma have also been implicated.[12]

The T-lymphocyte percentage is increased in the synovial fluid of JIA patients, although that percentage varies from subtype to subtype.[20] This elevation results in an increase in the number of macrophages, which are induced by secreted cytokines to produce interleukin (IL)-1, IL-6, and tumor necrosis factor alpha (TNF-α). This activity of cellular immunity leads to joint destruction.[21]

Clinical features

The most common signs and symptoms of JIA are arthralgias (39%), arthritis (25%), fever (18%), limping (9%), rash (8%), abdominal pain (1.3%), and uveitis (1.3%).[15] Forty percent of JIA patients are reported to have temporomandibular joint involvement at

How efforts to classify JIA have caused confusion[7-10]

Various classifications of juvenile arthritis have been proposed and used over the past 3 decades. First was the American College of Rheumatology's 1972 criteria for juvenile rheumatoid arthritis[7]; next came the European League against Rheumatism (EULAR) criteria for juvenile chronic arthritis, developed in 1977.[8] Being contemporaneous, the 2 classifications led to a complicated, dichotomous definition of JIA among clinicians and researchers.

As a result of this disarray, the 1997 Durban, South Africa, meeting of the Pediatric Standing Committee of the International League of Associations for Rheumatology (ILAR)[9] proposed that juvenile idiopathic arthritis be adopted as the umbrella term for the misunderstood terms juvenile rheumatoid arthritis and juvenile chronic arthritis. The intent of including "idiopathic" in the term was to acknowledge that the cause of these diseases was (and is still) unknown.

The novel classification proposed by the Pediatric Standing Committee was followed, in 2001, by an ILAR task force meeting in Edmonton, Alberta, Canada, on the classification of childhood arthritis. The outcome was a recommendation to add exclusion and inclusion criteria, to make all classes of JIA mutually exclusive.[10] Most recently, as discussed in the body of this article, updated ILAR guidelines on JIA classification emphasize 1) heterogeneity among the 7 disease subtypes and 2) the fact that overlapping and exclusive features exist from class to class.

some point in their life; mandibular asymmetry secondary to condylar resorption and remodeling[17] is the most common presenting complaint—not arthralgia or pain, as would be expected.

Most JIA patients (52%) first present to the emergency department; another 42% present to the office of a general medical practitioner.[15] On average, 3 visits to a physician, over the course of approximately 3 months, are made before a definitive diagnosis (usually by a pediatric rheumatologist) is made.[15]

Pertinent questions to ask a patient who has a confirmed diagnosis of JIA include the nature, severity, and duration of morning stiffness and pain, as well as any encumbering factors to regular functioning at home or school.[22] Different scoring charts can be used to determine the extent of pain and disability, including the Juvenile Arthritis Disease Activity Score (JADAS)[23] and the clinical JADAS (cJADAS),[24] which measure minimal disease activity[25] and clinically inactive disease[26] cutoffs.

Macrophage-activating syndrome increases risk of morbidity, mortality

An overactivation and expansion of T lymphocytes and macrophagic histiocytes with hemophagocytic activity, macrophage-activating syndrome (MAS) occurs in approximately 10% of JIA patients,[27] increasing their risk of morbidity and mortality. The syndrome, which typically presents as fever, seizures, hypotension, purpura, hepatitis, splenomegaly, and occasionally, multisystem organ failure, is seen in 30% to 40% of sJIA patients; approximately 11% of them experience sudden death as a consequence.[28]

The clinical setting of MAS includes presenting symptoms of fever and a salmon-pink macular rash (FIGURE). For many sJIA patients with MAS, the diagnosis is made when laboratory results show hyperferritinemia, thrombocytopenia, anemia, leukopenia, coagulopathy, and elevated levels of C-reactive protein and D-dimer.[27]

Different classes, different features

The following clinical profiles have been documented in different classes of JIA:

- **Systemic JIA** presents with intermittent fever of at least 2 weeks' duration, arthritis, and occasionally, a rash.
- **Extended oligo-articular JIA** involves pain, in a mono-articular lower-extremity joint, that can develop suddenly or insidiously, and is characterized by early-morning stiffness and uveitis (especially in early-onset, antinuclear antibody-positive JIA patients).
- **Poly-articular JIA** patients present with mild fever, weight loss, and anemia.
- **Enthesis-related arthritis** patients have findings of enthesopathy; asymmetric arthritis of the lower extremities, particularly the Achilles tendon[29]; and recurrent acute, symptomatic iridocyclitis.[30]
- **Juvenile psoriatic arthritis** can involve any joint but is readily differentiated from pJIA by involvement of distal interphalangeal joints and psoriatic skin and nail changes.[29]

Investigations

Imaging

Radiography is still the most widely used imaging tool for making the diagnosis of

JIA. Plain films demonstrate structural joint damage and disturbances of growth and maturation in bones. Radiography has poor sensitivity for detecting acute synovitis and limited utility in visualizing erosion changes early in the course of disease, however, which has led to increased use of ultrasonography (US) and contrast-enhanced magnetic resonance imaging (MRI) to diagnose JIA.[30]

Contrast-enhanced MRI is superior to US for detecting early inflammation and monitoring subsequent joint disease. Of course, MRI is more expensive than US, and less widely available. Other imaging options are computed tomography and positron emission tomography, but these scans are not as sensitive as contrast-enhanced MRI and have the disadvantage of radiation exposure (in the former) and cost (in the latter).

Laboratory testing

No diagnostic tests for JIA exist. Assays of acute-phase reactants, including C-reactive protein, the erythrocyte sedimentation rate, and serum amyloid-A proteins, can be utilized to demonstrate inflammation but not to confirm the diagnosis. For some classes of JIA, various tests, including rheumatoid factor, antinuclear antibody, human leukocyte antigen B-27, and cyclic citrullated peptide antibodies, can be used to confirm a specific class but, again, are not recommended for confirming JIA.[6]

The complete blood count, blood cultures, and tests of uric acid and lactate dehydrogenase can be ordered during treatment to monitor for complications, such as malignancy, infection, MAS, and sepsis.

Treatment is based on disease class

Nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular steroids are used in all JIA classes, as an adjunct to class-specific treatment, or as induction agents.[31] These therapies, although they alleviate acute signs and symptoms, such as pain, inflammation, swelling and joint contractures, are not useful for long-term treatment of JIA because they do not halt disease progression.

Systemic steroids can be utilized in exceptional cases, including chronic uveitis with arthritis or in patients with destructive arthritis and poor prognostic features, including cyclic citrullated peptide antibodies, positive RF, erosions, and joint-space narrowing.[32]

Other drugs. Options include traditional disease-modifying anti-rheumatic drugs (csDMARDs), such as methotrexate and leflunomide; biologic agents, such as TNF-a inhibitors (eg, etanercept, adalimumab, and infliximab); and anti-IL monoclonal antibody drugs (eg, the IL-6 inhibitor tocilizumab and IL-1 inhibitors anakinra, and canakinumab).[31] Indications by class include:

- csDMARDs as first-line therapy in persistent eoJIA and pJIA;
- TNF-α inhibitors for refractory eoJIA and for pJIA episodes[31];
- tocilizumab, recommended for sJIA patients who have persistent systemic signs; and

FIGURE

Macular rash of macrophage-activating syndrome in a systemic JIA patient

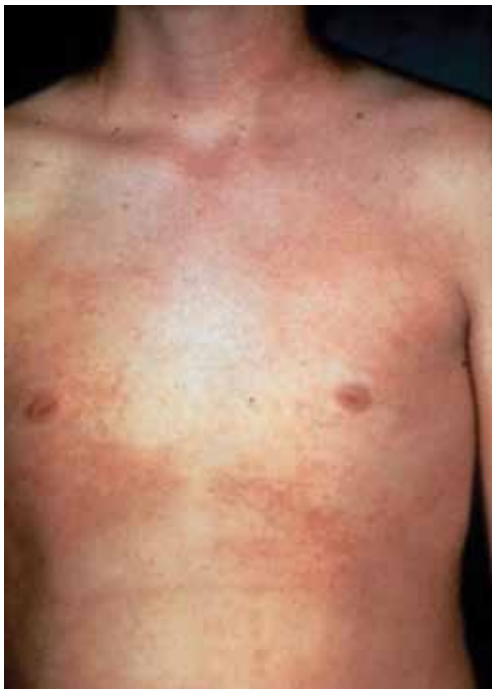

IMAGE COURTESY OF: CHARLES H. SPENCER, MD. REPRINTED WITH PERMISSION.

JIA, juvenile idiopathic arthritis.

Mandibular asymmetry secondary to condylar resorption and remodeling is the most common presenting complaint of juvenile idiopathic arthritis—not arthralgia or pain, as you might expect.

- anakinra and canakinumab for refractory SJIA patients.[32]

Failure

When treatment of JIA fails with a given drug, options include increasing the dosage; switching to another agent in the same drug class; switching to a different class; and combining an NSAID with a csDMARD or a biologic agent.[32] In class-specific JIA cases, a change in a drug regimen is warranted on the basis of the evidence-based historical clinical response rate.[32]

What is the prognosis?

Treatment of JIA with novel agents, such as biologics, has opened up the possibility that JIA patients can live not just with suppressed symptoms but immunologically inactive disease. This is the result of better understanding of the pathogenesis of JIA and the mechanism of action of targeted drugs, and identification of biomarkers that are helpful in predicting prognosis, adverse effects, and response to treatment.

JIA is often a lifelong disease; one-third of patients continue to exhibit symptoms into adulthood.[4] If their disease is properly managed, however, these patients do not develop typical features of rheumatoid arthritis, including hand, limb, and spine deformities. Last, patients with JIA who have only intermittent disease tend to do better over the long term than those whose disease is continual.[32]

The mortality rate of JIA has dropped: from 1% to 4% in the mid-1970s to 0.3% to 1% today[4]—an improvement in life expectancy that is echoed in enhanced quality of life for patients. According to the 4-level Steinbrocker functional classification scale[33] (used to rate the extent of physical disability), 15% of JIA patients were Class III (limited to few or no activities of the patient's usual occupation) or Class IV (bedridden with little or no self-care) in the period from 1976 to 1994—a percentage that had declined to 5% by 2002.[34]

On average, it takes 3 visits to a physician, over the course of about 3 months, before definitive diagnosis of JIA is made.

The family physician plays pivotal role in JIA care

For the family physician, appropriate initial intervention in the management of JIA is imperative. This includes ordering imaging (whether plain films or MRI), laboratory tests as described earlier (although not to make the diagnosis), and the use of NSAIDs, intra-articular steroids, and other induction agents. Once the diagnosis is made, and a drug regimen is put in place, you will need to monitor for adverse effects. This monitoring will need to occur when a patient is escalated to csDMARDs, biological agents, or systemic steroids; is maintained on an NSAID; or is placed on a combination regimen.

Before beginning therapy with a biologic agent, it's important to screen for hepatitis B, hepatitis C, human immunodeficiency virus infection, tuberculosis, and fungal infection (eg, *Histoplasma capsulatum, Coccidioides immitis*[32]). Be sure to make a timely referral to the ophthalmology service for a bi-annual eye exam and, in the event that surgery is necessary, conduct a preoperative evaluation, with the knowledge of how long before surgery a biologic agent must be withheld (duration varies by drug).[32] JFP

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References

1. Adriano LS, de França Fonteles MM, de Fátima Menezes Azevedo M, et al. Medication adherence in patients with juvenile idiopathic arthritis. *Rev Bras Reumatol Engl Ed.* 2017;57:23-29.
2. Akioka S. A better understanding of juvenile idiopathic arthritis with classification criteria. *Nihon Rinsho Meneki Gakkai Kaishi.* 2016;39:513-521.
3. Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. *Joint Bone Spine.* 2014;81:112-117.
4. Petty RE, Laxer RM, Lindsley CB, et al. *Pediatric Rheumatology.* Philadelphia, PA: Elsevier; 2016:188-201.e6.
5. Scott C, Brice N. Juvenile idiopathic arthritis–an update on its diagnosis and management. *S Afr Med J.* 2015;105:1077.
6. Giancane G, Consolaro A, Lanni S, et al. Juvenile idiopathic arthritis: diagnosis and treatment. *Rheumatol Ther.* 2016;3:187-207.
7. Criteria for the classification of juvenile rheumatoid arthritis. *Bull Rheum Dis.* 1972;23:712-719.
8. Wood PHN: Special meeting on nomenclature and classification of arthritis in children. In: Munthe E, ed. *The Care of Rheumatic Children.* Basel, Switzerland: EULAR Publishers; 1978:47-50.
9. Petty RE, Southwood TR, Baum J, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. *J Rheumatol.* 1998;25:1991-1994.
10. Petty RE, Southwood TR, Manners P, et al; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol.* 2004;31:390-392.
11. Basra HAS, Humphries PD. Juvenile idiopathic arthritis: what is the utility of ultrasound? *Br J Radiol.* 2017;90:20160920.

12. Weiss J, Ilowite NT. Juvenile idiopathic arthritis. *Pediatr Clin North Am.* 2005;52:413-442, vi.
13. Fujikawa S, Okuni M. A nationwide surveillance study of rheumatic diseases among Japanese children. *Acta Pediatric Jpn.* 1997:39:242-244.
14. Ozen S, Karaaslan Y, Ozdemir O, et al. Prevalence of juvenile chronic arthritis and familial Mediterranean fever in Turkey: a field study. *J Rheumatol.* 1998;25:2445-2449.
15. Aoust L, Rossi-Semerano L, Koné-PauL I, et al. Time to diagnosis in juvenile idiopathic arthritis: a French perspective. *Orphanet J Rare Dis.* 2017;12:43.
16. Moe N, Rygg M. Epidemiology of juvenile chronic arthritis in northern Norway; a ten-year retrospective study. *Clin Exp Rheumatol.* 1998;16:99-101.
17. Abramowicz S, Kim S, Prahalad S, et al. Juvenile arthritis: current concepts in terminology, etiopathogenesis, diagnosis, and management. *Int J Oral Maxillofac Surg.* 2016;45:801-812.
18. Prahalad S, Shear ES, Thompson SD, et al. Increased prevalence of familial autoimmunity in simplex and multiplex families with juvenile rheumatoid arthritis. *Arthritis Rheum.* 2002;46:1851-1856.
19. Gonzalez B, Larrañaga C, León O, et al. Parvovirus B19 may have a role in the pathogenesis of juvenile idiopathic arthritis. *J Rheumatol.* 2007;34:1336-1340.
20. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. *Lancet.* 2011;377:2138-2149.
21. Zhou J, Ding Y, Zhang Y, et al. CD3+CD56+ natural killer T cell activity in children with different forms of juvenile idiopathic arthritis and the influence of etanercept treatment on polyarticular subgroup. *Clin Immunol.* 2016;176:1-11.
22. Shoop-Worrall SJW, Verstappen SMM, Baildam E, et al. How common is clinically inactive disease in a prospective cohort of patients with juvenile idiopathic arthritis? The importance of definition. *Ann Rheum Dis.* 2017;0:1-8.
23. Nordal EB, Zak M, Berntson L, et al. Juvenile Arthritis Disease Activity Score (JADAS) based on CRP; validity and predictive ability in a Nordic population-based setting. *Pediatr Rheumatol Online J.* 2011;9(suppl 1):155.
24. Swart JF, Dijkhuizen EHP, Wulffraat NM, et al. Clinical Juvenile Arthritis Disease Activity Score proves to be a useful tool in treat-to-target therapy in juvenile idiopathic arthritis. *Ann Rheum Dis.* 2018;77:336-342.
25. Horneff G, Klein A, Ganser G, et al. Protocols on classification, monitoring and therapy in children's rheumatology (PRO-KIND): results of the working group polyarticular juvenile idiopathic arthritis. *Pediatr Rheumatol Online J.* 2017;15:78.
26. Shoop-Worrall SJW, Verstappen SMM, McDonagh JE, et al. Long-term outcomes following achievement of clinically inactive disease in juvenile idiopathic arthritis. *Arthritis Rheumatol.* 2018;70:1519-1529.
27. Ahn SS, Yoo BW, Jung SM, et al. In-hospital mortality in febrile lupus patients based on 2016 EULAR/ACR/PRINTO classification criteria for macrophage activation syndrome. *Sem Arthritis Rheum.* 2017;.47:216-221.
28. Yokota S, Mori M, Imagawa T, et al. Proposal for juvenile idiopathic arthritis guidance on diagnosis and treatment for primary care pediatricians and nonpediatric rheumatologists (2007). *Mod Rheumatol.* 2007;17:353-363.
29. Barut K, Adrovic A, Şahin S, et al. Juvenile idiopathic arthritis. *Balkan Med J.* 2017;34:90-101.
30. Colebatch-Bourn AN, Edwards CJ, et al. EULAR-PReS points to consider for the use of imaging in the diagnosis and management of juvenile idiopathic arthritis in clinical practice. *Ann Rheum Dis.* 2015;74:1946-1957.
31. Blazina Š, Markelj G, Avramovič MZ, et al. Management of juvenile idiopathic arthritis: a clinical guide. *Pediatr Drugs.* 2016;18:397-412.
32. Santos MJ, Conde M, Mourão AF, et al. 2016 update of the Portuguese recommendations for the use of biologic therapies in children and adolescents with juvenile idiopathic arthritis. *Acta Rheumatol Port.* 2016;41:194-212.
33. Steinbrocker 0, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. *JAMA.* 1949;140:659-662.
34. Oen K, Malleson PN, Cabral D, et al. Disease course and outcome of juvenile rheumatoid arthritis in a multicenter cohort. *J Rheumatol.* 2002;29:1989-1999.