

The Assessment in Spondyloarthritis International Society (ASAS) classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general: the spondyloarthritis concept in progress

Henning Zeidler,¹ Bernard Amor²

INTRODUCTION

The unifying concept initially termed *seronegative spondarthritides*, which first lumped together an interrelated yet heterogeneous group of disorders, was a pivotal step forward in the modern classification of rheumatic conditions.¹ However, classification of rheumatic diseases has evolved over the years following progress in knowledge of the clinical features, genetic predisposition, pathophysiology and aetiology of the various disorders. In this issue, Rudwaleit and colleagues² present new Assessment in Spondyloarthritis International Society (ASAS) classification criteria for peripheral spondyloarthritis (SpA) (*see article on page 15*). We will discuss the implication of this new set of classification criteria in view of the history and present state of the concept and terminology of SpA, the controversy of lumping and splitting, and the potential for the future use of the new criteria in research and clinical practice. Additionally, we put into perspective the recent elucidation of the frequency of chlamydial infections in undifferentiated SpA (uSpA) and the potential for their cure with combination antibiotic treatment, which might have implications for future classification of SpAs.

¹ Hannover Medical School, Hannover, Germany

² Department of Rheumatology, Hôpital Cochin, Paris, France

Correspondence to Professor Henning Zeidler, Wolfsburger Damm 26c, 30625 Hannover, Germany; henningzeidler@aol.com

HISTORY AND PRESENT STATE OF THE CONCEPT

The first classification criteria for ankylosing spondylitis (AS) were proposed in 1963 at the European Congress of Rheumatology in Rome based on the clinical experience of European rheumatologists, who viewed AS a disease entity separate from rheumatoid arthritis (RA), in contrast to US rheumatologists, who described rheumatoid spondylitis as a variant of RA.³ As the seminal event in the early 1970s, however, Moll *et al*¹ formulated the unified concept of seronegative polyarthritis, which they termed seronegative spondarthritides under consideration, the prefix 'spond-'emphasising the strong

association between each member of the group and AS. The diseases initially included were AS, psoriatic disease, Reiter's syndrome, the arthropathies of ulcerative colitis and Crohn's disease, Whipple's disease and Behçet syndrome with the suggested common characteristics: absence of rheumatoid factors, absence of subcutaneous nodules, peripheral arthritis, radiological sacroiliitis, with or without AS, evidence of clinical overlap, including psoriasisiform skin or nail lesions, ocular inflammation such as conjunctivitis and anterior uveitis, buccal ulceration, ulceration of small and large intestine, genital ulceration, genitourinary inflammation (particularly urethritis and/or prostatitis), erythema nodosum, pyoderma gangrenosum, thrombophlebitis and tendency to familial aggregation.

Very shortly thereafter, evidence for the concept was confirmed and enormously strengthened by the strong association with HLA-B27.⁴ Whipple's disease and Behçet syndrome, however, are no longer included in the SpAs owing to the lack of association with HLA-B27 and their possession of other additional features. On the other hand, later observations resulted in the inclusion of juvenile-onset spondyloarthritis and uSpA under the umbrella of the unified concept. Isolated anterior uveitis also may be part of the spectrum, even though it does not fulfil criteria for SpA (figure 1).

The outdated term Reiter's syndrome was replaced by reactive arthritis (ReA). The prefix '*seronegative*' was abandoned because of potential confusion with seronegative RA. Although, within the committee of pathology of the

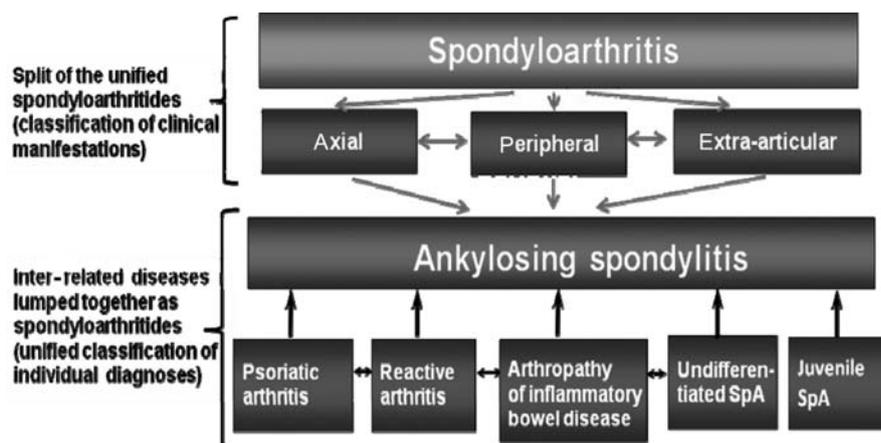


Figure 1 Complexity of inter-relationship between the new split of spondyloarthritis (SpA) according to the Assessment in Spondyloarthritis International Society classification criteria and the present family of disorders with interrelated features lumped together in the unified concept of SpA.

European League Against Rheumatism a consensus was reached and endorsed by the ASAS that the term ‘spondyloarthritis’ is preferable to ‘spondyloarthropathy’, to emphasise the inflammatory nature of these diseases,⁵ the term *spondyloarthropathies* is used in the USA in contrast to European rheumatology, which prefers the term *spondyloarthritides*. The term is often quoted in the plural form ‘the spondyloarthritides’ emphasising that this is a group of similar diseases with distinct clinical features and a common genetic predisposition, rather than one disease with different clinical presentations.⁶

CLASSIFICATION CRITERIA FOR AXIAL AND PERIPHERAL SpA: A NEW SPLIT OF A UNIFYING CONCEPT

The Amor criteria and the European Spondylarthropathy Study Group (ESSG) criteria were the first classification criteria which aimed at encompassing patients over the whole spectrum of SpA, including undifferentiated disease ignored in epidemiological studies because of the inadequacy of existing criteria.⁷⁻⁸ Overall, in various epidemiological and clinical studies the Amor criteria performed slightly better than the ESSG criteria in classifying early SpA.⁹ ESSG criteria require the presence of inflammatory spinal pain or synovitis (asymmetric or predominantly in the lower limbs) and thus have ‘entry criteria’. The Amor criteria, in contrast, are a list of 12 variables, none of which must be present (mandatory) to classify the disease as SpA. Therefore, the Amor criteria might be more helpful than the ESSG criteria for making a diagnosis in an individual patient. Nevertheless, these two sets of criteria

are not diagnostic criteria. Additionally, the difference in the performances of the two sets of criteria might be explained by two additional facts. In contrast to the Amor criteria, the ESSG criteria do not include a response to non-steroidal anti-inflammatory drugs, which is the 12th item of the Amor classification, and they omit HLA-B27 typing, now widely used in the rheumatological practice.

The advent of new imaging methods, especially MRI, to facilitate the possibility of early diagnosis of sacroiliitis, and the increasing use of new biological treatments has renewed interest in the classification of the SpAs. The new ASAS classification criteria for peripheral SpA address these pivotal advances and are the final step of a series of papers reporting the development and validation of new classification criteria for axial and peripheral SpA.¹⁰⁻¹³ The authors tested also the performance of the combined use of ASAS classification criteria for axial SpA and for peripheral SpA.² Both new sets of classification criteria were developed and tested in newly referred consecutive patients with undiagnosed chronic back pain and peripheral arthritis, and/or enthesitis and/or dactylitis, respectively. In the peripheral SpA study, radiographs of the sacroiliac (SI) joints were available in 85.3% but MRI of the SI joints in only 22.5% of all patients.² A direct comparison of the sensitivity and specificity against the ESSG and Amor criteria seem to reflect a better performance of the ASAS criteria (table 1). In contrast, former evaluations of the ESSG and Amor criteria in the early 1990s in different countries and settings resulted in better performance than the new combined ASAS criteria (table 1)^{9, 20}. It is unclear why two sets of criteria using the

same items can give such different sensitivities of 39.8% in peripheral SpA and 67.5% in the combined SpA for modified Amor criteria with MRI compared with 77.8 % in peripheral SpA and 79.5% in the combined SpA for modified ASAS criteria with MRI, respectively (table 1).

The new ASAS criteria raise several questions. What degree of spinal involvement allows a patient to be classified as having peripheral SpA and, vice versa, what degree of peripheral involvement allows classifying the patient as having axial disease? Many patients with SpA at some time of the disease may have either prominent peripheral and axial symptoms concurrently or peripheral and axial symptoms successively. The classification may therefore change from axial to peripheral and vice versa at different times in a given study, compromising the consistency of classification in long-term trials. What formal solution can be given to cope with this problem?

The criteria are restricted to patients with disease initiation before 45 years of age and therefore do not capture patients with peripheral SpA, such as psoriatic arthritis, ReA and uSpA, which often start at age >45 years. Why should this important group of patients not be integrated into a new set of criteria, which are intended to advance the present concept of SpA?

Like the ESSG criteria, the ASAS criteria are restricted by ‘entry criteria’. Extra-articular manifestations such as acute anterior uveitis and atrioventricular block, which may either precede SpA or be the predominant feature, are not covert (figure 1). Most importantly, MRI of SI joints must be available to obtain a better performance. Therefore, the new criteria at present cannot replace the ESSG and the Amor criteria in epidemiological studies and other situations in which MRI is not readily available. Moreover, most patients collected in the ASAS studies would be formerly diagnosed as uSpA, which by its terminology suggests different prognostic outcomes: an early stage of a definite SpA that will later develop into the full clinical picture; an abortive, self-limiting form; an overlap of the different subgroups of SpA and an unknown, aetiologically, as yet undefined, subcategory of SpA.¹⁴ In clinical practice, we need a further diagnosis to separate these patients from other SpAs.

Finally, the new ASAS criteria may reopen the controversy between splitting and lumping.¹⁵ The split removes the unified concept of SpAs, which initially were

Table 1 Comparison of the sensitivity and specificity of classification criteria for spondyloarthritis “(data derived from Rudwaleit *et al*,^{2, 12} Guignard *et al*,⁹ Schumacher and Bardin²⁰)”

Criteria	Sensitivity (%)	Specificity (%)
Amor	77–91	92–98
ESSG	84–91	91–100
ASAS axial SpA	82.9	84.4
Modified ESSG (with MRI)*	85.1	65.1
Modified Amor (with MRI)*	82.9	77.5
ASAS peripheral SpA	77.8	82.9
Modified ESSG (with MRI)*	62.5	81.1
Modified Amor (with MRI)*	39.8	97.8
ASAS combined criteria	79.5	83.3
Modified ESSG (with MRI)*	79.1	68.8
Modified Amor (with MRI)*	67.5	86.7

*The ESSG criteria and the Amor criteria were modified in that active sacroiliitis on MRI was added. ASAS, Assessment of SpondyloArthritis international Society; ESSG, European Spondylarthropathy Study Group; SpA, spondyloarthritis.

lumped together because of the inter-relationship of individual diagnoses, by separating the main musculoskeletal manifestations (figure 1). Conceptually, the new classification switches from a classification of inter-related nosological entities to a classification of inter-related clinical manifestations of the unified SpAs. Therefore, the new split represents a hybrid, first lumping together the diagnoses and thereafter splitting the SpAs into subgroups of predominant clinical manifestations. This new concept cannot replace in clinical practice the diagnostic use of the different individual diagnoses, including uSpA. Moreover, criteria for predominant or exclusive extra-articular SpA still have to be developed to encompass the whole spectrum of manifestations (figure 1). On the other hand, the ASAS criteria may serve to collect at a certain point of time a group of patients for clinical trials to test diagnostic and therapeutic interventions in a defined clinical subgroup regardless of the underlying individual disease.

CHLAMYDIAL INFECTION AND SpA: IMPLICATION FOR FUTURE AETIOLOGICAL CLASSIFICATION

The recent success in identifying infectious agent antigens or nucleic acids in the joints of patients with ReA suggests that infections have an important role in a subtype of SpAs, which we now lump together. In particular, urogenital tract infections and, more recently, *Chlamydia trachomatis*, have long been implicated as causative agents in AS.¹⁶ Recently, Carter *et al* described an increased frequency of *Chlamydia*-positive synovial tissue samples, as determined by PCR, in patients with chronic uSpA.¹⁷ Most importantly, the recent finding that combination antibiotic treatment is efficient and may even cure the disease might have implications for future classification of SpAs.^{18, 19} Carter *et al* used a modification of the ESSG criteria to classify the patients with *Chlamydia*-induced ReA who were eligible to receive combination antibiotic agents.

Nearly all the selected patients in the study by Carter *et al* had radiographic sacroiliitis, defined as an asymmetric appearance with at least grade II unilateral changes. Moreover, not all patients had peripheral arthritis, and most of them had axial arthritis. Therefore, the selected patients may also be classified as having reactive SpA, a term recently introduced

to distinguish between axial or peripheral manifestations.⁶ Furthermore, this subtype of patients with SpA may be now termed '*Chlamydia*-induced SpA' comparable to the well-accepted term *Chlamydia*-induced ReA.

PERSPECTIVE AND CONCLUSION

Altogether, there seems to be no doubt that we will need new classifications, and the new ASAS criteria based on a combination of symptoms, laboratory test results and MRI findings may provide important temporary support for clinical trials. To test their diagnostic performance the criteria should be evaluated in very early disease and in follow-up studies to provide information on the switch of manifestations and diagnosis of subtypes. Moreover, new findings emphasise the need for intensified search for the infective aetiology of AS and related SpAs, leading to future aetiological classifications of the SpAs.²⁰ Single infectious agents can produce different clinical syndromes and one clinical syndrome, such as ReA, can be caused by different infections. Working classifications that include the infectious triggers might be useful for future diagnostic and therapeutic studies such as the modification of the ESSG criteria as applied by Carter *et al* to classify *Chlamydia*-positive patients as having *Chlamydia*-induced SpA.¹⁷ Technology is now available to enlarge the current body of clinical, immunological and genetic studies using pivotal microbiological research and new antimicrobial therapeutic strategies.

Competing interests None.

Provenance and peer review Commissioned; externally peer reviewed.

Accepted 17 October 2010

Ann Rheum Dis 2011;**70**:1–3
doi:10.1136/ard.2010.135889

REFERENCES

- Moll JM, Haslock I, Macrae IF, *et al*. Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behcet's syndrome. *Medicine (Baltimore)* 1974;**53**:343–64.
- Rudwaleit M, van der Heijde D, Landewé R, *et al*. The Assessment of SpondyloArthritis international Society (ASAS) Classification Criteria for peripheral Spondyloarthritis and for Spondyloarthritis in general. *Ann Rheum Dis* 2011;**70**:15–21.
- Kellgren JH, Jeffrey MR, Ball J. *The Epidemiology of Chronic Rheumatism*. Oxford, England: Blackwell Scientific Publications 1963;1:326–27.
- Wright V. Seronegative polyarthritis: a unified concept. *Arthritis Rheum* 1978;**21**:619–33.

- François RJ, Eulderink F, Bywaters EG. Commented glossary for rheumatic spinal diseases, based on pathology. *Ann Rheum Dis* 1995;**54**:615–25.
- Zochling J, Brandt J, Braun J. The current concept of spondyloarthritis with special emphasis on undifferentiated spondyloarthritis. *Rheumatology (Oxford)* 2005;**44**:1483–91.
- Amor B, Dougados M, Miyiyawa M. [Criteria of the classification of spondyloarthropathies]. *Rev Rhum Mal Osteoartic* 1990;**57**:85–9.
- Dougados M, van der Linden S, Juhlin R, *et al*. The European Spondyloarthropathy Study Group preliminary criteria for the classification of spondyloarthropathy. *Arthritis Rheum* 1991;**34**:1218–27.
- Guignard S, Gossee L, Dougados M. *Diagnostic and Classification criteria*. In: Weisman M, van der Heijde D, Reveille J, eds. *Ankylosing Spondylitis and the Spondyloarthropathies*. Philadelphia, PA: Mosby Elsevier 2006:132–44.
- Sieper J, van der Heijde D, Landewé R, *et al*. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). *Ann Rheum Dis* 2009;**68**:784–8.
- Rudwaleit M, Landewé R, van der Heijde D, *et al*. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009;**68**:770–6.
- Rudwaleit M, van der Heijde D, Landewé R, *et al*. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;**68**:777–83.
- Rudwaleit M, Jurik AG, Hermann KG, *et al*. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. *Ann Rheum Dis* 2009;**68**:1520–7.
- Zeidler H, Brandt J, Schnarr S. *Undifferentiated spondyloarthritis*. In: Weisman M, van der Heijde D, Reveille J, eds. *Ankylosing Spondylitis and the Spondyloarthropathies*. Philadelphia, PA: Mosby Elsevier 2006:75–93.
- Nash P, Mease PJ, Braun J, *et al*. Seronegative spondyloarthropathies: to lump or split? *Ann Rheum Dis* 2005;**64** Suppl 2:ii9–13.
- Zeidler H, Rihl M. Time to prove the infective etiology of ankylosing spondylitis and related spondylarthritides: Comment on the article by Carter *et al*. *Arthritis Rheum* 2009;**60**:3519–20; author reply 3520–1.
- Carter JD, Gérard HC, Espinoza LR, *et al*. Chlamydiae as etiologic agents in chronic undifferentiated spondyloarthritis. *Arthritis Rheum* 2009;**60**:1311–6.
- Carter JD, Espinoza LR, Inman RD, *et al*. Combination antibiotics as a treatment for chronic Chlamydia-induced reactive arthritis: a double-blind, placebo-controlled, prospective trial. *Arthritis Rheum* 2010;**62**:1298–307.
- Rihl M, Kuipers JG, Köhler L, *et al*. Combination antibiotics for Chlamydia-induced arthritis: breakthrough to a cure? *Arthritis Rheum* 2010;**62**:1203–7.
- Schumacher HR, Bardin T. The spondyloarthropathies: classification and diagnosis. Do we need new terminologies? *Baillieres Clin Rheumatol* 1998;**12**:551–65.