

Disease classification

Classification criteria

Over the years, several classification systems for chronic arthritis in childhood have been proposed (Table 2.1) [1]. In the 1970s, two sets of criteria were developed: those for juvenile rheumatoid arthritis (JRA), devised by a committee of the American College of Rheumatology (ACR) [2], and those for juvenile chronic arthritis (JCA), established by the European League Against Rheumatism (EULAR) [3]. The inconsistencies between these two classifications and the disparity in terminology that they generated between Europe and North America were resolved in 1994 through the introduction of the new criteria created by the Pediatric Task force of the International League of Associations for Rheumatology (ILAR) [4]. The ILAR classification, which was revised in 1997 [5] and again in 2001 [1], introduced the unifying term of juvenile idiopathic arthritis (JIA) and outlined seven disease categories: systemic arthritis, rheumatoid factor (RF)-positive polyarthritis, RF-negative polyarthritis, oligoarthritis, psoriatic arthritis (PsA), enthesitis-related arthritis (ERA), and undifferentiated arthritis (Table 2.2) [1].

Challenges in classification

The current ILAR classification for JIA is primarily aimed at identifying homogeneous, mutually exclusive disease groups on the basis of clinical and laboratory features present in the first 6 months of illness [5]. This categorization is intended to facilitate research on etiopathogenesis and epidemiology, outcome studies, and therapeutic trials. However, it has

ACR JRA	EULAR JCA	ILAR JIA
Systemic arthritis	Systemic arthritis	Systemic arthritis
Pauciarticular arthritis	Pauciarticular arthritis	Oligoarthritis: • persistent • extended
Polyarticular arthritis	Polyarticular arthritis	Polyarthritis (RF-negative)
	JRA (RF-positive)	Polyarthritis (RF-positive)
	Spondyloarthropathies	Psoriatic arthritis
		Enthesitis-related arthritis
		Undifferentiated arthritis

Table 2.1 Comparison of classification criteria for chronic arthritis in childhood.

Note: spondyloarthropathies include juvenile ankylosing spondylitis, juvenile psoriatic arthritis, Reiter’s syndrome, and the arthropathies of inflammatory bowel disease; children with spondyloarthropathies are excluded from the ACR classification; RF positivity is not a differentiating criterion in the ACR classification although it is in the EULAR classification. ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; ILAR, International League of Associations for Rheumatology; JCA, juvenile chronic arthritis; JIA, juvenile idiopathic arthritis; JRA, juvenile rheumatoid arthritis; RF, rheumatoid factor. Adapted from © The Journal of Rheumatology Publishing Company Limited, 2001. All rights reserved. Petty et al [1].

Systemic arthritis
Arthritis with, or preceded by, daily fever of at least 2 weeks’ duration that is documented to be quotidian for at least 3 days, and accompanied by one or more of the following: • Evanescent, non-fixed, erythematous rash • Generalized lymph node enlargement • Hepatomegaly and/or splenomegaly • Serositis Exclusions: a,b,c,d (see below)
Oligoarthritis
Arthritis affecting 1–4 joints during the first 6 months of disease. Two subcategories are recognized: • Persistent oligoarthritis: affects no more than four joints throughout the disease course • Extended oligoarthritis: affects a total of more than four joints after the first 6 months of disease Exclusions: a,b,c,d,e (see below)
Polyarthritis (RF-negative)
Arthritis affecting 5 or more joints during the first 6 months of disease: tests for RF are negative Exclusions: a,b,c,d,e (see below)
Polyarthritis (RF-positive)
Arthritis affecting 5 or more joints during the first 6 months of disease: tests for RF are positive Exclusions: a,b,c,e (see below)

Table 2.2 The International League of Associations for Rheumatology classification of juvenile idiopathic arthritis (second revision) (continued on next page).

Psoriatic arthritis
• Arthritis and psoriasis or • Arthritis and at least 2 of the following: • Dactylitis • Nail pitting or onycholysis • Psoriasis in a first-degree relative Exclusions: b,c,d,e (see below)
Enthesitis-related arthritis
• Arthritis and enthesitis • Arthritis or enthesitis with at least two of the following: • Sacroiliac joint tenderness and/or inflammatory lumbosacral pain • Presence of HLA-B27 • Onset of arthritis in a male after 6 years of age • Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative Exclusions: a, d,e (see below)
Undifferentiated arthritis
Arthritis that does not fulfil inclusion criteria for any category, or is excluded by fulfilling criteria for more than one category
Exclusion criteria for the classification of JIA
A. Psoriasis in the patient or a first-degree relative B. Arthritis in an HLA-B27-positive male with arthritis onset after 6 years of age C. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative D. Presence of IgM rheumatoid factor on at least two occasions more than 3 months apart E. Presence of systemic arthritis

Table 2.2 The International League of Associations for Rheumatology classification of juvenile idiopathic arthritis (second revision) (continued). HLA, human leukocyte antigen; JIA, juvenile idiopathic arthritis; RF, rheumatoid factor. Adapted from © The Journal of Rheumatology Publishing Company Limited, 2001. All rights reserved. Petty et al [1].

been recommended that the ILAR classification system be viewed as ‘a work in progress’, and pediatric rheumatologists have been urged to participate in the process by making their opinions known and by testing the proposed criteria in their patient series [6]. In the past years, several investigators have evaluated the ILAR criteria and offered numerous suggestions for revision [7–18].

Based on a critical review of the accumulated evidence and his personal view, Professor Alberto Martini has proposed a refinement in the classification of childhood arthritis that would enable a better identification of clinically homogeneous entities in a recent editorial [19]. This is a summary of the points made in the editorial.

The demonstration of the prominent activation of the innate immune system and of the major pathogenic role played by interleukin (IL)-1 suggests that systemic JIA is an autoinflammatory disease of polygenic origin. This illness should be regarded as a syndrome, rather than as a single disease, encompassing a heterogeneous group of disorders sharing autoinflammatory pathways. The disease spectrum should include those patients who present with the same systemic features as seen in systemic JIA, even if such patients never develop arthritis (and, therefore, do not fit the ILAR criteria for systemic JIA [5]). As the identical extra-articular features suggest that this condition is closely related to systemic JIA despite the lack of arthritis, and by analogy with adult-onset Still's disease whose diagnosis does not require the presence of arthritis, systemic arthritis could be renamed Still's disease.

The large majority of patients with oligoarthritis are part of a seemingly homogeneous disease entity, which is seen only in children and is characterized by several common features, including asymmetry of arthritis, early onset (before 6 years of age), female predilection, positive antinuclear antibodies (ANA), high risk for developing chronic iridocyclitis, and consistent human leukocyte antigen (HLA) associations. Although the ILAR classification distinguishes two categories of oligoarthritis, based on the course of arthritis after the first 6 months of disease, ANA-positive patients with either persistent or extended oligoarthritis have been found to share similar characteristics, suggesting that they represent the same disease, differing only in the number of joints involved over time [16,17].

Robust evidence has been provided to suggest that a portion of patients who possess the same clinical features are incorrectly classified as RF-negative polyarthritis on the basis of a difference in the spread of arthritis, or as PsA because of the presence of psoriasis or particular psoriatic features [16,18]. Notably, previous studies have demonstrated that the reliability of clinical examination of joints in children with JIA is poor [20]. Furthermore, a high prevalence of subclinical synovitis, as detected by ultrasound, has been found in children with JIA. Some patients labeled as having oligoarthritis, or found to have no synovitis on clinical evaluation, were determined to have polyarthritis with the use of ultrasound [21]. These observations have led us to postulate that all

patients who share the above features be grouped into a new category of ANA-positive, early-onset arthritis, irrespective of the number of affected joints or the presence of psoriasis [16–18]. This proposal was corroborated by a gene expression study in oligoarticular and polyarticular JIA, which showed that patients with early-onset (≤ 6 years) arthritis are marked by a B-cell signature independent of the number of joints involved [22]. In addition, high-resolution HLA class I and class II typing found similarities between early-onset oligoarticular and polyarticular JIA [23].

Once patients with early-onset, ANA-positive arthritis are removed from the criteria, the RF-negative polyarthritis category would mainly comprise patients with an ANA-negative, symmetric polyarthritis – a condition similar to the adult counterpart. Similarly, if patients with early-onset, ANA-positive arthritis are excluded from the PsA category (see below) the remainder would be those with the same characteristics as adult PsA.

Enthesitis-related arthritis (ERA) is not specific to childhood but is a type of undifferentiated spondyloarthritis. Most patients are HLA-B27-positive and a variable percentage of these patients experience involvement of the sacroiliac joints during the disease course. All forms of spondyloarthritis observed in adults can occur in children, and the major difference between the adult and pediatric populations is the much greater proportion of undifferentiated spondyloarthritis in childhood. For these reasons, Professor Martini suggested abandoning the term ERA and using similar nomenclature to that used for adults by placing the prefix juvenile before each form of spondyloarthritis (eg, juvenile undifferentiated spondyloarthritis and juvenile ankylosing spondylitis).

The category of PsA, as defined by the Vancouver criteria [24], is also heterogeneous [16,25] as it comprises two rather different populations of patients: one that belongs to the ERA category and constitutes, as with adult PsA, a form of spondyloarthritis; and another that possesses the same aforementioned characteristics of ANA-positive, early-onset arthritis [16,18]. The main difference with the latter patient group is that patients with PsA have a tendency to develop dactylitis, have a higher frequency of arthritis involving wrists and small joints of the hands and feet, and may have a greater susceptibility to progress to

polyarticular disease in the absence of effective therapies [26]. The ILAR criteria for PsA, which exclude patients with enthesitis, preclude the identification of those patients who have a form of PsA similar to that seen in adults [27]. Thus, the association of psoriasis with arthritis does not define a unique entity. Various hypotheses, although not mutually exclusive, can be formulated to explain these observations. First, PsA in children constitutes a distinctive although not yet well characterized disease. Second, the presence of psoriasis enhances the susceptibility of the patient to arthritis or modifies the clinical phenotype of a particular JIA subset. Third, the association of both psoriasis and arthritis in some patients is just coincidental [16].

Future advances in the classification of JIA will probably be fostered by immunologic, genomic, and proteomic studies of the different categories as well as by the analysis of the patterns of response to cytokine inhibitors. Such investigations will help to unravel the heterogeneity of the current disease categories and strengthen the previous attempts to identify more homogeneous subgroups. For example, genomic studies have shown that a cluster of genes related to cellular immunity and myeloid cell lineage are expressed more distinctly in patients with late-onset oligoarthritis [22]. More recently, cytokine profiling at disease onset was found to support the classification of young ANA-positive patients as a separate category [28]. The evaluation of the effectiveness of anakinra in patients with systemic arthritis has led us to identify a subset of patients who are exquisitely sensitive to IL-1 blockade, supporting the hypothesis that systemic arthritis represents a heterogeneous group of disorders, some of which may be autoinflammatory in nature [29]. By using probabilistic principal components analysis, meaningful biologic and clinical characteristics, including levels of proinflammatory cytokines and measures of disease activity, were found to define axes/indicators that identified homogeneous patient subgroups by cluster analysis [30].

Altogether, the above issues make it clear that different diseases are responsible for chronic arthritis in children, as in adults. With the exception of early-onset ANA-positive arthritis, which is specific to childhood, all of the different types seem to represent the pediatric counterpart of diseases seen also in adults. This has led Professor Martini to propose

abandonment of the term JIA because it implies the misleading concept that JIA is a single disease and that the diverse subtypes just represent phenotypic variants [19].

References

- 1 Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton 2001. *J Rheumatol*. 2004;31:390-392.
- 2 Brewer EJ JR, Bass J, Baum J, et al. Current proposed revision of JRA criteria. *Arthritis Rheum*. 1977;20:195-199.
- 3 Wood P. Special Meeting on: nomenclature and classification of arthritis in children. In: Munthe E, ed. *The Care of Rheumatic Children*. Basle, Switzerland: EULAR Publisher; 1987:47-50.
- 4 Fink CW. Proposal for the development of classification criteria for idiopathic arthritides of childhood. *J Rheumatol*. 1995;22:1566-1569.
- 5 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.
- 6 Petty RE. Classification of childhood arthritis: a work in progress. *Baillieres Clin Rheumatol*. 1998;12:181-190.
- 7 Ramsey SE, Bolaria RK, Cabral DA, Malleson PN, Petty RE. Comparison of criteria for the classification of childhood arthritis. *J Rheumatol*. 2000;27:1283-1286.
- 8 Foeldvari I, Bidde M. Validation of the proposed ILAR classification criteria for juvenile idiopathic arthritis. *J Rheumatol*. 2000;27:1069-1072.
- 9 Fantini F. Classification of chronic arthritides of childhood (juvenile idiopathic arthritis): criticisms and suggestions to improve the efficacy of the Santiago-Durban criteria. *J Rheumatol*. 2001;28:456-459.
- 10 Hofer MF, Mouy R, Prieur AM. Juvenile idiopathic arthritides evaluated prospectively in a single center according to the Durban criteria. *J Rheumatol*. 2001;28:1083-1090.
- 11 Krumrey-Langkammerer M, Hafner R. Evaluation of the ILAR criteria for juvenile idiopathic arthritis. *J Rheumatol*. 2001;28:2544-2547.
- 12 Merino R, De Inocencio J, Garcia-Consuegra J. Evaluation of ILAR classification criteria for juvenile idiopathic arthritis in Spanish children. *J Rheumatol*. 2002;28:2731-2736.
- 13 Berntson L, Fasth A, Andersson-Gare B, et al. Construct validity of ILAR and EULAR criteria in juvenile idiopathic arthritis: a population based incidence study from the Nordic countries. *J Rheumatol*. 2001;28:2737-2743.
- 14 Berntson L, Fasth A, Andersson-Gare B, et al. The influence of heredity for psoriasis on the ILAR classification of juvenile idiopathic arthritis. *J Rheumatol*. 2002;29:2454-2458.
- 15 Burgos-Vargas R, Rudwaleit M, Sieper J. The place of juvenile onset spondyloarthropathies in the Durban 1997 ILAR classification criteria of juvenile idiopathic arthritis [editorial]. *J Rheumatol*. 2002;29:869-874.
- 16 Martini A. Are the number of joints involved or the presence of psoriasis still useful tools to identify homogeneous entities in juvenile idiopathic arthritis? *J Rheumatol*. 2003;30:1900-1903.
- 17 Ravelli A, Felici E, Magni-Manzoni S, et al. Patients with antinuclear antibody-positive juvenile idiopathic arthritis constitute a homogeneous subgroup irrespective of the course of joint disease. *Arthritis Rheum*. 2005;52:826-832.
- 18 Ravelli A, Varnier GC, Oliveira S, et al. Antinuclear-antibody-positive patients should be grouped as a separate category in the classification of juvenile idiopathic arthritis. *Arthritis Rheum*. 2011;63:267-275.
- 19 Martini A. It is time to rethink juvenile idiopathic arthritis classification and nomenclature. *Ann Rheum Dis*. 2012;71:1437-1439.

- 20 Guzman J, Burgos-Vargas R, Duarte-Salazar C, Gomez-Mora P. Reliability of the articular examination in children with juvenile rheumatoid arthritis: interobserver agreement and sources of disagreement. *J Rheumatol*. 1995;22:2331–2336.
- 21 Magni-Manzoni S, Epis O, Ravelli A, et al. Comparison of clinical versus ultrasound-determined synovitis in juvenile idiopathic arthritis. *Arthritis Rheum*. 2009;61:1497–1504.
- 22 Barnes MG, Grom AA, Thompson SD, et al. Biologic similarities based on age at onset in oligoarticular and polyarticular subtypes of juvenile idiopathic arthritis. *Arthritis Rheum*. 2010;62:3249–3258.
- 23 Hollenbach JA, Thompson SD, Bugawan TL, et al. Juvenile idiopathic arthritis and HLA class I and class II interactions and age-at-onset effects. *Arthritis Rheum*. 2010;62:1781–1791.
- 24 Southwood TR, Petty RE, Malleson PN, et al. Psoriatic arthritis in children. *Arthritis Rheum*. 1989;32:1007–1013.
- 25 Stoll ML, Zurakowski D, Nigrovic LE, Nichols DP, Sundel RP, Nigrovic PA. Patients with juvenile psoriatic arthritis comprise two distinct populations. *Arthritis Rheum*. 2006;54:3564–3572.
- 26 Nigrovic PA, Sundel RP, Petty RE. Juvenile psoriatic arthritis. In: Cassidy JT, Petty RE, Laxer RM, Lindsley CB, eds. *Textbook of Pediatric Rheumatology*. 6th edn. Philadelphia, PA: Elsevier Saunders; 2011;287–297.
- 27 Stoll ML, Lio P, Sundel RP, Nigrovic PA. Comparison of Vancouver and International League of Associations for rheumatology classification criteria for juvenile psoriatic arthritis. *Arthritis Rheum*. 2008;59:51–58.
- 28 van den Broek T, Hoppenreijns E, Meerding J, et al. Cytokine profiling at disease onset: support for classification of young antinuclear antibody-positive patients as a separate category of juvenile idiopathic arthritis. *Ann Rheum Dis*. 2015;74:470–472.
- 29 Gattorno M, Piccini A, Lasigliè D, et al. The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum*. 2008;58:1505–1515.
- 30 Eng SW, Duong TT, Rosenberg AM, Morris Q, Yeung RS. The biologic basis of clinical heterogeneity in juvenile idiopathic arthritis. *Arthritis Rheum*. 2014;66:3463–3475.

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