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EDITORIAL

# Classification criteria for chronic arthritis in children: a work in progress

Lamot L[1,2], Ravelli A[3,4]

*"What's in a name? That which we call a rose,*
*By any other word would smell as sweet."*

The admired adage from William Shakespeare's play Romeo and Juliet is probably not true only for sweet matters of love, but also for bitter concerns of diseases, which is perfectly illustrated by the example of chronic arthritis in children, a group of diseases in which nomenclature and criteria heterogeneity lasted until late 1990s, when the term juvenile idiopathic arthritis (JIA) was introduced[1]. Before that, two classification systems were proposed separately in the 1970s by the American college of Rheumatology (ACR) and the European League Against Rheumatism (EULAR). This disparity introduced many inconsistencies, which were often source of confusion[2, 3]. Even the name proposed for the disease was different: the ACR criteria used the term juvenile rheumatoid arthritis, whereas the EULAR called it juvenile chronic arthritis. Nevertheless, the two systems laid a ground for the basic criteria used to define this heterogeneous group of diseases, such as the age limit, the disease duration necessary for diagnosis and the characteristics of arthritis and extraarticular disease. They also provided the definition for active arthritis, as the presence of swelling due to synovitis or, if swelling was absent or not detectable, as the association of tenderness or pain on motion and limitation of motion, thus emphasising the importance of physical examination. Nonetheless, the two classification criteria differed in several important aspects, including the duration of arthritis necessary for diagnosis (six weeks in ACR criteria and three months in EULAR criteria), the recognition of separated categories for juvenile ankylosing spondylitis, psoriatic arthropathy and arthropathies associated with inflammatory bowel disease in EULAR criteria, and the need to demonstrate RF positivity for juvenile rheumatoid arthritis in ACR criteria[4].

Considering these drawbacks, it is not surprising that in 1995 a Classification Taskforce was created within the Pediatric Standing Committee of the International League Against Rheumatism (ILAR), which was committed to propose a new classification for idiopathic arthritides of childhood[1]. The main aim of the novel criteria was to define homogeneous categories within the disease spectrum in order to facilitate clinical and basic research, as well as to eliminate the discrepancies resulting from the application of ACR and EULAR classifications. Although many elements of the previous criteria were maintained, the new criteria introduced the use of exclusion criteria to abolish overlap between disease subtypes and foster homogeneity within the six outlined categories, which included systemic JIA, persistent and extended oligoarthritis, rheumatoid factor-negative polyarthritis, rheumatoid factor-positive polyarthritis, psoriatic arthritis and enthesitis-related arthritis. A seventh category of "undifferentiated arthritis" was created, which included the forms that cannot be classified in any category or fulfil the criteria for more than one category.

Although the original ILAR criteria and the subsequent revisions[5, 6] have been widely accepted by physicians and researchers all over the world[7, 8], they have been subject to a number of criticisms[9-12]. Some are general, such as the arbitrary choice of the age at disease onset, the duration of disease needed to define a category, the number of inflamed joints that defines oligoarticular and polyarticular categories, and the clinical, rather than US or MRI, definition of joint inflammation, while others pertain to particular categories. Specifically, many authorities have emphasized that systemic JIA should be regarded as an autoinflammatory disease outside the JIA spectrum. Moreover, it has been argued that a substantial number of patients with systemic JIA develop arthritis more than six months after the onset of fever, which prevents them from meeting the ILAR criteria for the systemic or any other forms of JIA in the initial stage. Regarding the polyarticular category, a debate is ongoing as to whether anti-CCP antibodies, a marker of the disease in adult rheumatoid arthritis (RA), should be part of the criteria, the presence of two positive RF tests should be mandatory for the diagnosis, and positive serology should be prioritized over the number of affected joints. Many investigators have suggested to use antinuclear anti-

[1]Department of Pediatrics, University Hospital Center Zagreb, Zagreb, Croatia; [2]Department of Pediatrics, University of Zagreb School of Medicine, Zagreb, Croatia; [3]Department of Neuroscience, Rehabilitation, Ophtalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, 16147 Genoa, Italy; [4]Scientific Direction, IRCSS Istituto Giannina Gaslini, 16147 Genoa, Italy.

**Correspondence to:** Lovro Lamot
E-mail: lovro.lamot@gmail.com

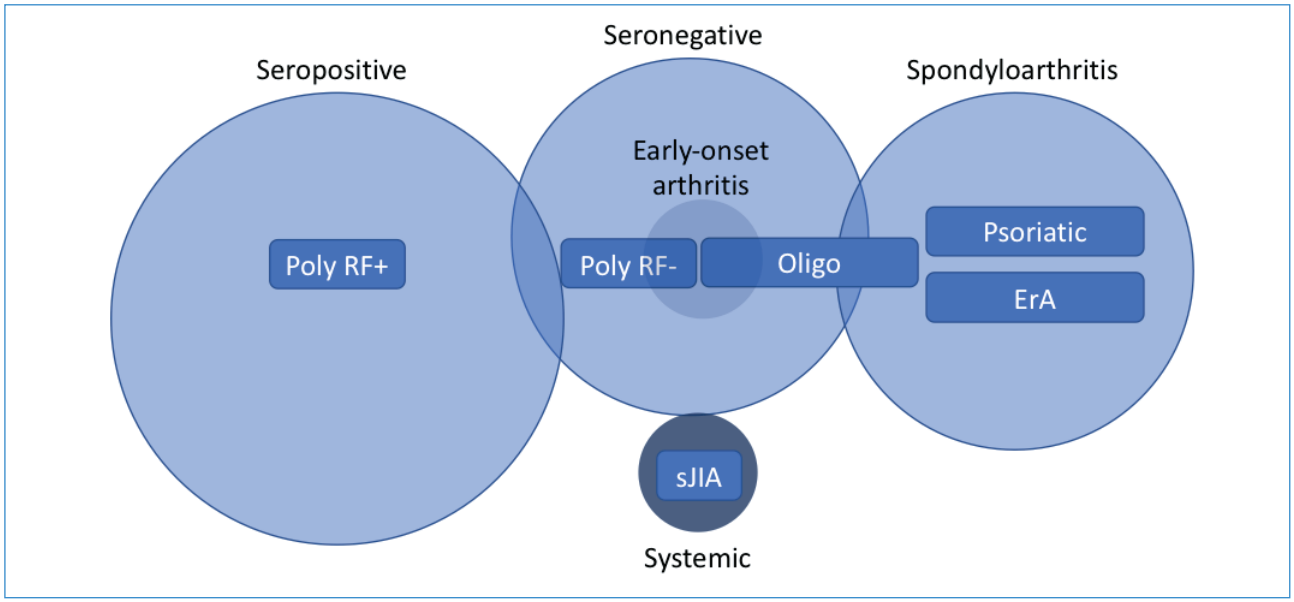


**Figure 1.** Clusters of arthritis in children and adults. The current ILAR categories of arthritis in children are shown in boxes, while the categories of arthritis in adults are written beside the circles. Early-onset arthritis is placed as a subcategory within seronegative arthritis.
Adapted from: Nigrovic PA, Raychaudhuri S, Thompson SD. Review: Genetics and the Classification of Arthritis in Adults and Children. Arthritis Rheumatol. 2018;70(1):7-17.

bodies (ANA) as classification criterion, because their positivity identifies a disease subset with several shared characteristics, which include early age of onset, female predominance, asymmetry in affected joints and risk for chronic iridocyclitis[13].

The ILAR categories whose definition is most challenging are probably juvenile psoriatic arthritis and enthesitis related arthritis, which aim to enclose the majority of patients with juvenile spondyloarthritis[14]. However, due to issue of mutually exclusive criteria, patients who present with both signs of psoriasis and spondyloarthritis are categorized as having undifferentiated arthritis. Moreover, it has been argued that onset of arthritis and psoriasis is not always synchronous and that the family history of psoriasis might be difficult to verify. Besides, some important forms of the disease, such as inflammatory bowel disease (IBD)-related arthritis, reactive arthritis (ReA), and juvenile ankylosing spondylitis (jAS) are not addressed by ILAR criteria. Finally, many studies have shown the superiority of various imaging modalities, most notably MRI, for the early detection of sacroiliitis, while per the ILAR criteria only the presence of clinical signs is requested.

Although two revisions of ILAR criteria have been issued in the past 27 years[5, 6], they have failed to address the concerns raised about the heterogeneity of some disease categories. Numerous reports have provided suggestions on how ILAR criteria should be modified to take into account the emerging genetic, transcriptomic, and proteomic data obtained in children with chronic arthritis[11, 12]. Importantly, a revision of the criteria should facilitate the transition of paediatric patients who enter the late adolescence/early adulthood to the care of adult rheumatologists, who are used to diagnose the majority of their patients with inflammatory arthritis as seronegative or seropositive RA, and may find it difficult to understand the complex categorization of childhood arthritides into six mutually exclusive categories plus the category of undifferentiated arthritis. With the aim of harmonizing the paediatric and adult approaches, the distinction based of an age threshold has been questioned and the creation of clusters based on the application of human genetics has been suggested (Figure 1). The new classification criteria for JIA, proposed by Pediatric Rheumatology International Trials Organization (PRINTO) are well in line with this way of thinking[15]. By these criteria, JIA comprises a group of inflammatory disorders that begin before 18 years of age and persist for at least 6 weeks, diagnosed after the exclusion of other known conditions. The categories outlined by this classification are “systemic JIA”, which is thought to be equivalent to adult-onset Still’s disease, “RF-positive JIA”, which is considered superimposable to seropositive RA, “enthesitis/spondylitis-related JIA”, which is equated to undifferentiated SpA, and “early-onset ANA-positive JIA”, a form that is distinctive of children and does not have a counterpart in adults. The new criteria maintained the categories

for misfits, which included "other JIA", including the forms that do not fit the criteria for the other categories, and "unclassified JIA", including the forms that meet the criteria for more than one category. While formal validation of these criteria is under way, the ongoing basic/translational and clinical studies will help make the future classification of childhood arthritides more rational and precise.

## REFERENCES


1. Fink CW. Proposal for the development of classification criteria for idiopathic arthritides of childhood. J Rheumatol. 1995;22(8):1566-9.
2. Criteria for the classification of juvenile rheumatoid arthritis. Bull Rheum Dis. 1972;23(5):712-9.
3. Nomenclature and Classification of Arthritis in Children. European League Against Rheumatism, EULAR Bulletin No 4. 1977.
4. Petty RE, Laxer RM, Wedderburn LR. Chapter 15 - Juvenile Idiopathic Arthritis. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, editors. Textbook of Pediatric Rheumatology (Seventh Edition). Philadelphia: W.B. Saunders; 2016. p. 188-204.e6.
5. Petty RE, Southwood TR, Baum J, Bhettay E, Glass DN, Manners P, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol. 1998;25(10):1991-4.
6. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31(2):390-2.
7. Foeldvari I, Bidde M. Validation of the proposed ILAR classification criteria for juvenile idiopathic arthritis. International League of Associations for Rheumatology. J Rheumatol. 2000;27(4):1069-72.
8. Merino R, de Inocencio J, Garcia-Consuegra J. Evaluation of revised International League of Associations for Rheumatology classification criteria for juvenile idiopathic arthritis in Spanish children (Edmonton 2001). J Rheumatol. 2005;32(3):559-61.
9. Martini A. Are the number of joints involved or the presence of psoriasis still useful tools to identify homogeneous disease entities in juvenile idiopathic arthritis? J Rheumatol. 2003;30(9):1900-3.
10. Duffy CM, Colbert RA, Laxer RM, Schanberg LE, Bowyer SL. Nomenclature and classification in chronic childhood arthritis: time for a change? Arthritis Rheum. 2005;52(2):382-5.
11. Martini A. It is time to rethink juvenile idiopathic arthritis classification and nomenclature. Ann Rheum Dis. 2012;71(9):1437--9.
12. Nigrovic PA, Raychaudhuri S, Thompson SD. Review: Genetics and the Classification of Arthritis in Adults and Children. Arthritis Rheumatol. 2018;70(1):7-17.
13. Ravelli A, Felici E, Magni-Manzoni S, Pistorio A, Novarini C, Bozzola E, 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(3):826-32.
14. Tse SM, Laxer RM. New advances in juvenile spondyloarthritis. Nat Rev Rheumatol. 2012;8(5):269-79.
15. Martini A, Ravelli A, Avcin T, Beresford MW, Burgos-Vargas R, Cuttica R, et al. Toward New Classification Criteria for Juvenile Idiopathic Arthritis: First Steps, Pediatric Rheumatology International Trials Organization International Consensus. J Rheumatol. 2019;46(2):190-7.