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SERONEGATIVE ARTHRITIS (MA KHAN, SECTION EDITOR)

# Current Concept of Spondyloarthritis: Special Emphasis on Early Referral and Diagnosis

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**Abstract** Ankylosing spondylitis is the prototype of inflammatory rheumatic diseases grouped under the term *spondyloarthritis* or *spondyloarthropathy* (SpA). New classification criteria for SpA have now been proposed; the patients are subgrouped into (1) a predominantly axial disease, termed *axial* SpA, which includes AS, and (2) peripheral SpA. There is an unacceptable delay in the diagnosis of axial SpA, and there are still no validated diagnostic criteria for SpA. An early diagnosis has now become increasingly important because effective therapies in the form of TNF antagonists have become available that are even more effective if used in early stages of the disease. Therefore, new strategies are being proposed that will assist in making an early diagnosis and will also help primary care physicians in screening for these patients so that they can be referred to rheumatologists when the disease is still in its early stages. These strategies may be less efficient for early referral of children and adolescents suffering from SpA, because their most important early manifestation is not inflammatory back pain but peripheral arthritis and enthesitis. There is, therefore, a need to develop a different strategy for children and adolescents with SpA through the use, preferably, of the ASAS/EULAR classification criteria for peripheral SpA, more so than the classification criteria for axSpA.

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## Introduction

Ankylosing spondylitis (AS) is the leading chronic inflammatory rheumatic disease of the axial skeleton [1], and is the prototype of a group of diseases grouped under the term *spondyloarthritis* or *spondyloarthropathy* (SpA) (see Fig. 1). The diagnosis of AS requires X-ray evidence of sacroilitis (defined as bilateral grade 2 or unilateral grade 3 or 4) according to the modified New York classification criteria for AS [3]. Deciding about the existence of sacroiliitis on plain radiographs is not always very easy, even for rheumatologists and radiologists [4]. The new definition of inflammatory back pain (IBP) and the detection of inflammation in the sacroiliac joints and the spine by magnetic resonance imaging (MRI) has helped in the early identification of axial SpA in the "nonradiographic stage" of the disease, years before anything becomes evident on X-ray [5, 6].

The presence of sacroiliac joint inflammation (sacroiliitis) on musculoskeletal imaging (X-ray or MRI) in the presence of clinical manifestations is virtually diagnostic. The name, AS, is more restrictive, since it requires X-ray evidence of sacroiliitis, and such a requirement is one of the reasons that the diagnosis is often delayed by 5–10 years [7, 8], and during this period of diagnostic uncertainty, many patients may undergo unnecessary or even invasive investigations and receive inappropriate treatment.

## The Concept of Axial SpA

Axial SpA comprises a heterogeneous group of diseases that have many overlapping clinical feature; the important

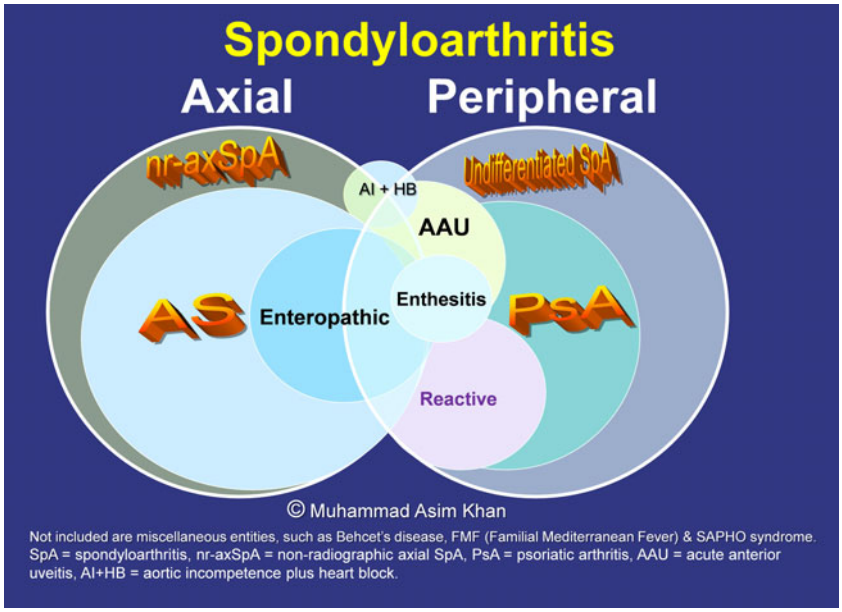


**Fig. 1** Venn diagram showing spondyloarthritis and interrelated disorders. (Courtesy of Dr. Muhammad Asim Khan; with permission)

hallmarks include lack of association with rheumatoid factor, strong association with HLA-B27, and occurrence of sacroiliitis and impaired spinal mobility in those with axial SpA [1, 2]. Patients with SpA can be subgrouped, as shown in Fig. 1, into two main subgroups [9]: predominantly axial SpA, abbreviated as axSpA, which includes AS, and peripheral SpA. Magnetic resonance imaging (MRI) is now considered to be a very useful tool as an aid to early recognition of inflammation of the axial skeleton, since it can detect active inflammatory changes at the sacroiliac joints with or without structural damage. This is clinically very useful for recognizing axSpA when plain radiographs of SIJ seem normal or equivocal [10••]. This stage of axSpA should be defined as nonradiographic axial SpA (nr-axSpA), rather than the preradiographic stage, since it is quite possible that not all the patients will eventually develop radiographic evidence of sacroiliitis and spondylitis. A vast majority of the patients with nr-axSpA probably evolve into AS over time. Nearly 12 % of patients with nr-axSpA developed definite radiographic sacroiliitis and met modified New York criteria for AS after 2 years [11], and 10 % of undifferentiated SpA progressed to AS over 2 years and 24.3 % after 5–10 years [12, 13]. A recent study of the German SpA Inception Cohort (GESPIC) revealed that 14.3 % of patients with nr-axSpA showed spinal radiographic progression over a 2-year period, and the presence of baseline syndesmophytes, elevated erythrocyte sedimentation rate or C-reactive protein levels, and cigarette smoking were the independent predictors of the disease progression over 2 years [14••].

Need for an early diagnosis has become increasingly important because effective therapies in the form of TNF antagonists have become available that are even more effective if used in early stages of the disease. Therefore, new strategies are being developed that will assist in making an early diagnosis and will also help primary care physicians in screening for these patients, so that they can be referred to a rheumatologist when the disease is still in its early stages.

To optimize the diagnostic accuracy at a very early stage, it is crucial to use a comprehensive approach and to have a deep understanding of the disease and its clinical picture. The clinician should gather a complete history, paying close attention to all the elements of this systemic disease. A single clinical feature is not sufficient to make the diagnosis: The more features that are present that are suggestive of the disease, the higher is the likelihood of the disease presence.

## The New ASAS/EULAR Classification Criteria for Axial SpA

New ASAS/EULAR classification criteria have been proposed for axSpA in subjects with chronic back pain with onset before age 45 (Fig. 2). It is now recognized that sacroiliac joint and/or spinal inflammation, as detected by MRI (T1 and STIR technique without gadolinium enhancement) is good enough evidence for the presence for axial skeletal inflammation. It is worth noticing that there are still no validated diagnostic criteria for SpA.

The new classification criteria for axSpA have two arms: the imaging arm and the clinical arm. (Fig. 2). The imaging arm requires presence of sacroiliitis as detected by conventional radiography (radiographic axial SpA; abbreviated as r-axSpA, a term synonymous with AS) or by MRI (non-radiographic axial SpA; abbreviated as nr-axSpA) and at least one of the clinical features ("red flags") of SpA. The clinical arm requires presence of HLA-B27 and at least two of the clinical features (Fig. 2).

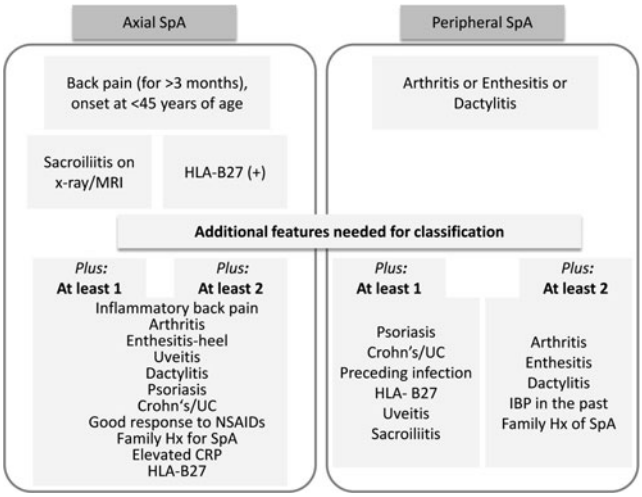


**Fig. 2** Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axial and peripheral spondyloarthritis. (Adapted from Rudwaleit et al. [15])

These criteria were validated against expert clinical judgment in a cohort of 649 patients with chronic back pain [9]. The imaging arm showed excellent specificity (97.3 %), suitable for selecting patients for clinical or drug studies, but it has an unacceptably low sensitivity (66.2 %). The clinical arm has reasonably good sensitivity and specificity (~80 % for both). The presence of the imaging or the clinical criteria gives an 82.9 % sensitivity and 84.4 % specificity, good enough for use for clinical diagnosis of axial SpA, since there are no validated diagnostic criteria as yet.

After the publication of the ASAS classification criteria for axSpA, the efficacy of anti-TNF treatments—adalimumab [16], infliximab [17], and etanercept [18, 19]—has been demonstrated in patients with nr-axSpA. Because of good response rates, the last update of the ASAS consensus recommendations for the use of anti-TNF agents in AS included the use of these drugs in nr-axSpA patients who cannot be adequately managed with conventional (nonbiologic) therapy [20].

## The New ASAS/EULAR Classification Criteria for Peripheral SpA

Incidentally ASAS/EULAR classification criteria (Fig. 2) have also been proposed for peripheral SpA [15]. They state that in the presence of arthritis or enthesitis or dactylitis, one needs at least one or more of the "major" features that characterize psoriasis, inflammatory bowel disease, uveitis, HLA-B27, preceding infections, or sacroiliitis (X-ray or MRI), or two or more of the following features: arthritis, enthesitis, dactylitis, inflammatory back pain (IBP) in the past, and family history of SpA. Please note that although current IBP is not considered one of the manifestations of peripheral SpA in this proposal, radiographic evidence of sacroiliitis may be present among some of these patients [9].

## Strategies for the Early Recognition of Axial SpA

Chronic back pain is one of the major health problems among populations in western industrialized countries and a major cause of medical expenses, absenteeism, and disability [21]. The probability of having axSpA in patients with chronic back pain increases from 5 % to 16 % when the patient's back symptoms meet the new definition of inflammatory back pain (IBP) [22]. Although the diagnostic value of IBP is limited, assessing the existence of IBP in these patients is one of the most feasible ways for referral, since it is the leading symptom in most patients with axSpA. Also, HLA B27 positivity or MRI-defined sacroiliac joint inflammation or damage may be the other ways for referral; however, the costs and limited availability, especially for MRI, restrict their use as the referral parameters [22, 23••, 24].

Chronic back pain due to inflammation in the axial skeleton in patients with axial SpA usually begins insidiously in late adolescence and early adulthood, causing chronic back pain and stiffness [1, 2]. Males are affected roughly twice as commonly as females. Data from developed countries indicate that the average age of onset is around 24 years; onset before age 10 or after age 45 is rare. Approximately 15 % of patients have onset of their disease in childhood (before age 16), but this percentage may be as high as 40 % in some developing countries [1, 2].

Back symptoms tend to worsen after prolonged periods of inactivity ("gel phenomenon") and are therefore worse at late hours of the night or early in the morning. The pain and stiffness tend to be eased by moving about (limbering up), by physical activity or exercise, or by a hot shower or use of NSAIDs. Some patients may wake up at night to exercise or move about for a few minutes before returning to bed. The patient often has difficulty getting out of bed on waking up because of pain and stiffness and may roll sideways off the bed, trying not to flex or rotate the spine. The back pain and stiffness can be quite severe at this early stage, and the pain tends to be accentuated with coughing, sneezing, or maneuvers that cause a sudden twist of the back [1, 2].

These symptoms alone should trigger suspicion of axSpA. Because of the very high prevalence of back pain in the population at large, it is helpful to elicit such clinical history features that help differentiate the common ubiquitous noninflammatory causes from the inflammatory back pain of axial SpA. Sometimes pain and stiffness in the mid-thoracic or the cervical region or chest wall pain may be the initial symptom, rather than the more typical low backache. This may be a relatively more common presentation in women. Pain and stiffness in the cervical spine generally tend to develop after some years but occasionally occur in the early stages of the disease, and some patients may have recurrent severe episodes of stiff neck (torticollis) [1, 2].

## Strategies for Improved Referral from Primary Care Physicians

Improved referral from primary care physicians is expected to shorten the time to diagnosis of axSpA. The referral strategies were tested in studies for the early recognition of axSpA [23••, 24–26]. In the first study, from a center in Berlin, Germany, general practitioners and orthopedists referred patients if they had IBP, were positive for HLA B27, or already had sacroiliitis in any imaging modality [26]. Of the 350 patients referred, 45.4 % were diagnosed as suffering from axSpA (34.2 % when referred with a single parameter and 62.6 % if referred with at least two parameters). Of the patients diagnosed with axSpA, the proportion of nr-axSpA was 49.7 %, and AS was the remaining 50.3 % [26].

In another study, from Austria, 33 % of 92 patients referred according to Calin criteria for IBP were diagnosed with SpA [25]. The findings of the Berlin study were tested in a nationwide multicenter trial conducted in Germany [23••]. This study, named the Multicenter AS Survey Trial to Evaluate and Compare Referral Parameters in Early SpA-MASTER, tested two different strategies for referral: The first was the same one as that used in the Berlin study, and the second one additionally included at least two SpA features that characterized IBP, HLA B27, sacroiliitis detected on any modality of imaging (if available), a positive family history for AS, and a good response of back pain to NSAIDs. Patients with other SpA manifestations (such as uveitis) could also be referred [23••]. Of the 560 patients, 318 were referred according to strategy 1 and 242 according to strategy 2. Of the patients referred by strategy 1 criteria, 41.8 % were diagnosed with axSpA (38.4 % nr-axSpA and 61.6 % AS), and those referred according to strategy 2, 36.8 % were diagnosed with axSpA (38.2 % nr-axSpA and 61.8 % AS). The most frequently used parameter for the referral was IBP (87.6 %) [23••].

In another nationwide study, 35.1 % of patients were diagnosed with axSpA, when referred according to a computer algorithm based on the presence of IBP criteria or response to NSAIDs [24].

The referral strategies I and II (with slight modification) were then tested in the first international randomized study, named RADAR (Recognizing and Diagnosing Ankylosing Spondylitis Reliably), with participation of rheumatologists from 16 countries [27]. Primary care referral sites in 16 countries were randomized (1:1) to refer chronic back pain (CBP) patients to a rheumatologist according to one of the following two referral strategies:

1. Strategy I, one of three criteria: IBP, HLA-B27+, or sacroiliitis on imaging (SI); or
2. Strategy II, two of six criteria: IBP, HLA-B27+, SI, family history, good response to NSAIDs, and extra-articular manifestations.

The rheumatologist then established a diagnosis. The objective of the RADAR study was to show that a referral strategy for patients with CBP (defined as back pain of unknown origin, for >3 months, onset before age 45, and no diagnosis of axSpA or AS established yet) based on strategy I performs as well as strategy II and leads to diagnosis of axial SpA in >35 % of patients.

The primary analysis compared the proportion of CBP patients diagnosed as having axSpA with the use of the two referral strategies. Of the 504 patients referred according to strategy I and 568 patients according to strategy II, 35.6 % and 39.8 % were diagnosed with axSpA, respectively. Out of 397 patients thus diagnosed with axSpA, 77 % were judged as having AS, and the remaining 23 % as having nr-axSpA by the local rheumatologists [27].

IBP was nearly always used; it showed good concordance with rheumatologists and had high sensitivity and negative predictive value. Combining IBP with other criteria, such as HLA-B27 and sacroiliitis, increases the likelihood of diagnosis (Fig. 3). Only the strategy using IBP, HLA-B27, and sacroiliitis had >80 % sensitivity, specificity, and predictive values.

The importance of MRI is increasingly recognized as a diagnostic tool for assessing inflammation or destruction in the sacroiliac joints and the spine [28, 29]. The recent ASAS criteria for the classification of axial SpA included sacroiliac joint inflammation on MRI as a major criterion [9], and subsequently, the Assessment in SpA International Society–Outcome Measures in Rheumatology (ASAS/OMERACT) MRI working group defined positive MRI for the sacroiliac joints [30]. Furthermore, the definition for a positive MRI for the inflammation at the spine was considered necessary, since spondylitis with or without sacroiliitis (5.4 %) may also occur in axSpA [30]. This group recently published descriptions of spinal MRI lesions and a definition of a positive MRI of the spine in axial SpA [31••].

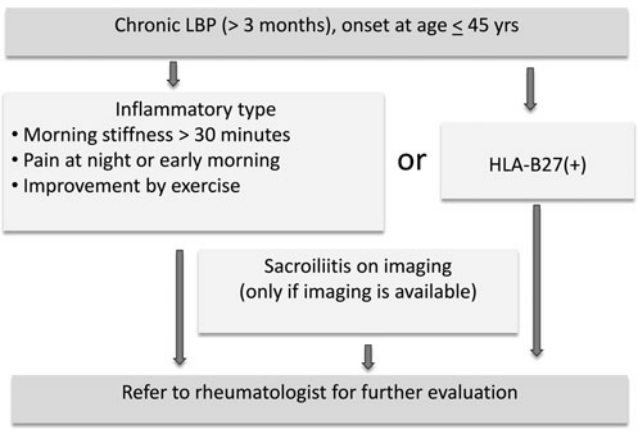


**Fig. 3** Proposed referral strategy for axial spondyloarthritis for primary care physician. (Adapted from Rudwaleit and Sieper [10••])

These consensual approaches should be followed while interpreting the MR images of the SI joints or the spine.

According to the consensual approach of the ASAS/OMERACT, bone marrow edema on STIR or osteitis on T1 post-gadolinium highly suggestive of SpA must be clearly present and located in the typical anatomic areas (subchondral or periarticular bone marrow) in order to define sacroiliitis [30]. The sole presence of other active inflammatory lesions without concomitant edema/osteitis was not considered sufficient for the definition of sacroiliitis on MRI. Only one edema lesion on a particular coronal slice is not sufficient for the definition of sacroiliitis, and lesions should be present on at least two consecutive slices; however, if there were more than one lesion on a single slice, it would suffice for the definition of sacroiliitis [30]. The contribution of abnormalities detected on spinal imaging for the diagnosis of axSpA is unclear; however, this may facilitate interpretation of subtle and diagnostically inconclusive lesions observed in the sacroiliac imaging [32•]. The inflammatory or structural spinal lesions typical for axSpA are an anterior or posterior vertebral-based inflammatory lesion and a fatty deposition at the vertebral corners [31••].

## Comments Pertaining to Screening or Referral Tool for Juvenile Spondyloarthritis

The referral strategies that have been discussed above were evaluated for early recognition of axSpA [23••, 24–26]. In juvenile SpA, which is referred to as the enthesitis-related arthritis (ERA) subtype under the International League of Associations for Rheumatology (ILAR) classification of juvenile idiopathic arthritis, the most important early manifestation is not IBP but peripheral arthritis and enthesitis, predominantly affecting the lower limbs [33]. Spinal involvement is uncommon at presentation but may develop, often beginning in the second decade of life, and then lead to impairments in spinal mobility akin to the adult-onset form of AS. Therefore, the currently proposed strategies for improved early referral from primary care physicians to shorten the time to diagnosis of axSpA in children and adolescents may be less efficient or may be inappropriate [34••]. There is, therefore, a need to develop a different strategy for children and adolescents with SpA through the use, preferably, of the ASAS/EULAR classification criteria for peripheral SpA, more so than the classification criteria for axSpA.

## Conclusions

There is an unacceptable delay in diagnosis of SpA, and there are still no validated diagnostic criteria. An early diagnosis has now become increasingly important because of the availability of more effective therapies in the form of TNF antagonists that are even more effective if used in early stages of the disease. Therefore, new strategies are being proposed that will help primary care physicians in screening for these patients so that they can be referred to rheumatologists when the disease is still in its early stages. However, these strategies may be less efficient for early referral of children and adolescents suffering from SpA, because their most important early manifestation is not IBP but peripheral arthritis and enthesitis. Therefore, the classification criteria for peripheral SpA may be more appropriate for early detection of juvenile SpA in children and adolescents than the classification criteria for axSpA, but a different strategy may need to be developed.

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- •• Of major importance

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