Ankylosing Spondylitis— Axial Spondyloarthritis

Third Edition

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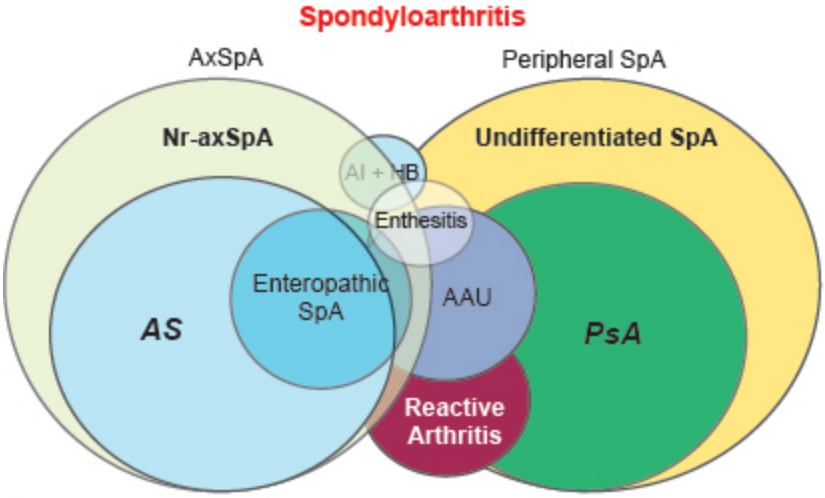
Introductory Overview

I (MAK) am very pleased that, with the help of my co-author (NA), we have been able to finish the third edition of this book in year 2023. We hope that rheumatologists, internists, physiatrists, and other specialists, as well as researchers, trainees, physical therapists, physician assistants, nurse practitioners, and other healthcare providers will find this book to be clinically useful.

This book deals with axial spondyloarthritis (axSpA) that encompasses ankylosing spondylitis (AS) and spondylitic disease without radiographic evidence of sacroiliitis that is currently termed non-radiographic axSpA (nr-axSpA).[1-5] Together they form the predominantly axial subgroup of spondyloarthritis (SpA), whereas psoriatic arthritis (PsA), enteropathic arthritis (associated with Crohn's disease [CD] and ulcerative colitis [UC]), reactive arthritis, and undifferentiated SpA form the predominantly peripheral subgroup of SpA (**Figure 1.1**). These diseases show a strong association with HLA-B27, but the strength of this association varies among these various forms and among some of the racial/ethnic groups worldwide.[1-4]

For many years, AS/axSpA was considered to be a predominantly male disease but a relatively recent study from Switzerland, shows that the male to female ratio has declined from 2.57:1 in 1980 to 1.03:1 by the end of 2016.[6] Although the age of onset of AS is similar, women have a significantly longer delay in diagnosis, and a significantly lower TNFi efficacy and drug survival. Men show a little stronger association with HLA-B27 and a higher radiographic progression, but the disease burden is similar between males and females.[7]

FIGURE 1.1 — Components of Spondyloarthritis



AAU, acute anterior uvelitis, AI+HB, aortic incompetence plus heart block.

The various forms of SpA are divided into predominantly axial and predominantly peripheral forms.

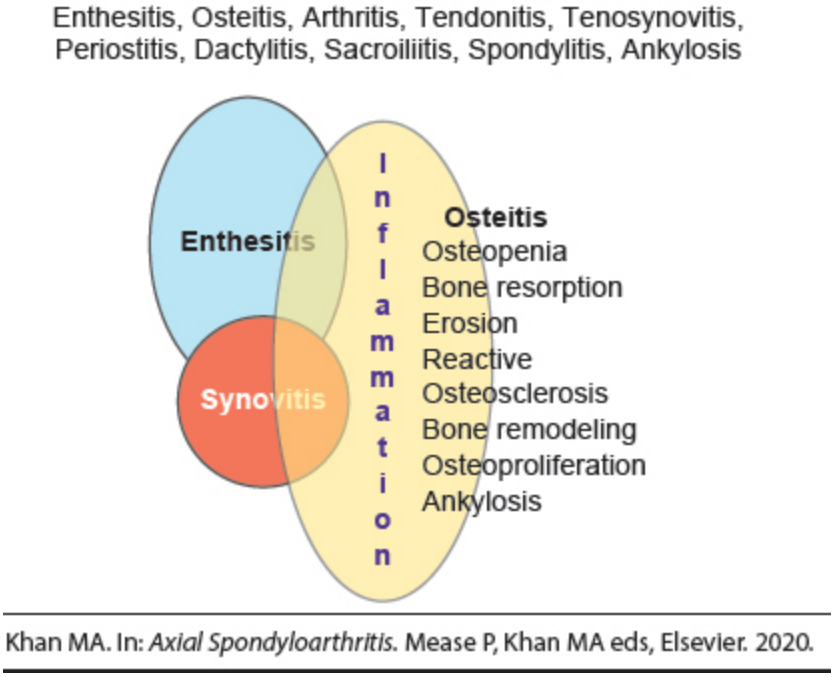
Ozgocmen S, Khan MA. *Curr Rheumatol Rep*. 2012; 14(5):409-414.

AS is the prototypic form of SpA with potentially most severe outcome and is characterized by predominantly axial skeletal symptoms and radiographic evidence of sacroiliitis, as defined by the modified New York (mNY). For practical purposes it has been also called radiographic axSpA (r-axSpA), as discussed in *Chapter 5*. The typical sites of inflammation are the entheses and "synovio-entheseal complex" where ligaments and tendons insert into bone and form sites of high biomechanical stress.[3] This is also accompanied by reactive osteitis, periostitis, and osteoproliferation. The wide spectrum of musculoskeletal features is shown in **Figure 1.2**, and axSpA also may be accompanied by many extraskeletal manifestations, the commonest of them being acute anterior uveitis, and co-morbid conditions (**Figure 7.1**). **Figure 1.3** shows the wide clinical spectrum of axSpA.

The key pathological element is enthesitis, but sacroiliitis is the main diagnostic feature of AS/axSpA. Diagnostic criteria for spondylitic disease that encompasses AS were proposed in 1987 but they have not as yet been validated[8] (**Table 11.2**). In the absence of any validated diagnostic criteria, clinicians sometimes inappropriately use the Assessment of

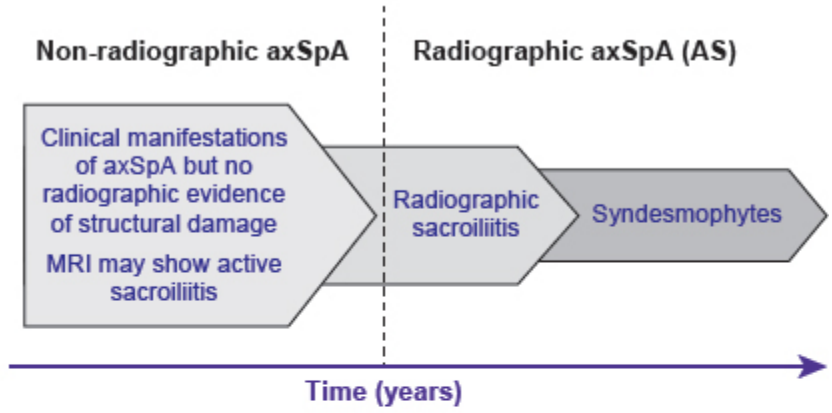
Spondyloarthritis International Society (ASAS) classification criteria for axSpA for diagnosis,[9,10] and this is unfortunately perpetuated in part by the statement in the abstract of the original paper describing the final selection of these criteria that they "may help rheumatologists in clinical practice in diagnosing axSpA in those with chronic back pain."[11] The diagnostic approach in clinical practice is aimed at the estimation of the probability of a suspected disease based on the patient's clinical history, physical examination, investigations, and the exclusion of alternative explanations that are not included in the ASAS classification criteria.[3,9]

FIGURE 1.2 — Synovio-Entheseal Complex Involvement and Resultant Clinical and Pathological Features of SpA



Khan MA. In: *Axial Spondyloarthritis.* Mease P, Khan MA eds, Elsevier. 2020.

FIGURE 1.3 — The Concept of axSpA



This figure schematically shows a unifying concept of axSpA that has a wide clinical spectrum. Inflammatory back pain is the leading symptom that may be present throughout the disease course without any occurrence of structural damage. As further explained in the text, the decreasing sizes of the three chevrons from the left to the right of this figure are meant to emphasize that only a portion of patients with nr-axSpA will progress to r-axSpA/AS, whereas others may remain as nr-axSpA, perhaps forever or have a self-limiting disease course. This figure also shows that not all patients with radiographic sacroiliitis progress to form syndesmophytes with resulting spinal ankylosis.

Khan MA, van der Linden S. *ACR Open Rheumatol.* 2019;1(5):336-339.

There is still 3 to 10 years (mean 6 years) delay between onset of axSpA and its final diagnosis, and as discussed in *Chapter 11*, it is hoped that advances in our understanding of its biology via novel imaging, genetic, and biomarker studies will probably enable the resolution of many current issues and facilitate early diagnosis that is sorely needed now that there has been substantial progress made in its treatment. However, when compared with rheumatoid arthritis (RA), the treatment options for AS/axSpA are relatively limited, although the choices are expected to increase. A set of recommendations for the treatment of AS and nr-axSpA, developed as a joint effort by the American College of Rheumatology (ACR), the Spondylitis Association of America (SAA), and the Spondyloarthritis Research and Treatment Network (SPARTAN), has recently been updated.[12]

The strong genetic association of AS with HLA-B27 has been known for 48 years, and by now more than 100 additional disease predisposing

genetic loci have been discovered, and some of them are shared between AS, UC, and CD.[13-15] Intestinal inflammation, observed in >60% of patients with AS, intestinal microbial dysbiosis, and Th17 immunity are all linked to the pathophysiology of this disease, and the gut inflammation is characterized by an overexpression of IL-23 and possibly other cytokines that regulate lamina propria NKp44(+) natural killer (NK) cells that appear to play a tissue-protective role.[13,15,16]

A truly remarkable study was published by Sherlock and associates in 2012[17] (discussed in *Chapter 4*), the results of which were well summarized in a figure by Lories and McInnes[18] (**Figure 4.10**) that demonstrated that an excess of IL-23 is sufficient in generating specific prototypic SpA manifestations because mice injected with IL-23 genetic mini-circles (to overexpress IL-23) develop enthesitis and subsequently arthritis (including sacroiliitis), osteoproliferation, psoriasis, and inflammation of the aortic root.[17,19] Expression of inflammatory genes (eg, TNF-α, IL-6, chemokines, and matrix metalloproteinases) was observed in the inflamed paws, but TNF blockers did not inhibit development of this IL-23–mediated disease. Inflammation occurred independently of the classic CD4+ Th17 cells. Rather, IL23R+RORyt+ CD4-CD8- innate lymphoid-like T cells were found to be residing in both the entheses and the aortic root. Remarkably, treatment of these mice with anti-IL-17 or anti-IL-22 ameliorated enthesitis and arthritis, but it was most effective when given in combination.[18] IL-23 and Th17 signature cytokines (IL-17 and IL-22) thus provide another link between mucosal and joint immunity. IL-23 and IL-17 expression has been reported to be upregulated in the gut, peripheral blood, and synovium of SpA patients.[20] IL-23 mediates inflammatory process through IL-17 and TNF, while IL-22 predisposes to new bone formation. Recently, a novel pathogenetic model has been proposed which postulated that changes in the local metabolic environment (pH, salt) may play a key role in the development of AS by induction of a Th17 pro-inflammatory phenotype through activation of glycosphingolipid sensors (encoded by the *GPR* genes – in particularly *GPR65*) and serum and glucocorticoid-regulated kinase-1 (SGK1) (**Figure 4.11**).[21]

Anti-IL-12/23 P40 monoclonal antibody, ustekinumab, has been approved for the treatment for psoriasis and PsA. and IL-17 inhibitors (IL-17is) secukinumab and ixekizumab have now been approved by both the

Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of psoriasis, PsA, and AS.[22-27] Since the release of the first edition of this book, the FDA approved certolizumab pegol, secukinumab, and ixekizumab to treat nr-axSpA, based on the studies conducted using designs addressing the key concerns raised by the FDA in the past, after reviewing the initial application files of adalimumab and certolizumab submitted for approval for the indication of nr-axSpA.[28-32]

Janus kinase inhibitors (JAKis) have been used for the treatment of RA as the latest drug class of disease-modifying category. This class of drugs are now emerging as new potential therapeutics for AS, after the successful results obtained in phase 2 and phase 3 trials of tofacitinib (pan-JAK inhibitor), upadacitinib (selective JAK1 inhibitor) and filgotinib (selective JAK1 inhibitor) in AS.[33-36] Their efficacy appears to be comparable to each other as well as to the available biologics drugs, which unfortunately loose efficacy or fail in a considerable number of patients with AS. Upadacitinib has just been approved in the European Union (EU) countries for the treatment of adults patients with active AS (who have responded inadequately to conventional therapy) and active PsA (who had inadequate response or are intolerant to one or more DMARDs).[36] It is hoped that JAKis can address some of the unmet need in the treatment of such patients, if the recent safety concerns raised by the FDA regarding the increased cardiovascular and cancer adverse events associated with tofacitinib relative to TNF inhibitors observed in RA patients can be resolved.[37,38] Drug maker of filgotinib has paused the two ongoing phase 3 trials for AS upon the request of additional safety data by the FDA regarding the testicular toxicity of the drug in RA trials.[39]

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Classification Criteria

Classification criteria are designed to define for clinical and epidemiological studies a highly disease-specific group of patients.[1] The first criteria for AS were based on the clinical experience of rheumatologists at a meeting held in Rome in Italy in 1961, but since then our understanding of the disease demographics has been changing resulting in subsequent revisions and also new criteria that are all listed in **Table 2.1**.[2-14] Thus the Rome criteria were revised at a meeting in New York in the US in 1996 by removal of thoracic pain and uveitis that were deemed to have low specificity or sensitivity, resulting in the New York criteria.[5]

Incorporation of criteria for chronic inflammatory back pain, as proposed by Calin and colleagues in 1977 (**Table 2.2**),[6] resulted in mNY criteria, first proposed in 1983,[7] and published a year later.[8] They are the most widely used validated criteria to classify AS, with 98% specificity and 83% sensitivity. According to these criteria, a patient can be classified as having definite AS in the presence of at least one of the clinical features (inflammatory back pain, limitation of mobility of the lumbar spine, or limitation of chest expansion) and the radiologic evidence of definite sacroiliitis.

Diagnostic criteria for AS have also been proposed but they have not been properly validated.[9,10] Amor Criteria (**Table 2.3**),[12] published in 1990, and the European Spondyloarthropathy Study Group (ESSG) criteria published a year later (**Table 2.4**),[11] were developed encompassing the wider clinical spectrum of SpA that facilitate earlier disease recognition.[13]

The availability of MRI with its ability to detect early inflammatory changes in the sacroiliac joint for early recognition of axSpA, the advent of new and more effective therapies, and the need to separately identify axial and peripheral forms of SpA were the reasons for the most recently

proposed criteria by the ASAS classification criteria for axSpA in 2009 (**Table 2.1**) and 2 years later for peripheral SpA.[14]

TABLE 2.1 — Classification Criteria for Ankylosing Spondylitis and Axial Spondyloarthritis

The Rome Classification Criteria for AS	The NY Classification Criteria for AS	The Modified NY Classification Criteria for AS	ASAS Criteria for Classification of AxSpA
			Entry Criterion: ■ Chronic back pain and age of onset before 45 years
Clinical Criteria			**Clinical Criteria (SpA Features)**
■ Low back pain and stiffness for >3 months, not relieved by rest ■ Pain and stiffness in the thoracic region ■ Limited motion in the lumbar region ■ Limited chest expansion ■ History of evidence of iritis or its sequelae	■ Limitation of motion of the lumbar spine in all 3 planes (anterior flexion, lateral flexion, and extension). ■ A history of pain or the presence of pain at the dorsolumbar junction or in the lumbar spine ■ Limitation of chest expansion to 1 inch (2.5 cm) or less, measured at the level of the 4th intercostal space.	■ Low back pain and stiffness for at ≥3 months duration which improves with exercise, but not with rest. ■ Limited lumbar spinal motion in sagittal (sideways) and frontal (forward and backward) planes ■ Chest expansion decreased relative to normal values corrected for age and sex.	■ HLA-B27 ■ Inflammatory back pain ■ Arthritis ■ Enthesitis (heel) ■ Uveitis ■ Dactylitis ■ Psoriasis ■ Crohn's disease/ulcerative colitis ■ Good response to NSAIDs ■ Family history for SpA ■ Elevated CRP
Radiologic Criteria			**Radiologic (Imaging) Criteria**
■ Bilateral sacroiliitis.	■ Sacroiliitis (grading: 0 to 4). Normal 0; suspicious 1; minimal 2; moderate 3; ankylosis	■ Bilateral sacroiliitis grade 2 to 4. ■ Unilateral sacroiliitis grade 3 or 4	■ Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA; or ■ Definite radiographic sacroiliitis according to modified NY criteria
Fulfillment of the Criteria			
Definite AS: ■ Four out of 5 clinical criteria are present; or ■ Bilateral sacroiliitis is associated with any single clinical criterion	Definite AS: ■ Bilateral grade 3-4 sacroiliitis in the presence of at least one clinical criterion; or ■ Unilateral grade 3-4 or bilateral grade 2 sacroiliitis with clinical criterion 1 or with both clinical criteria 2 and 3 Probable AS: ■ Bilateral grade 3-4 sacroiliitis is present without any clinical criterion	Definite AS: ■ One radiologic criterion is associated with at least one clinical criterion Probable AS: ■ Three clinical criteria are present or one radiologic criterion is present without any clinical criterion	AxSpA: ■ Back pain ≥3 months and age at onset <45 years and one of the below ■ Sacroiliitis on Imaging + ≥1 SpA Feature; or ■ HLA-B27 + ≥2 other SpA features Radiographic axSpA: ■ axSpA with definite radiographic sacroiliitis Non-radiographic axSpA: ■ axSpA without definite radiographic sacroiliitis

Robinson PC, et al. *Nat Rev Rheumatol*. 2021;17(2):109-118.

TABLE 2.2 — Inflammatory-Type Back Pain Criteria

Inflammatory-type back pain (of AS) is present if there is a clinical history of or current symptoms of spinal pain (in low, middle, and/or upper back, and/or neck region) with at least four of the following five components:

1. At least 3 months' duration
2. Onset before age 45
3. Insidious (gradual) onset
4. Improved by exercise
5. Associated with morning spinal stiffness

Calin A, et al. *JAMA*. 1977;237:2613-2614.

The ASAS axSpA criteria were developed using a cohort of 649 patients with chronic back pain referred to rheumatologists for suspicion of axSpA. The initial criteria based on roughly 40% of the cohort were subsequently validated by using the remainder (60%) cohort, utilizing "expert" rheumatologists' opinions. The final criteria for axSpA, the concise form of which is shown in **Table 2.5**, is based on two sets. One set utilizes the clinical and imaging (by conventional pelvic radiography or by MRI) findings and the other is based on the HLA-B27 status and the clinical findings.

The presence of sacroiliitis (by radiography or by MRI) plus at least one SpA feature (imaging arm) or the presence of HLA-B27 plus at least two SpA features (clinical arm) has 82.9% sensitivity and 84.4% specificity. ASAS has also developed and evaluated the accuracy of the new classification criteria and compared them with the ESSG and the Amor criteria, using the opinion of an expert panel as the reference standard. The ASAS criteria had a sensitivity of 77.8% and a specificity of 82.9%. The modified ESSG criteria had a sensitivity and a specificity of 62.5% and 81.1%, respectively, and the Amor criteria had a sensitivity and a specificity of 39.8% and 97.8%, respectively.[15]

TABLE 2.3 — Amor Criteria for Spondyloarthropathy

Parameters	Scoring
A. Clinical symptoms or past history of:	
1. Lumbar or dorsal pain at night or morning stiffness of lumbar or dorsal region	1
2. Asymmetric oligoarthritis	2
3. Buttock pain	1
	or
Alternating buttock pain	2
4. Sausage-like toe or digit	2
5. Heel pain or other well-defined enthesitis	2
6. Iritis	2
7. Nongonococcal urethritis or cervicitis within 1 month before the onset of arthritis	1
8. Acute diarrhea with 1 month before the onset of arthritis	1
9. Psoriasis, balanitis, or inflammatory bowel disease (UC or CD)	2
B. Radiologic findings	
10. Sacroiliitis (bilateral grade 2 or unilateral grade 3)	3
C. Genetic background	
11. Presence of HLA-B27 or family history of AS, reactive arthritis, uveitis, psoriasis, or inflammatory bowel disease	2
D. Response to treatment	
12. Clear-cut improvement within 48 hours after NSAID intake or rapid relapse of pain after their discontinuation	2

A patient is considered to be suffering from a spondyloarthropathy if the sum is at least 6.

Amor B, et al. *Rev Rhum Mal Osteoartic*. 1990;57(2):85-89.

TABLE 2.4 — European Spondyloarthropathy Study Group Criteria

Inflammatory spinal pain	History of or current symptoms of spinal pain (low, middle, and upper back, or neck region) with at least four of the following five components:
	1. At least 3 months in duration
	2. Onset before 45 years of age
	3. Insidious (gradual) onset
	4. Improved by exercise
	5. Associated with morning spinal stiffness
Synovitis	Past or present asymmetric arthritis, or arthritis predominately in the lower limbs
Spondyloarthropathy	Presence of inflammatory spinal pain *or* synovitis *and* one or more of the following conditions:
	■ Family history: first- or second-degree relatives with AS, psoriasis, acute iritis, reactive arthritis, or IBD
	■ Past or present psoriasis, diagnosed by a physician
	■ Past or present UC or CD, diagnosed by a physician and confirmed by radiography or endoscopy
	■ Past or present alternating buttocks pain
	■ Past or present spontaneous pain or tenderness on examination of the site of the insertion of the Achilles tendon or plantar fascia (enthesitis)
	■ Episode of diarrhea occurring within 1 month before onset of arthritis
	■ Nongonococcal urethritis or cervicitis occurring within 1 month before onset of arthritis
	■ Bilateral grade 2 to 4 sacroiliitis or unilateral grade 3 or 4 sacroiliitis according to the following grading system: 0=normal, 1=possible, 2=minimal, 3=moderate, 4=completely fused (ankylosed)

Dougados M, et al. *Arthritis Rheum*. 1991;34(10):1218-1227.

TABLE 2.5 — ASAS Classification Criteria for Axial Spondyloarthritis

Patients With Back Pain ≥3 Months and Age at Onset <45 Years		
Sacroiliitis on Imaging Plus ≥1 SpA Feature	**OR**	**HLA-B27 Plus ≥2 Other SpA Features**
Sacroiliitis on Imaging ■ Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA *OR* ■ Definite radiographic sacroiliitis according to mNY criteria		***SpA Features*** ■ Inflammatory back pain ■ Arthritis ■ Enthesitis (heel) ■ Uveitis ■ Dactylitis ■ Psoriasis ■ CD/UC ■ Good response to NSAIDs ■ Family history for SpA ■ HLA-B27 ■ Elevated CRP

Rudwaleit M, et al. *Ann Rheum Dis*. 2009;68:777-783.

The accuracy of the imaging-arm of the ASAS criteria alone was studied in a case-control study of 48 patients with and without rheumatologist-diagnosed SpA found a sensitivity of only 66% but a specificity of 94%.[16] On the other hand, as mentioned earlier, the mNY criteria set for classification of AS is very highly specific (98% specificity) and very useful clinically if the criteria set is met; but it is not sensitive enough (83% sensitivity) to encompass all patients with AS.[8] The positive predictive value of the confirmation of the initial diagnosis of axSpA after 3 to 5 years of follow-up has been found to be over 90%.[17]

The complex multi-arm selection design of the ASAS classification criteria introduces considerable heterogeneity between patients with radiographic and nr-axSpA, and between the imaging and the clinical arm.[18] Application of MRI of the SI joints (SIJ) has resulted in a considerably higher prevalence rate of axSpA, along with a higher proportion of females and a lower prevalence figures for HLA-B27 among people classified as axSpA.[19] Data suggest misclassification bias can result in some chronic back pain patients getting falsely labeled as suffering from axSpA. Moreover, the criteria lack, in particular, construct and content validity.[19] Suggestions regarding how to improve the ASAS criteria have been published,[19] and attempts are underway to improve this criteria set. However, it can be stated that these new criteria may enable early recognition of axSpA in patients who present with chronic back pain with onset before age 45, but only after other causes for the patient's clinical presentation have been excluded.

AxSpA seems to progress to radiographic sacroiliitis relatively more slowly in women than in men. Therefore, among patients classified as nr-axSpA by the ASAS criteria, women comprise >50% of the patients. This confirms the original observation published more than 36 years ago that that women relatively more often present with "spondylitic disease without radiographic evidence of sacroiliitis."[20] The term "non-radiographic" is currently used to describe this form of axSpA, but it has not been firmly established that nr-axSpA and AS represent one single disease entity because differences between the two entities have been reported regarding gender, HLA-B27 status, burden of inflammation, clinical course, and response to anti-TNF treatment.[3,18-22] A 35-year follow-up study of a cohort of patients with axSpA and their first-degree relatives revealed considerable heterogeneity of axSpA.[23] One of its major findings was a divergence between AS and nr-axSpA in sex ratios, with a male:female ratio of 2.5:1 for AS, compared to 1:1 for nr-axSpA. Moreover, although data on progression are limited, it appears that not all patients who are diagnosed with nr-axSpA progress to AS, and it may be too early to accept the concept that axSpA is one disease with a spectrum from nr-axSpA to radiographic-axSpA (AS).

A study reported that only a minority (26%) of patients with nr-axSpA progressed to AS when followed for up to 15 years.[24] These authors have

therefore stated that "the classification criteria for nr-axSpA identifies many patients who are unlikely to progress to AS," and they have proposed that nr-axSpA is a prolonged prodromal state that requires longer follow-up to document its evolvement to AS.[24] It has been suggested that nr-axSpA may represent an early stage of AS but may also just be an abortive form of a disease which does cause much pain but which may also never lead to structural changes of the axial skeleton.[25] Moreover, the cut-off between nr-axSpA and AS seems artificial and unreliable, and therefore the term nr-axSpA is much more important for classification than to diagnose patients with axSpA.[25] A latent class and transition analysis conducted in two early axSpA cohorts revealed that there is a considerable overlap between axSpA and peripheral SpA, larger than expected when the ASAS criteria were developed.[26] This analysis, additionally, identified a group of patients representing a grey zone, called "axial SpA at risk." Of these individuals ≥ 84% fulfilled the ASAS criteria, although they were considered to neither have SpA nor to ever develop it.[26]

Incidentally, the EMA approved the use of three TNF inhibitors (etanercept, adalimumab, and certolizumab) for the treatment of patients with nr-axSpA following the initial phase 3 trials conducted in this patient population. However, in United States, the FDA raised several key concerns, such as the uncertainty in the long-term clinical course of this entity and potential misdiagnosis of nr-axSpA in patients with fibromyalgia in the absence of objective signs of inflammation, and did not approve initial applications of adalimumab and certolizumab for the treatment of nr-axSpA.[27] The FDA has later approved certolizumab pegol, secukinumab, and ixekizumab for the treatment of nr-axSpA, based on clinical trials which addressed and resolved the key issues raised by the FDA.[28-30]

However, due to the absence of any diagnostic criteria for AS/axSpA, clinicians sometimes inappropriately use the classification criteria for diagnosis. This was unfortunately perpetuated in part by the statement in the abstract of the original paper describing the validation and final selection of the ASAS classification criteria for axSpA that stated that these criteria "may help rheumatologists in clinical practice in diagnosing axSpA in those with chronic back pain."[14] A recent international survey performed in five countries demonstrated that a substantial majority of rheumatologists are using the classification criteria for diagnostic purpose, while 40%

rheumatologists think that the criteria need to be modified.[31] It is of utmost importance to emphasize that the classification criteria and diagnostic criteria differ in several aspects (**Table 2.6**).[13]

The diagnostic approach is aimed at the estimation of the probability of a suspected disease, whereas the classification approach should be applied to patients with an established diagnosis to define a group, eg, for clinical and genetic research (**Table 2.7**).[32] To establish the diagnosis of a disease in clinical practice, we need to exclude other conditions that may explain the patient's symptoms, and such exclusions are not included in the ASAS classification criteria. As clinicians we make decisions about likelihood of a diagnosis that is based on the patient's clinical history, physical examination, investigations and exclusion of alternative explanations. This decision is not based on whether the patient fulfills the classification criteria. It is hoped that, in near future, advances in our understanding of the biology of axSpA via novel imaging, genetic and biomarker studies will enable the resolution of many current issues in axSpA diagnosis and classification.[33]

TABLE 2.6 — Comparison of the Classification and the Diagnostic Criteria

Diagnostic Criteria	Classification Criteria
Used by a physician to make a diagnosis	Applied to patients in whom the diagnosis has already been made
When making the diagnosis, the value of diagnostic tests/parameters depends on the prevalence of the disease (pretest probability)	Prevalence of the disease is not important, since all patients should have the disease (have been previously diagnosed)
The purpose of diagnostic criteria/algorithms is to help diagnose individual patients	The purpose of classification criteria is to provide a unique language for researchers to evaluate homogeneous groups of patients, which facilitates comparisons of clinical or experimental studies
Criteria for diagnosis should have a high *sensitivity* in order to identify as many patients with the disease as possible	Criteria for classification should have a high *specificity* (close to 100%) in order to avoid misclassification (inclusion of patients who do not have the disease)
Should allow for flexibility in diagnostic confidence (definite, probable, possible)	Gives a yes or no answer (criteria fulfilled or not fulfilled)
Applies to the individual patient	Applies to groups of patients

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TABLE 2.7 — Main Differences Between Classification and Diagnostic Approaches

	Diagnostic Approach	Classification Approach
Aim	To establish the diagnosis of a disease in clinical practice	To define a homogeneous group of patients for research purposes
The starting point	Suspicion of a disease with a certain level of a pre-test probability	Established diagnosis of a disease
Differential diagnoses or other conditions that might explain symptoms	Always considered	Not considered
Values of the positive diagnostic tests	Different and depend on the test itself, earlier screening or diagnostic tests performed, geographic region and background population	Few levels with the same value of parameters on the same level
Values of the negative diagnostic tests	Negative test results are considered; their diagnostic values depend on the same factors as for positive test results	Not considered except the situation that there are not enough positive test results to fulfil the criteria
Outcome	Probability of the disease presence	Yes or no answer (classification criteria fulfilled or not fulfilled) with a certain level of sensitivity and specificity
External reference ('gold standard')	None	Expert opinion derived during classification criteria development

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