Editorial

The Place of Juvenile Onset Spondyloarthropathies in the Durban 1997 ILAR Classification Criteria of Juvenile Idiopathic Arthritis

Under the organization of the International League of Associations for Rheumatology (ILAR), a group of experts in pediatric rheumatology have developed and reviewed a new classification for the various forms of arthritis in children[1,2]. Originally, their main goal was to develop criteria that would enable the identification of homogeneous groups of children with chronic arthritis to facilitate research in immunogenetics and other basic sciences, epidemiology, outcome studies, and therapeutic trials. Despite its worldwide use, the American College of Rheumatology (ACR) diagnostic criteria for juvenile rheumatoid arthritis (JRA)[3] and the European League Against Rheumatism (EULAR) classification criteria for juvenile chronic arthritis (JCA)[4] had to be improved[5].

The ILAR classification of juvenile idiopathic arthritis (JIA) developed in Durban in 1997[2] includes 7 subgroups, which are clinically identifiable by 6 months of disease: (1) systemic arthritis, (2) oligoarthritis, (3) polyarthritis (rheumatoid factor negative), (4) polyarthritis (rheumatoid factor positive), (5) enthesitis related arthritis, (6) psoriatic arthritis (PsA), and (7) other arthritis. According to various studies, the ILAR classification performs well when compared with ACR and EULAR classifications; and even most children with idiopathic arthritis fit quite well into the different ILAR subgroups. Most of the studies, however, have found difficulties regarding the subgroup of enthesitis related arthritis (ERA). These difficulties mainly refer to children having enough criteria to be considered in the ERA subgroup and children fulfilling the European Spondylarthropathy Study Group (ESSG) classification criteria of the spondyloarthropathies (SpA)[6] who are ultimately classified into another JIA subgroup because of ERA exclusion criteria or the simultaneous fulfillment of more than one JIA classification criteria.

In this regard, the possibility that the one classification does not correspond to the other and that children and adolescents with SpA may not be appropriately classified is of major concern. Discrepancies between the 2 sets of criteria would probably increase the gap between juvenile and adult onset SpA concepts and counter the original goal of ILAR. We have therefore undertaken to analyze reports on the performance of ILAR classification of JIA in regard to the ERA subgroup in children with arthritis and have identified points of controversy. Consequently, we propose alternatives to solve these problems. In general, data regarding all other subgroups are not analyzed in this study unless indicated otherwise.

STUDIES ANALYZING THE ERA CRITERIA IN CHILDREN WITH JIA CLASSIFIED ACCORDING TO ILAR

Three studies have analyzed the ERA subgroup of children with JIA without comparing ILAR criteria[2] with ESSG criteria[6] (Table 1). In the Cleary, *et al*[7] study, the charts of 57 patients with HLA-B27 associated JCA were classified according to ILAR criteria identifying 30 (52.6%) patients who fulfilled ERA criteria based on the inclusion criteria. Interestingly, there was only one patient in the group who had SpA as diagnosis based on enthesitis; all the other 56 children had been classified into the JCA pauciarticular, polyarticular, or systemic subgroups. Krumrey-Langkammerer, *et al*[8] and Hofer, *et al*[9] studies found 22 and 31 children with positive findings for ERA among 145 and 194 with JIA according to ILAR[2]. In Krumrey-Langkammerer, *et al*[8], 11 children fulfilled criteria for the category "other arthritis" based on oligoarthritis or polyarthritis (rheumatoid factor negative). Apparently, there were 5 other children not included in the ERA subgroup because of psoriasis in the family, but data is unclear. Six patients in Hofer, *et al*[9] have either systemic features or psoriasis in the family which excluded them from ERA

Table 1. Studies analyzing the subgroup of children fulfilling ERA diagnostic criteria.

Criteria Fulfilled	Cleary[7†] n (%)	Krumrey-Langkammerer[8] n (%)	Hofer[9] n (%)
A. ERA inclusion*	30 (100.0)	22 (100.0)**	31 (100.0)
B. ERA exclusion	6 (20.0)	NM	6 (19.3)
Systemic features	0	NM	3 (9.7)
Psoriasis in the family	6 (20.0)	NM	3 (9.7)
C. Other arthritis	7 (23.3)	11 (50.0)	12 (38.7)
Oligoarthritis	0	NM	4 (12.9)
Seronegative polyarthritis	7 (23.3)	NM	8 (25.8)
"True" ERA cases: a – b + c	17 (56.7)	11 (50.0)	13 (41.9)

† HLA-B27 positive children with juvenile chronic arthritis. * In the end not all cases were considered to have ERA because some had exclusion criteria or fulfilled other arthritis criteria. ** At least 22 patients fulfilled ERA; date uncertain. NM: not mentioned.

(Table 1). Twelve patients (38.7%) in the same study fulfilled one additional subgroup criterion and were therefore considered to be in the "other arthritis" subgroup. Remarkably, only 17 (56.7%) children in Cleary, *et al*[7] and 13 (41.9%) in Hofer, *et al*[9] remained in the ERA classification subgroup after considering exclusion criteria or the other arthritis classification category.

STUDIES COMPARING ERA CRITERIA IN THE ILAR CLASSIFICATION AND THE ESSG CRITERIA FOR THE CLASSIFICATION OF SPA

Foeldvari and Bidde[10] and Ramsey, *et al*[11] studies found high concordance between ESSG criteria and ERA criteria (Table 2). Ten out of 11 patients with SpA by ESSG criteria in the former study [10] and 8 of 9 in the latter[11] fulfilled ERA criteria. At the other end of the spectrum, Merino, *et al*[12] and Fantini[13] found 47.0% and 37.3% agreement between the 2 sets of criteria in 17 and 59 patients with SpA according to ESSG, respectively. Figures in such studies represent the "true" number of cases fulfilling ERA criteria once those having any of the 2 listed exclusions and cases fitting the "other arthritis" category were eliminated from the ERA subgroup.

There were 3 patients, one each in Foeldvari and Bidde[10], and Ramsey, *et al*[11], and 2 in Merino, *et al*[12], having the exclusion criteria referring to family history of psoriasis. In addition, 4 more cases, one in the former[10] and 6 in the latter[12] studies, were classified into the other arthritis subgroup. Fantini[13] did not specifically mention the fate of 37 children with SpA who did not fulfill the ERA criteria. However, that 157 (23%) of 683 with chronic arthritis included in the analysis fell into the other arthritis subgroup because they did not fit any category (n = 98) or because they fit more than one category (n = 59) suggests SpA patients would have the same fate.

Overall, the population and study methods differ from one study to another. In Foeldvari and Bidde[10], there were 97 children previously diagnosed according to ACR[3], ESSG[6], and the Vancouver criteria for juvenile PsA[14]; Ramsey, *et al*[11] reviewed charts of 70 children diagnosed by the same criteria; Merino, *et al*[9] included 125 children diagnosed by EULAR[4], ESSG[6], and Vancouver criteria[14]; and Fantini[13] did not mention which diagnostic criteria were used for the overall group of children included in his study, but regarding ERA, he used ESSG criteria[6].

Table 2. Studies comparing ESSG criteria for the classification of SpA and ILAR criteria for ERA subgroup.

Criteria Fulfilled	Foeldvari[10]	Ramsey[11]	Merino[12]	Fantini[13]
ESSG	11	9	17	59†
ERA inclusion* (%)	10 (90.0)	8 (88.9)	8 (47.0)	22 (37.3)
ERA exclusion	1	1	1	NM
Other arthritis	1	0	8	NM
ERA but not ESSG	1	0	1	NM

† Includes subgroups: intestinal bowel disease (3), psoriatic arthritis (17), ankylosing spondylitis (10), and undifferentiated SpA (29). * In the end, not all cases were considered to have ERA because some had exclusion criteria or fulfilled other arthritis criteria. NM: not mentioned.

THE ERA SUBGROUP IN THE ILAR CLASSIFICATION OF JIA

Diagnostic criteria for ERA include the most important clinical signs of juvenile onset SpA: enthesitis and arthritis (Table 3). Thus, children with undifferentiated SpA, specifically those with isolated forms of arthritis and the seronegative enthesopathy and arthropathy (SEA) syndrome and indeed those with AS, may be appropriately diagnosed according to these criteria. In this regard, there is no doubt on the usefulness of ERA criteria. In examining the details, however, 2 items appear contradictory: a family history of HLA-B27 associated disease as an inclusion criterion versus psoriasis in relatives as an exclusion criterion (the list of HLA-B27 associated diseases classically includes PsA). It is also interesting to note that while psoriasis in the family is on the list of ERA exclusion criteria, the presence of psoriasis in the patient is not listed as an exclusion criterion for ERA.

In addition, there is the possibility that patients with ERA may fulfill the other arthritis classification criteria and therefore be excluded from the ERA subgroup. Nearly all studies[7-10,12] found patients fulfilling ERA as well as the polyarthritis (rheumatoid factor negative) or oligoarthritis subgroup criteria. Children with SpA may present various forms of disease and even fulfill all 3 JRA types of onset[15]. Interestingly, Hofer, *et al*'s[9] comparison of patients fulfilling ERA alone, ERA and polyarthritis, and ERA and oligoarthritis criteria, based on number of diagnostic criteria, found no significant differences between groups in regard to age at onset, male to female ratio, or prevalence of HLA-B27.

Table 3. ILAR proposed classification criteria for juvenile idiopathic arthritis: enthesitis related arthritis subgroup[2].

Arthritis and enthesitis or
Arthritis or enthesitis with at least 2 of
- A. Sacroiliac joint tenderness and/or inflammatory spinal pain
- B. Presence of HLA-B27
- C. Family history in at least one first or second degree relative of medically confirmed HLA-B27 associated disease
- D. Anterior uveitis that is usually associated with pain, redness, or photophobia
- E. Onset of arthritis in a boy after age 8 years

Exclusions
1. Psoriasis confirmed by a dermatologist in at least one first or second degree relative
2. Presence of systemic arthritis (as defined in the criteria)

JUVENILE SPA NOT INCLUDED, YET EXCLUDED FROM ILAR CLASSIFICATION

Two issues represent a major problem in the ILAR classification in regard to juvenile onset SpA. One is the exclusion of children with a family history of psoriasis and the other is the absence of reactive arthritis (ReA) and inflammatory bowel disease (IBD) as forms of SpA.

Psoriatic arthritis. There is evidence that juvenile onset PsA, as a whole, represents a particular form of juvenile arthritis[14,16-18]. The comparison of juvenile PsA with juvenile onset ankylosing spondylitis (AS) and JRA shows significant differences, especially in the prevalence of HLA-B27, enthesopathy, and axial disease[14]. Yet, most series on juvenile PsA have found a variable proportion of patients with the most characteristic features of SpA or even AS[14,16,19,20].

Shore and Ansell's study[16] of 60 patients with juvenile PsA found radiographic abnormalities of the sacroiliac joints (SI) in 20 patients followed up for 8 years; 8 children, 4 of them with radiographic sacroiliitis, had low back pain and restricted spinal movement. The prevalence of HLA-B27 in the group of patients with SI radiographic changes was increased. Southwood, *et al*[14] found involvement of the SI joints and the spine in 11% each of 35 patients with juvenile PsA and enthesopathy in 13%; 5 of 8 patients with HLA-B27 had features of SpA. Interestingly, Roberton, *et al*'s[21] 6 year followup that included some patients from Southwood, *et al*[14], as well as new cases, reported a lower incidence of SI (5%) and spinal involvement (2%), but no patients with enthesopathy or SpA. Despite not being statistically significant, the prevalence of HLA-B27 in both studies was increased. In Hamilton, *et al*[19], the prevalence of ≥ 2 grade radiographic sacroiliitis was 30% and 2 of 4 patients had syndesmophytes, but no increase of HLA-B27 prevalence. Truckenbrodt and Häfner[20] considered that the pattern of arthritis in 33 of 48 patients with juvenile PsA corresponded to type II oligo JRA[22]: 15 of 33 had HLA-B27, 12 had enthesopathy, and 8 sacroiliitis. The prevalence of HLA-B27 found by Ansell, *et al*[23] in a greater number of patients (n = 70) was 20% versus 6% in controls ($p_c = 0.04$).

In regard to family history of psoriasis, nearly all studies have excluded patients from the group of SpA according to the ESSG[6] or ERA subgroup because of psoriasis in first or second degree relatives. By combining 5 different studies[7,9,10-12], 12 (12.2%) of 98 patients were excluded from one or the other category because of such exclusion criteria. The Krumrey-Langkammerer, *et al*[8] data suggest that 5 of 16 patients had such a history and although Fantini[13] did not give exact figures, he refers to this criterion among those preventing classification of his cases in the ERA subgroup. Ramsey, *et al*[11], Fantini[13], and Hofer, *et al*[9] have discussed the problem of making the ERA diagnosis in children with a family history of psoriasis and have suggested modifications. In contrast to Southwood, *et al*[14], preliminary data from a multicenter study in Europe[24] suggest an increased prevalence of psoriasis in the families of children with juvenile SpA or oligoarthritis.

The inclusion of psoriasis in the family as an exclusion criterion makes the ERA consistent with one of the 3 Vancouver minor criteria for the diagnosis of juvenile PsA[2,14]. Likewise, based on the ILAR criteria, psoriasis in the family makes children with arthritis more likely to be classified as PsA rather than SpA although some may also fulfill ERA criteria. Thus, the relevance given to psoriasis in the family, even in second degree relatives, is greater than that given to the child's clinical picture.

Reactive arthritis. The reactive arthritides comprise a number of diseases following various types of infections, including those triggered by *Chlamydia*, *Salmonella*, *Yersinia*, *Shigella*, or *Campylobacter*. The type of ReA that follows infection by these bacteria presents as a form of undifferentiated SpA or Reiter's syndrome, which over the long term may evolve into AS, particularly in HLA-B27 positive patients[25-27]. ReA and Reiter's syndrome therefore have been members of the SpA group.

The ILAR classification does not include ReA as part of JIA and ERA[2]. The reason seems clear: the ILAR classification only considers diseases currently having no known cause, i.e., "idiopathic" arthritis. In this case, the importance given to idiopathic is greater than that to clinical features or the relation between HLA-B27 associated forms of ReA and SpA. In general, the term ReA also seems confusing because it implies that the isolation and identification of the disease triggering bacteria have been carried out. However, the search for bacteria is only successful in a small proportion of patients, which means that many patients with ReA actually have an idiopathic form of the disease. Attempts to establish the role of diagnostic tests[28] as well as diagnostic and classification criteria have been made[29,30]. Diagnostic tests may identify the etiologic agent in about 50% of the cases depending on the clinical picture and tests selected[31,32]. Diagnosis of ReA in children has usually been made in patients developing arthritis or Reiter's syndrome after a specific episode of infection or those having positive serological tests against bacteria[33]. As seen in adults, children with ReA or Reiter's syndrome may have a chronic course and evolve to AS[34-36]. On the other hand, bacterial DNA has been identified in synoviaI fluid cells of patients with long-standing juvenile onset AS or undifferentiated SpA[37]. In this sense, ReA constitutes a link rather than an exclusion to ERA and SpA.

Inflammatory bowel disease. In the ILAR criteria, IBD appears only as descriptor of ERA, but the term is not defined. As seen in adults, IBD in children with SpA may consist of non-specific inflammatory changes or Crohn's disease and ulcerative colitis. The former is frequently found in patients with no gut symptoms. The 2 latter forms are rare, but may be clearly associated with HLA-B27,

undifferentiated SpA, or even AS. In any case, IBD should be considered a subgroup of juvenile onset SpA. Fantini[13], described 3 patients with IBD in his study.

The ESSG criteria. ESSG criteria are intended to cover the whole spectrum of SpA, especially early undifferentiated cases[6]. In contrast to ILAR, the ESSG criteria encompass all subgroups of SpA including PsA, ReA, and IBD associated arthritis (Table 4). The definition provided for family history in the ESSG criteria includes AS, psoriasis, acute uveitis, ReA, and IBD.

Prieur, *et al*[38] evaluated the performance of ESSG criteria in 310 children seen prospectively in one center. The study included 33 patients with definite SpA (AS, PsA, IBD associated arthritis and undifferentiated forms) and 19 with possible SpA because of isolated signs of disease. Although sensitivity reached 69.7%, specificity was 92.2%, resulting in 89.7% accuracy in definite cases (in possible cases, sensitivity was lower). Sensitivity and accuracy increased to 78.7% and 90.3%, respectively, in a large multicenter study including 2982 European children with rheumatic diseases conducted by the same author[39]. Except for sensitivity, all other parameters were very close to those reported in the adult population[40]. As expected, however, the item "inflammatory back pain" had the lowest sensitivity (9.1%) in that study[38]. Along with ESSG criteria, Prieur, *et al*[38,39] assessed performance of other sets of criteria, including the Amor, *et al*[41] criteria for the classification SpA, with results quite similar to the ESSG.

RECOMMENDATIONS TO RESOLVE PROBLEMS ARISING WITH ERA CLASSIFICATION CRITERIA

Based on the analysis of ERA and according to the studies reported thus far, there seem to be 2 important problems:

Table 4. ESSG classification criteria for the spondyloarthropathies[6].

Inflammatory spinal pain or
Synovitis, asymmetric or predominantly lower limbs and
One or more of the following criteria

1. Positive family history
2. Psoriasis
3. Inflammatory bowel disease
4. Urethritis, cervicitis, or acute diarrhea within one month before arthritis
5. Buttock pain alternating between right and left gluteal areas
6. Enthesopathy
7. Sacroiliitis

one relates to ERA performance within the ILAR classification criteria and another to ERA and ESSG equivalence as classification criteria. These problems are mainly related to exclusion criteria, and on the other hand, to the possibility that patients with ERA fulfill another diagnostic category and therefore can be classified in the other arthritis subgroup.

Exclusion criteria. The criterion of psoriasis in at least one first or second degree relative on the list of exclusions for ERA does not seem entirely justified. We recommend deleting this item from the ERA exclusion list.

If PsA in the patient is considered an exclusion criterion for ERA, it should then be required that neither clinical signs of SpA nor HLA-B27 are present.

ERA fulfilling another diagnostic category. Oligoarthritis or polyarthritis (rheumatoid factor negative) overlapping with ERA account for most of the cases classified as other arthritis. Our recommendation in this case is to include all minor inclusion criteria for ERA (items A to E, Table 3) in the exclusion criteria list of oligoarthritis or polyarthritis (rheumatoid factor negative). Previously, Hofer, *et al*[9] recommended the addition of enthesitis or sacroiliitis in a boy over 8 years of age to the list of criteria for polyarthritis (rheumatoid factor negative).

ERA and ESSG equivalence. The ERA and ESSG criteria appear to match each other well. ERA criteria include the combination of enthesitis and arthritis as a single and major criterion, or alternatively, one of these in combination with other characteristic data of juvenile onset SpA. ESSG criteria also include the most important features of children with early onset SpA, but inflammatory back pain becomes first in rank order and enthesopathy is only a minor criterion. Therefore a child with isolated enthesitis and a positive family history of HLA-B27 associated disease could not be classified as SpA.

In this context, both sets of criteria may properly classify children with SpA, but ERA criteria correspond better to the clinical picture of juvenile onset SpA because the relevance of enthesopathy in the whole group is much greater than inflammatory back pain, an infrequent event in children with recent onset SpA[42,43]. Likewise, the role of HLA-B27 in classifying children could be more relevant than in adults with SpA. Other differences between the 2 sets of criteria, for example, the role of uveitis, age at onset and gender in ERA, are minor.

Table 5. Performance of the ESSG classification criteria in children (Prieur, 1993 and 1992) and adult populations (Amor, 1991).

Author	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Likelihood Ratio	Accuracy
Prieur[38], (n = 310)	69.7	92.2	53.5	96.0	9.1	89.7
Prieur[39], (n = 2982)	78.7	92.2	58.8	96.8	85.3	90.3
Amor[40], (n = 2228)	87.1	86.4	60.3	99.2	24.1	98.8

ERA and ESSG criteria perform differently because they refer to different concepts. ERA criteria appear to restrict the classification of children to a small subgroup where PsA, ReA, and IBD associated arthritis are not considered part of the group. ESSG criteria reflect more the concept of SpA as a group of HLA-B27 diseases of the entheses and synovial joints of children sometimes having enteric or genital infections as triggers, spondylitis and sacroiliitis, or a wide spectrum of extraarticular features throughout the course of the disease[43].

Despite "growing pains," ILAR criteria for the classification of JIA reflect the interest and need for improving knowledge in the pediatric rheumatology field[44,45]. Some issues analyzed here have already been recognized by ILAR members and are the subject of further discussion. As part of this process, it is desirable to reach agreement on the SpA field boundaries and review ERA criteria. The achievement of this goal is worthwhile and will surely facilitate communication between pediatric and adult rheumatologists and indeed the understanding of SpA in the transition from childhood to adulthood.

Added in Proof: Bernston, *et al*[46], in their study of the nordic countries, validated ILAR criteria in relation to EULAR criteria in a prospective, incidence, and population based setting, and analyzed their feasibility. Two major conclusions of the paper — the low validity of ILAR criteria because of patient exclusion from subgroup classification and the possible fulfillment of 2 diagnoses per patient — concern ERA: although 35 of 321 patients with JIA fulfilled criteria for ERA inclusion, 18 (51.4%) of them had to be excluded from ERA because they fulfilled a second diagnostic category, and 5 (14.3%) had a positive family history of psoriasis. The diagnosis of 7 children with juvenile AS — either arthritis with radiographic sacroiliitis or arthritis, enthesitis, and clinical signs of sacroiliitis — was not faced with ERA.

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