Improving diagnosis of ankylosing spondylitis and spondyloarthritis in general

Ankylosing spondylitis is a chronic inflammatory disease belonging to a group of spondyloarthritides that are characterized by the involvement of the axial skeleton (sacroiliac joints and spine), certain pattern of the peripheral joint involvement, typical extra-articular manifestations, relatively high prevalence in the general population (approximately 2% for the whole spondyloarthritides group) and a large (approximately 9 years) diagnosis delay. In the last few years, important steps towards the shortening of this delay have been made. In this review, the current concept of the disease, the most typical manifestations of ankylosing spondylitis and spondyloarthritides in general, recent advances in the imaging of spondyloarthritides, the approach for the early diagnosis of ankylosing spondylitis/spondyloarthritides in routine clinical practice, new classification criteria of axial and peripheral spondyloarthritides, and early referral strategies are discussed.

KEYWORDS: ankylosing spondylitis ■ ASAS ■ criteria ■ diagnosis ■ MRI ■ spondyloarthritis

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Learning objectives

Upon completion of this activity, participants should be able to:

- Analyze the epidemiology of spondyloarthritis
- Assess the clinical presentation of spondyloarthritis
- Develop a diagnostic approach for a patient with possible spondyloarthritis
- Evaluate the use of ancillary studies in cases of suspected spondyloarthritis

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Spondyloarthritis concept

The term 'spondyloarthritis' (SpA) is an umbrella term for a group of diseases sharing common clinical and genetic features, such as involvement of the axial skeleton (sacroiliac joints and spine), a certain pattern of the peripheral joint involvement (usually asymmetric oligoarthritis with predominant affection of the lower limbs), development of enthesitis, dactylitis, acute anterior uveitis, presence of psoriasis or inflammatory bowel disease and association with HLA-B27 antigen. Depending on the predominant clinical manifestations, SpAs can be classified either as an axial SpA (characterized by predominant involvement of the spine and/or sacroiliac joints: ankylosing spondylitis [AS], nonradiographic axial SpA, certain forms of psoriatic arthritis and arthritis associated with inflammatory bowel disease [i.e., Crohn's disease or ulcerative colitis]) or as a peripheral SpA (predominant manifestations are peripheral arthritis, enthesitis and/or dactylitis: psoriatic arthritis, arthritis associated with inflammatory bowel disease, reactive arthritis, certain forms of undifferentiated [oligo-]arthritis fulfilling the SpA criteria). Nonradiographic (i.e., without definite sacroiliitis on x-ray) axial SpA and AS are now considered as two possible stages of one disease (axial SpA) [1], the rate of progression from nonradiographic (without radiographic sacroiliitis) to radiographic (with definite radiographic sacroiliitis, i.e., AS) stage is approximately 12% over 2 years [2], although there are patients who remain at the nonradiographic stage during the entire course of the disease without progression to established AS.

Epidemiology

AS – the prototype disease of the SpA group – has an estimated prevalence of approximately 0.5% [3,4] in the white European and north American populations, while the estimated prevalence for the whole group of SpA is approximately 1.5–2% [3,4]. The prevalence of AS and the whole group of SpA is closely related to the prevalence of the HLA-B27 antigen in a given population. HLA-B27 is most prevalent in northern countries and is highest in Eskimo populations and among Haida Indians (up to 50%) [5,6] giving a high prevalence of AS of approximately 6% [6]. In the central European population, the HLA-B27 is as common as 6 to 9% [5,7], while in Japanese or central and south African populations its prevalence (and the SpA prevalence, accordingly) is close to 0%. Males are approximately 2.5-times more often affected than females and in general have more severe disease (more radiographic damage). In up to 40% of the patients with AS, significant functional impairment may occur with a close relationship between the grade of impairment and the duration of the disease [8,9].

In the majority of patients the first symptoms of SpA (usually back pain) start in the third or fourth decade of life. Only approximately 5% of the patients report the symptoms' onset after the age of 45 years [10]. At the same time the diagnosis of AS is commonly delayed by 8–10 years after the first symptom onset [10] (this might be even longer in a case of juvenile onset [11]) that currently represents the major challenge in this area.

Importance of early diagnosis

There are several reasons for the large diagnosis delay in AS/SpA. One of the most obvious is a set of criteria (the modified New York criteria for AS) requiring the presence of radiographic sacroiliitis for the definite AS diagnosis (**Box 1**) [12]. Published in 1984 they still remain a basis for the AS diagnosis in many situations but they are obviously useless in patients who have yet to develop radiographic sacroiliitis. At the same time patients with early (nonradiographic) axial SpA have the same level of pain and stiffness in comparison with patients with more advanced disease (established AS) [13] and, therefore, require effective treatment. Early diagnosis would lead to early initiation of appropriate and effective therapy [14,15] and could improve outcome. Moreover, short disease duration and good functional status has been identified as predictors of good clinical response to the TNF-α blocking agents [16,17].

Another major reason for the large diagnosis delay in AS/SpA is a lack of SpA-awareness among primary care physicians. Indeed, SpA is

Box 1. The modified New York criteria for ankylosing spondylitis.

Clinical criteria

- Low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved by rest
- Limitation of motion of the lumbar spine in both the sagittal and frontal planes
- Limitation of chest expansion relative to normal values correlated for age and sex

Radiological criterion

- Sacroiliitis Grade ≥2 bilaterally, or Grade 3–4 unilaterally

Definite ankylosing spondylitis is present if the radiological criterion is associated with at least one clinical criterion.
Adapted with permission from [12].

responsible for only approximately 5% of the cases of chronic back pain in the general population [18]. A simple and effective screening strategy allowing quick identification of patients with high probability of axial SpA among the large group of patients with chronic back pain on the primary care level for a further referral to a rheumatologist is urgently needed.

SpA features relevant for the early diagnosis

Clinical manifestations

The leading clinical symptom of AS/axial SpA is back pain. Back pain in general is extremely prevalent: at least two thirds of the world populaiton experience back pain during their lives [19]. However, back pain in SpA has several typical features distinguishing it from pain of another origin and giving a certain picture of 'inflammatory back pain'. Inflammatory back pain is a chronic back pain (duration >3 months) starting insidiously and usually prior to 45 years of age, having a peak intensity in the second half of the night and early morning hours, improving with exercise and not improving (even worsening) at rest and accompanied with morning stiffness (usually lasting more than 30 min) (**Box 2**). A less frequent but more specific feature of inflammatory back pain is an alternating buttock pain.

Currently, three sets of criteria for inflammatory back pain exist (Calin's criteria [20], Berlin criteria [21] and the most recent Assessment of Spondyloarthritis [ASAS] criteria [22]), all combining the features described above.

Of note, inflammatory back pain can be observed in 20–25% of patients with noninflammatory (mechanical) causes of chronic back pain [20,21] that somewhat limits the diagnostic value of inflammatory back pain as a symptom of axial SpA. Although the presence of inflammatory back pain alone does not suffice to make a diagnosis of axial SpA, the presence of inflammatory back pain is an important symptom that should prompt further diagnostic tests for axial SpA.

In addition to inflammatory back pain, two details of patient's medical history have an important value in early AS/SpA diagnosis: major reduction in back pain within 48 h in response to a full dose of NSAIDs and positive family history of SpA.

Other common SpA features (peripheral arthritis, enthesitis, dactylitis, uveitis, psoriasis and inflammatory bowel disease) might not be present at disease onset but might develop later. Therefore, the presence of these symptoms significantly increases the probability of SpA but their absence does not decrease it [23,24].

Laboratory tests

The association of SpA with the presence of the HLA-B27 antigen is widely known. More than 80% of patients with AS [13,25] and more than 70% of the patients with axial SpA [13] are positive for HLA-B27 (as opposed to 8% in the general Caucasian population [25]) which makes this marker important for SpA diagnosis. However, despite the strong association between AS and HLA-B27, AS develops only in a minority (approximately 5%) of HLA-B27-positive subjects [7]. Twin studies demonstrated that HLA-B27 contributes to less than 40% of the genetic susceptibility to AS [26]. Therefore, attempts to identify other genes within and outside the MHC associated with AS and SpA are still ongoing. Recently, a scan of 14,500 single nucleotide polymorphisms revealed two new loci related to AS: ERAP1 (ARTS1) and IL23R [27].

Box 2. Typical features of inflammatory back pain.

- Insidious onset
- Morning stiffness in the spine for >30 min
- Improvement of pain and stiffness with exercise and not with rest
- Pain at night, usually in the second half with improvement upon getting up

Inflammatory back pain starts typically prior to 45 years of age and has a duration of more than 3 months.

Acute phase reactants (C-reactive protein and erythrocyte sedimentation rate) have only a limited value in the early SpA diagnosis since approximately 50% of patients with SpA have normal values of these tests [28]. However, C-reactive protein is relevant for the disease activity assessment since it correlates with clinical parameters such as spinal pain [28] and predicts radiographic progression in the sacroiliac joints and in the spine [2,29]. C-reactive protein serum level is also included in the recently proposed ASAS-endorsed AS Disease Activity Score [30,31].

Imaging

Imaging is considered as a cornerstone of the AS and axial SpA diagnosis. The diagnosis of definite AS according to the modified New York criteria [12] relies on the presence of definite sacroiliitis (at least Grade 2 bilaterally or Grade 3 unilaterally) on the x-ray. The established radiographic sacroiliitis grading system [12] takes into account the following changes:

- Grade 0: normal;
- Grade 1: suspicious changes;
- Grade 2: minimal abnormality – small localized areas with erosion or sclerosis, without alteration in the joint width;
- Grade 3: unequivocal abnormality – moderate or advanced sacroiliitis with one or more of: erosions, evidence of sclerosis, widening, narrowing or partial ankylosis;
- Grade 4: severe abnormality – total ankylosis.

wDespite a major historical value and wide clinical use there are several problems with this grading system. First, the sacroiliitis grades are poorly demarcated from each other, resulting in a large uncertainty of the x-ray interpretation. Second, reading of the radiographs of the sacroiliac joints is challenging and depends on many factors: quality of the image, chosen x-ray technique, individual variation of the sacroiliac anatomy and reader's experience [2,32]. Third, development of definite radiographic sacroiliitis takes months to years, making this imaging technique unsuitable for early diagnosis.

Nonetheless, due to wide availability and low costs, the x-ray imaging of the sacroiliac joints remains the first imaging technique to apply in case of suspicion of AS. Importantly, spinal changes typical for AS and visible on the x-ray (first of all, syndesmophytes) usually develop even later than sacroiliitis and not in all patients with AS, therefore, spinal x-ray cannot be recommended as an early diagnostic procedures.

In case of unequivocal abnormality on the x-ray of sacroiliac joints (Figure 1) no further diagnostic procedures are usually needed. However, suspicious abnormalities require further clarification.

Computed tomography (CT) is nearly a gold standard in detection of 'chronic' changes in the sacroiliac joints, such as erosions, sclerosis, joint space narrowing/widening and ankylosis. However, relatively high irradiation associated with this procedure, high costs and inability to detect early inflammatory changes prior to structural damage limit the value of this imaging method. This method is indicated, first of all, in patients with a long history of spinal pain in a situation when conventional x-ray of the sacroiliac joints provides no conclusive results and in cases of differential diagnosis with degenerative changes, osteitis condensans ilii, fractures and so on. In Figure 2A, conventional x-ray of the pelvis of a 29 year old female patient with inflammatory back pain demonstrates questionable joint space narrowing on the left side and possible erosions and sclerosis on the right side. CT of the sacroiliac joints (Figure 2B) shows normal left sacroiliac joints and confirms the presence of multiple erosions and subchondral sclerosis in the right sacroiliac joint.

In contrast to CT, MRI of sacroiliac joints allows true early identification of patients with axial SpA, because this method is able to visualize not only structural damage, but also active inflammation occurring prior to any 'chronic' structural changes visible with other imaging methods. With more than 90% sensitivity and specificity, no ionizing irradiation, detailed visualization of structures of interest this method nearly becomes a routine procedure for the early SpA diagnosis; the only limiting factor is a relatively high cost of the investigation; contraindications (metal implants, cardiac pacemaker) are rare.

In routine clinical practice, two MRI sequences are relevant for the diagnosis of axial SpA: short τ inversion recovery and T1-weighted sequences. T2-weighted sequences and T1-weighted postcontrast fat-suppressed sequences are supplementary. Short τ inversion recovery as a method of visualization of active inflammatory lesions has an outstanding value in early SpA diagnosis. In T1-weighted images some postinflammatory changes, less relevant for early diagnosis, but providing additional important information (e.g., for the differential diagnosis) can be recognized: fatty lesions (fat

depositions), erosions and, to a lesser extent, sclerosis and ankylosis.

Recently, ASAS together with the OMERACT group developed a definition of an active sacroiliitis in MRI [33]. According to this consensus the following types of active inflammatory lesions are considered as compatible with SpA: bone marrow edema/osteitis, synovitis, enthesitis and capsulitis (TABLE 1). Importantly, only bone marrow edema/osteitis is essential for defining active sacroiliitis. The presence of synovitis, enthesitis and capsulitis without bone marrow edema/osteitis is compatible with SpA but is not sufficient for making a diagnosis of active sacroiliitis.

FIGURE 3 provides an example of a patient without definite radiographic sacroiliitis but with active sacroiliitis as depicted by the short τ inversion recovery-MRI and even with some chronic inflammatory lesions visible in a T1-weighted image.

The diagnostic value of other imaging methods such as quantitative scintigraphy [34], contrast-enhanced Doppler-ultrasonography of sacroiliac joints [35] and PET [36] is limited and use of these methods for the routine diagnosis of AS/SpA can not be recommended. Doppler-ultrasonography, however, is a powerfull tool for the detection of peripheral SpA manifestations: arthritis, enthesitis and dactylitis.

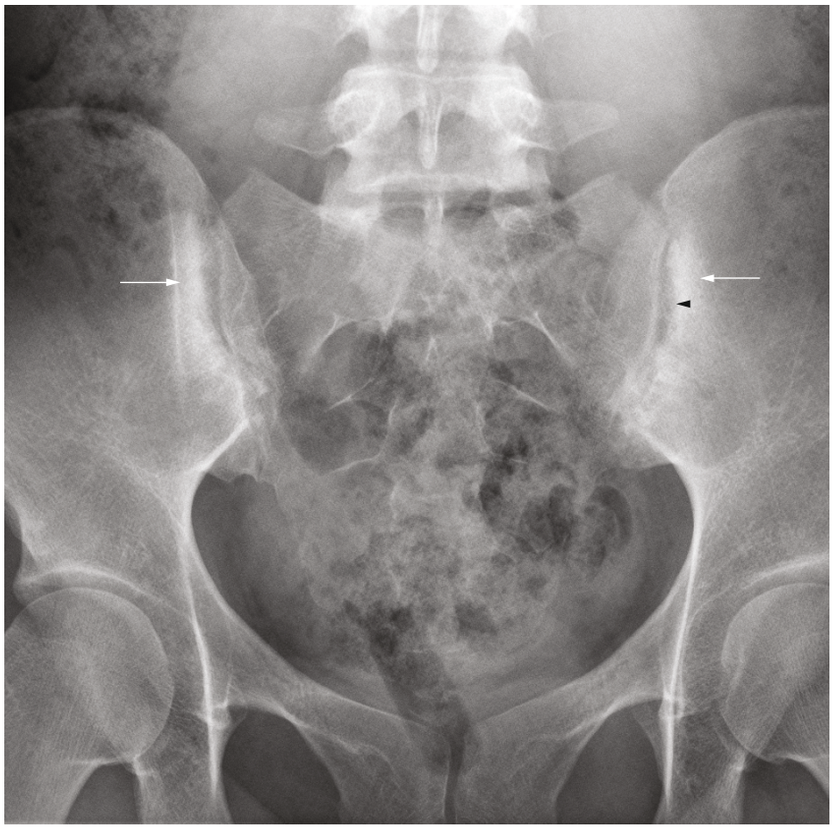

Figure 1. X-ray of the pelvis of a 31-year-old female patient with a history of inflammatory back pain over the last 7 years. Subchondral sclerosis (arrows) and multiple erosions giving a picture of the joint space widening (arrowhead) indicating bilateral radiographic sacroiliitis of Grade 3.

An approach for early SpA diagnosis in clinical practice

All clinical, laboratory and imaging manifestations described above have different diagnostic value. Both the sensitivity and specificity of each parameter can be combined in a so-called likelihood ratio (LR). Positive LR (LR+) can be calculated as: LR+ = sensitivity/(1 - specificity); and negative LR (LR-) as: LR- = (1 - sensitivity)/specificity. Higher LR+ values mean a higher probability of axial SpA if the manifestation is present and lower LR- values mean a lower SpA probability if the manifestation is absent [1,24,25]. In TABLE 2 sensitivity, specificity and LRs of the parameters relevant for the early diagnosis of SpA are presented [24].

Multiplication of LR+ or LR- of all test results gives a LR product, which can be converted into the individual probability of axial SpA using the diagram presented in FIGURE 4. It is recommended, however, to ignore the absence of some manifestations (peripheral arthritis, enthesitis, dactylitis, uveitis, psoriasis and inflammatory bowel disease) at the time of evaluation and to exclude their LR- from the LR product calculation, since these manifestations might not be present at the disease onset but develop later and, therefore, their absence does not decrease the axial SpA probability [24].

For example, in a patient with inflammatory back pain, HLA-B27 positivity and good response to NSAIDs the LR product = 3.1 × 5.1 × 9.0 = 142.3 and a pretest probability of 5% due to chronic back pain gives a post-test SpA probability of approximately 88% (axial SpA is probable). In case of presence of active inflammatory lesions in the sacroiliac joints as detected by MRI, the LR product = 3.1 × 5.1 × 9.0 × 9.0 = 1280.6 gives approximately 100% probability of axial SpA. However, absence of sacroiliitis on MRI would give a LR product = 3.1 × 5.1 × 9.0 × 0.11 = 15.7 making the diagnosis of axial SpA rather unlikely.

New classification criteria for SpA

In contrast to diagnostic criteria, classification criteria are not intended for use in clinical practice for making decisions on diagnosis. Classification criteria are a tool for clinical trials providing 'yes' or 'no' answers, while diagnostic

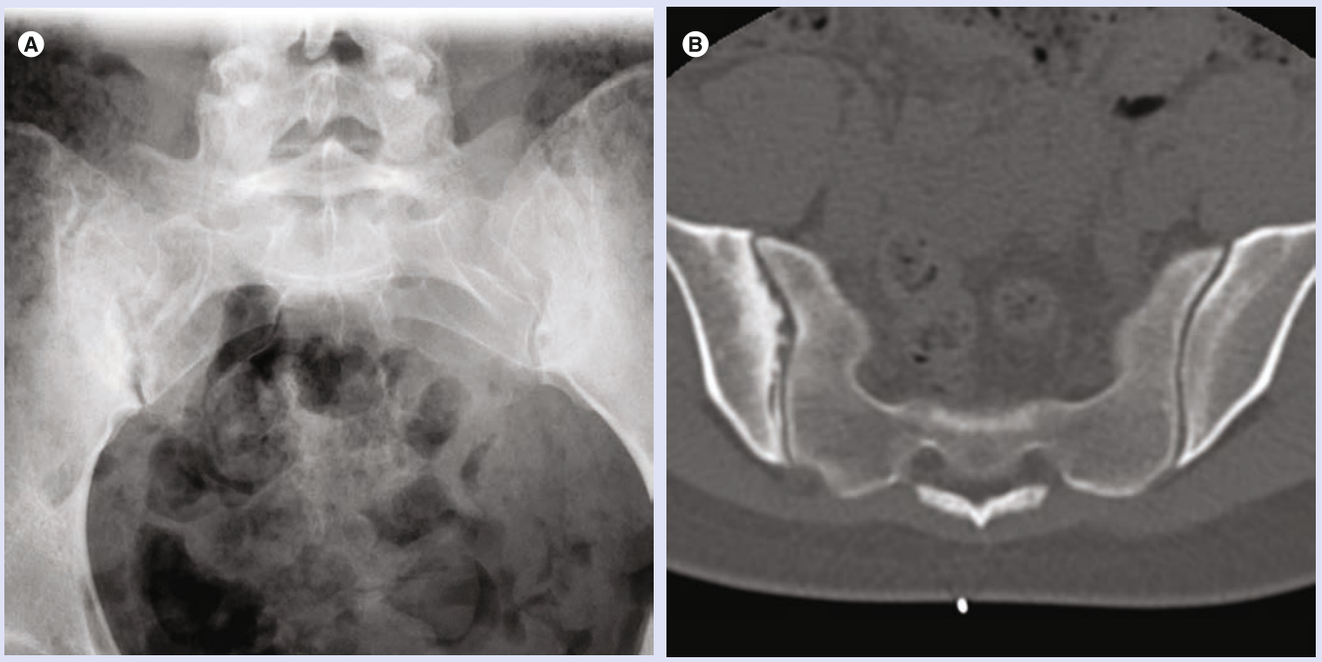

Figure 2. Conventional pelvic x-ray and computed tomography of the sacroiliac joints of a 29-year-old female patient with a history of inflammatory back pain over the last 5 years. (A) X-ray. Suspicious changes on the left side (possible joint space narrowing) and minimal definite changes (localized area of sclerosis and possible erosions in the lower portion of the sacroiliac joint) on the right side. **(B)** Computed tomography. No changes on the left side and definite structural changes (multiple erosions, sclerosis) on the right side.

criteria operate rather with disease probability. Nonetheless, due to lack of true diagnostic criteria for AS/SpA, classification criteria, such as the already discussed modified New York criteria [12], have been frequently used for decision making in clinical practice. Two historical sets

Table 1. Definition of active inflammatory lesions on MRI compatible with active sacroiliitis.

Active inflammatory lesion	Definition
Bone marrow edema/osteitis	Hyperintense signal on STIR images and usually as a hypointense signal on T1 images. The more intense the signal the more likely that it reflects active inflammation. A strong hyperintense signal is similar to that of blood vessels or spinal fluid. A hyperintense signal on contrast-enhanced, T1-weighted, fat-saturated images (T1 post-Gd) reflects increased vascularisation and is referred to as osteitis Bone marrow edema/osteitis is an indicator of active sacroiliitis but may be found in other diseases as well Affected bone marrow areas are typically located periarticularly (subchondral bone marrow) Bone marrow edema may be associated with signs of structural damage such as sclerosis or erosions
Synovitis	Synovitis is best detected as a hyperintense signal on contrast-enhanced, T1-weighted, fat-saturated images in the synovial part of the sacroiliac joints (intensity similar to blood vessels). STIR sequences do not differentiate between synovitis and physiological joint fluid Synovitis on MRI as a single feature (without bone marrow edema) is very rare and does not suffice for making a diagnosis of sacroiliitis for classification purposes
Enthesitis	Depicted as a hyperintense signal on STIR images and/or on contrast-enhanced, T1-weighted, fat-saturated images at sites where ligaments and tendons attach to bone, including the retroarticular space (interosseous ligaments). The signal may extend to bone marrow and soft tissue
Capsulitis	Capsulitis has similar signal characteristics to those of synovitis but these changes involve the anterior and posterior capsule. Anteriorly, the joint capsule gradually continues into the periosteum of the iliac and sacral bones and thus corresponds to an enthesis. Capsulitis may therefore extend far medially and laterally into the periosteum

The presence of definite subchondral bone marrow edema/osteitis highly suggestive of sacroiliitis is mandatory for defining of active sacroiliitis. The presence of synovitis, capsulitis or enthesitis only without subchondral bone marrow edema/osteitis is compatible with but not sufficient for making a diagnosis of active sacroiliitis.
STIR: Short τ inversion recovery.
Adapted from [33].

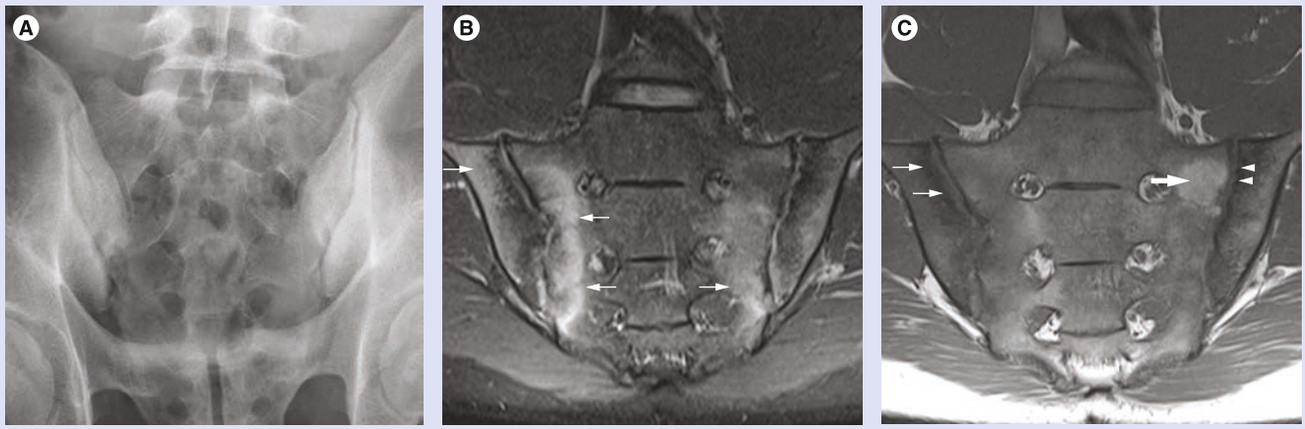

Figure 3. X-ray and MRI (STIR and T1-weighted sequences) of sacroiliac joints of a 29-year-old male patient with a history of inflammatory back pain over the last 3 years. (A) Conventional x-ray of sacroiliac joints (pelvis) demonstrates only suspicious changes (blurred joint contours) without clear sclerosis, erosions or joint space width changes: sacroiliitis Grade 1 bilaterally. **(B)** MRI of sacroiliac joints in STIR sequence: large areas of hyperintense signal (arrows) corresponding to bone marrow edema/osteitis compatible with active sacroiliitis. **(C)** MRI of sacroiliac joints in T1-weighted sequence: erosions (arrowheads), fatty lesion/fat deposition (thick arrow), subchondral sclerosis (hypointense in both STIR and T1 sequences, thin arrows).
STIR: Short τ inversion recovery.

of criteria for SpA in general (Amor criteria [37] and the European Spondyloarthropathy Study Group (ESSG) criteria [38]) were widely used in the past decades but have several limitations (e.g., absence of sacroiliitis on MRI as a criterion, no differentiation into axial and peripheral SpA and no possibility to classify patients with enthesitis without synovitis as SpA), which forced the ASAS group to develop new classification criteria for axial [39,40] and peripheral SpA (FIGURE 5) [41].

The criteria for axial SpA can be applied for patients with chronic back pain independently from the presence or absence of peripheral manifestations (e.g., arthritis, enthesitis and dactylitis). These criteria have two arms (FIGURE 5A):

- 'Imaging' arm – in order to fulfill the criteria patients should have sacroiliitis on x-ray or MRI and at least one additional SpA parameter;
- 'Clinical' arm – for patients without sacroiliitis on imaging, HLA-B27 plus at least two further SpA parameters must be present.

The sensitivity of the axial SpA criteria is 82.9% and the specificity is 84.4% [40].

In patients with peripheral manifestations only (peripheral arthritis compatible with

Table 2. Sensitivity, specificity and likelihood ratios of single parameters, which are relevant for the early diagnosis of ankylosing spondylitis/axial spondyloarthritis.

Parameter	Sensitivity (%)	Specificity (%)	LR+	LR-
Inflammatory back pain	75	76	3.1	0.33
Peripheral arthritis	40	90	4.0	0.67†
Enthesitis (heel)	37	89	3.4	0.71†
Dactylitis	18	96	4.5	0.85†
Anterior uveitis	22	97	7.3	0.80†
Psoriasis	10	96	2.5	0.94†
Crohn's disease/ulcerative colitis	4	99	4.0	0.97†
Positive family history for SpA	32	95	6.4	0.72
Good response to NSAIDs	77	85	5.1	0.27
HLA-B27 positivity	90	90	9.0	0.11
Elevated ESR/CRP	50	80	2.5	0.63
Sacroiliitis on MRI	90	90	9.0	0.11

†Since peripheral arthritis, enthesitis, dactylitis, uveitis, psoriasis and inflammatory bowel disease are not always present at the disease onset it is recommended to ignore their absence upon evaluation of the disease probability.
CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; LR: Likelihood ratio; SpA: Spondyloarthritis.
Adapted with permission from [24].

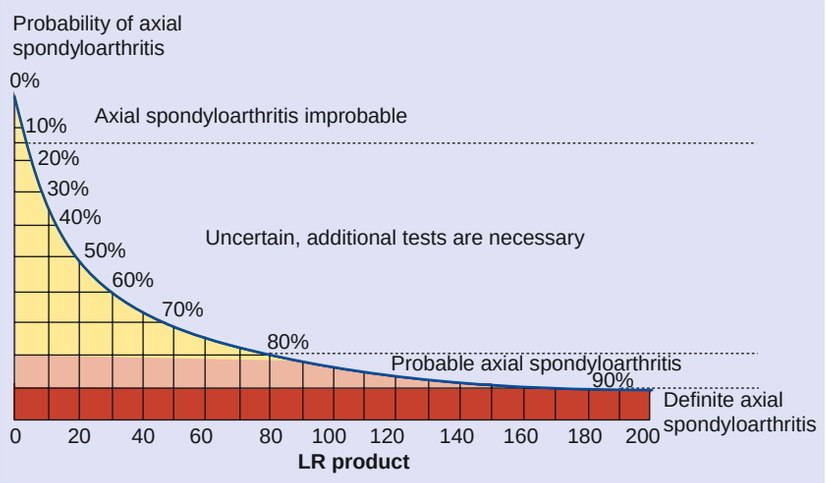

Figure 4. Relationship between the likelihood ratio product and the resulting post-test probability of axial spondyloarthritis, based on an assumed pretest probability of 5%.
LR: Likelihood ratio.
Data taken from [24].

SpA – usually predominantly affecting lower limbs and/or asymmetric; enthesitis or dactylitis) one or two SpA feature (depending on the features being positive – Figure 5B), must be present in order to fulfill the peripheral SpA criteria. The sensitivity of these criteria was estimated as 77.8% and specificity as 82.2% [41].

Development of SpA criteria sets is an important step not only in improvement of early diagnosis but also in improvement of access of patients with early (nonradiographic) axial SpA to anti-TNF therapy: in the recent update of the international ASAS recommendations on the use of anti-TNF agents, fulfillment of ASAS classification criteria for axial SpA was included as an alternative to fulfillment of the modified New York criteria for AS [15]. There are several ongoing clinical trials investigating efficacy of anti-TNF agents in patients with axial SpA without radiographic sacroiliitis and in patients fulfilling the peripheral SpA criteria. Positive results of these trials would not only increase the number of treatment options for patients with early SpA but also provide important support for the proposed SpA concept.

Referral recommendation for primary care

Early diagnosis of AS/SpA is not possible without early referral of patients to rheumatologists. There is still an unmet need for awareness improvement and referral strategy implementation on the primary care level. In 2005, our group proposed a referral strategy (Table 3) suitable for screening of patients with high probability of axial SpA among patients with chronic low back pain [42].

This strategy was evaluated for the first time in the Berlin area; the patients were referred by orthopedist (representing the primary care level for the majority of patients with back pain in Germany) and general practitioners to one center specialized on SpA. The definite diagnosis of axial SpA was made in 45.4% of 350 referred patients [43]. In patients with only one positive screening parameter, axial SpA was diagnosed in 34.2% of the cases, while in patients with at least two positive parameters a diagnosis of axial SpA was made in 62.6% of the cases [43].

In order to validate the referral strategy and to confirm the results of the initial study, we recently performed a multicenter AS survey trial to evaluate and compare referral parameters in early SpA. In this trial we compared two strategies: strategy one: the original strategy with three referral parameters described above, and strategy two with five parameters (at least two were required to be positive) – the same three parameters as in strategy one and additionally a positive family history of AS or a good treatment response to NSAIDs. Importantly, the simple strategy one was not worse but even slightly better than the more complex strategy two: 41.8% out of 318 patients referred via strategy one and 36.8% out of 242 patients referred via strategy two were diagnosed with definite axial SpA (AS or nonradiographic axial SpA) [44].

Use of inflammatory back pain as a single referral parameter might be an option for countries, in which HLA-B27 testing or imaging procedures are not usual on the primary care level or on the levels prior to referral to the rheumatologist. As shown in two recent studies, approximately one third of the patients referred to rheumatologist because of inflammatory back pain were diagnosed with axial SpA [45,46]. The main issue in such a strategy is a correct interpretation of the back pain as 'inflammatory' that requires an appropriate training and some experience. In contrast to inflammatory back pain, HLA-B27 and sacroiliitis on imaging are more objective parameters and should be applied as well where possible.

Conclusion

A substantial improvement of the early diagnosis of AS and the whole group of SpAs has occurred in the last decade. A new concept of SpA, introduction of MRI as one of the key diagnostic tools in detecting the earliest signs of inflammation, application of the early referral strategy,

development of new classification criteria for SpA have contributed to the continuous process of the early diagnosis improvement.

Future perspective

Improvement of the early diagnosis of AS/SpA is not possible without implementation of the major advances discussed above into routine clinical practice. This, in turn, is not possible without width dissemination of the SpA knowledge and increasing awareness of SpA among rheumatologists and other specialists dealing with chronic back pain. The ASAS group recently introduced a unique project: ASAS Slide Library containing approximately 250 slides covering all major topics of the SpA concept, epidemiology, diagnosis

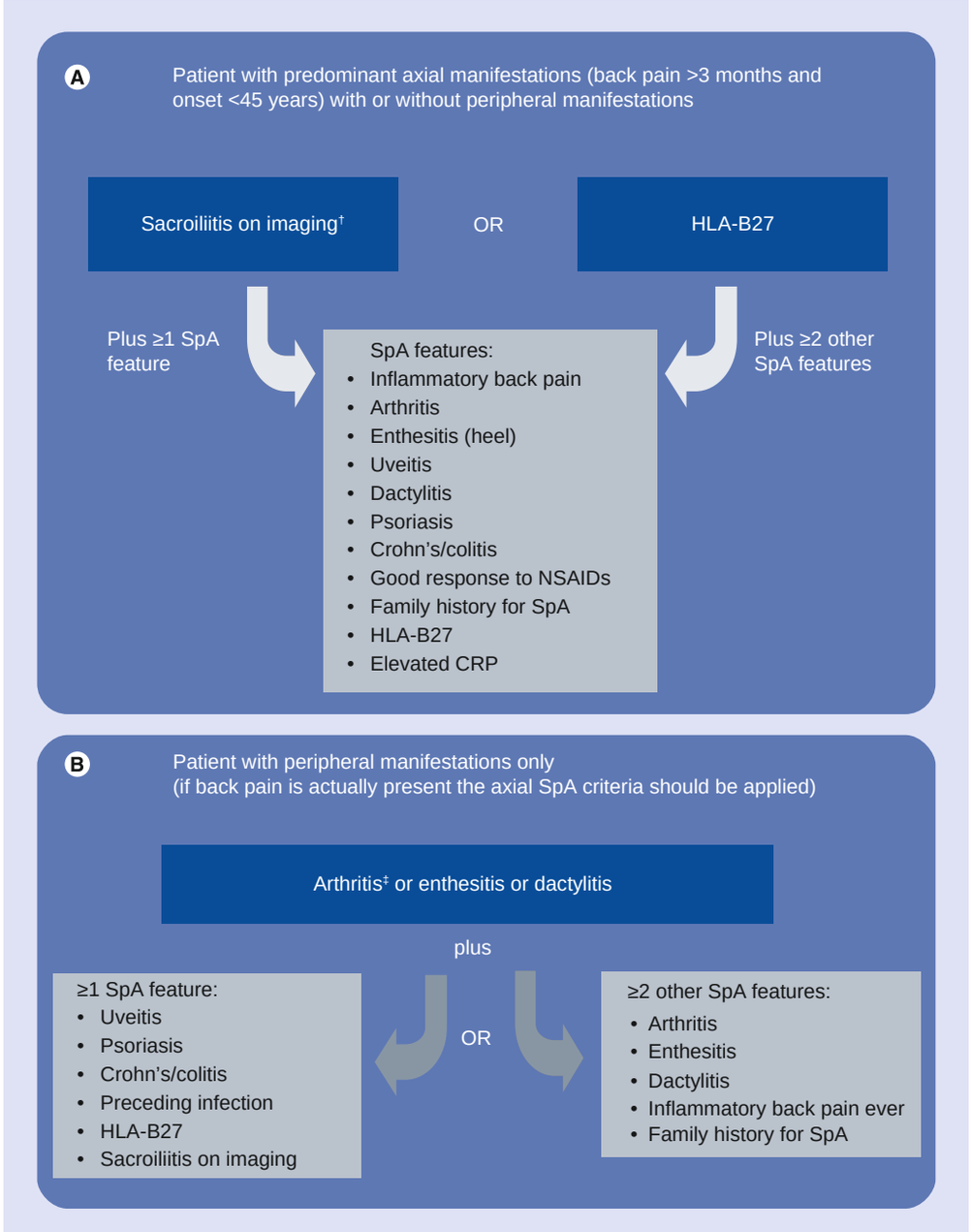

Figure 5. The Assessment of Spondyloarthritis classification criteria for axial and peripheral spondyloarthritis. (A) Axial spondyloarthritis [39,40]. **(B)** Peripheral spondyloarthritis [41].
†Sacroiliitis on imaging refers to definite radiographic sacroiliitis according to the modified New York criteria [12] or sacroiliitis on MRI according to the Assessment of Spondyloarthritis consensus definition [33].
‡Peripheral arthritis: usually predominantly lower limb and/or asymmetric arthritis.
CRP: C-reactive protein; SpA: Spondyloarthritis.

Table 3. Early referral strategy for recognition of patients with high probability of axial spondyloarthritis on the primary care level.

Step 1	A patient with chronic back pain (>3 months) and first symptoms at age <45 years
Step 2 (at least one of the following must be positive)	Inflammatory back pain or HLA-B27 positive or sacroiliitis on any imaging†
Step 3	Refer to rheumatologist

†Only if available, not recommended routinely for screening on the primary care level.
Data taken from [42].

and treatment [101]. The slide library originally developed in English has been already translated into eight languages (Chinese, German, Greek, Hungarian, Portuguese, Russian, Spanish and Turkish; translations into Croatian, French, Italian and Ukrainian are now ongoing) and has being updated annually. Importantly, the use of the ASAS slide is free for educational use and we expect continuous growth of this collection in the next years.

We expect that patients with suspicion of SpA will be referred to a rheumatologist earlier due to consecutive application of the early referral strategy on the primary care level. The use of MRI for the early diagnosis of AS/SpA will increase. We can also expect development of the definition of chronic inflammatory changes of sacroiliac joints seen in MRI that can even lead to the replacement of the x-ray by MRI as a first imaging tool if SpA is suspected.

It is anticipated that the concept of axial SpA considering nonradiographic axial SpA and AS as two possible stages of one disease will be widely accepted by clinicians. Positive results of the ongoing trials investigating anti-TNF therapy in nonradiographic axial SpA and expected label extension of anti-TNF drugs covering the whole group of axial SpA would improve acceptance of the axial SpA concept. Similarly, positive results of the trials investigating anti-TNF therapy in peripheral SpA will increase the interest to this previously poorly defined and poorly treated subgroup of patients and will improve diagnosis and treatment.

Executive summary

Concept of spondyloarthritis

- The term 'spondyloarthritis' (SpA) is a collective term for a group of diseases sharing common clinical and genetic features.
- All spondyloarthritides can be classified as axial (predominant involvement of the spine and/or sacroiliac joints) or peripheral (peripheral joint and entheseal involvement).
- Nonradiographic axial SpA and ankylosing spondylitis (AS) are considered as two possible stages of one disease.

Epidemiology

- AS has a prevalence of approximately 0.5% in the central European and north American white populations, while the prevalence of the entire SpA group is approximately 1.5–2%.

Importance of early diagnosis

- Early diagnosis of AS/SpA leads to early initiation of effective treatment and improves an outcome.

SpA features relevant for early diagnosis

- The most important clinical manifestation of AS and all axial SpAs is inflammatory back pain. Good response of back pain to NSAIDs and family history of spondyloarthritides are also relevant. Other common SpA features (peripheral arthritis, enthesitis, dactylitis, uveitis, psoriasis and inflammatory bowel disease) are not necessarily present at the disease onset.
- HLA-B27 and, to a lesser extent, acute phase reactants are laboratory tests, which are relevant for the early SpA diagnosis.
- X-ray of the sacroiliac joints is usually the first imaging procedure in patients with suspicion of AS; radiographic sacroiliitis, however, might not yet be present at the early disease stage.
- MRI is able to detect the earliest signs of inflammation in the sacroiliac joints and, therefore, is especially relevant for early diagnosis.

An approach for the early SpA diagnosis in clinical practice

- An easy approach for the calculation of the individual probability of SpA based on the positive and negative predictive value of the clinical, laboratory and imaging parameters was developed.

New classification criteria for SpA

- The Assessment of Spondyloarthritis International Society recently developed new classification criteria for axial and peripheral SpA covering nearly the whole spectrum of the spondyloarthritides.

Referral recommendation for the primary care

- We recommend that patients with chronic back pain (and back pain onset prior to 45 years of age) seen on the primary care level should be referred to a rheumatologist if at least one of the following features is present: inflammatory character of the back pain, HLA-B27 or sacroiliitis on any imaging.

References

Papers of special note have been highlighted as:
▪ of interest
▪▪ of considerable interest

1 Rudwaleit M, Khan MA, Sieper J. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? *Arthritis Rheum.* 52(4), 1000–1008 (2005).

2 Poddubnyy D, Rudwaleit M, Haibel H *et al.* Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. *Ann. Rheum. Dis.* 70(8), 1369–1374 (2011).

3 Braun J, Bollow M, Remlinger G *et al.* Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. *Arthritis Rheum.* 41(1), 58–67 (1998). Erratum in *Arthritis Rheum.* 52(12), 4049–4050 (2005).

4 Helmick CG, Felson DT, Lawrence RC *et al.* Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum.* 58(1), 15–25 (2008).

5 Khan MA. HLA-B27 and its subtypes in world populations. *Curr. Opin. Rheumatol.* 7(4), 263–269 (1995).

6 Gofton JP. Observer variation in grading sacroiliac radiography in HLA-B27 positive individuals. *J. Rheumatol.* 11(1), 107–109 (1984).

7 van der Linden SM, Valkenburg HA, de Jongh BM, Cats A. The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. A comparison of relatives of spondylitis patients with the general population. *Arthritis Rheum.* 27(3), 241–249 (1984).

8 Zink A, Braun J, Listing J, Wollenhaupt J. Disability and handicap in rheumatoid arthritis and ankylosing spondylitis – results from the German rheumatological database. German Collaborative Arthritis Centers. *J. Rheumatol.* 27(3), 613–622 (2000).

9 Feldtkeller E, Bruckel J, Khan MA. Scientific contributions of ankylosing spondylitis patient advocacy groups. *Curr. Opin. Rheumatol.* 12(4), 239–247 (2000).

10 Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol. Int.* 23(2), 61–66 (2003).

11 Ozgocmen S, Ardicoglu O, Kamanli A *et al.* Pattern of disease onset, diagnostic delay, and clinical features in juvenile onset and adult onset ankylosing spondylitis. *J. Rheumatol.* 36(12), 2830–2833 (2009).

12 van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum.* 27(4), 361–368 (1984).

13 Rudwaleit M, Haibel H, Baraliakos X *et al.* The early disease stage in axial spondylarthritis. Results from the German spondyloarthritis inception cohort. *Arthritis Rheum.* 60(3), 717–727 (2009).

14 Braun J, van den Berg R, Baraliakos X *et al.* 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann. Rheum. Dis.* 70(6), 896–904 (2011).

15 van der Heijde D, Sieper J, Maksymowych WP *et al.* 2010 update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann. Rheum. Dis.* 70(6), 905–908 (2011).

16 Rudwaleit M, Claudepierre P, Wordsworth P *et al.* Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis. *J. Rheumatol.* 36(4), 801–808 (2009).

17 Vastesaeger N, van der Heijde D, Inman RD *et al.* Predicting the outcome of ankylosing spondylitis therapy. *Ann. Rheum. Dis.* 70(6), 973–981 (2011).

18 Underwood MR, Dawes P. Inflammatory back pain in primary care. *Br. J. Rheumatol.* 34(11), 1074–1077 (1995).

19 Deyo RA, Weinstein JN. Low back pain. *N. Engl. J. Med.* 344(5), 363–370 (2001).

20 Calin A, Porta J, Fries JF, Schurman DJ. Clinical history as a screening test for ankylosing spondylitis. *JAMA* 237(24), 2613–2614 (1977).

21 Rudwaleit M, Metter A, Listing J, Sieper J, Braun J. Inflammatory back pain in ankylosing spondylitis a reassessment of the clinical history for application as classification and diagnostic criteria. *Arthritis Rheum.* 54(2), 569–578 (2006).

22 Sieper J, van der Heijde D, Landewe 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.* 68(6), 784–788 (2009).

▪ **The most recent set of criteria for inflammatory back pain developed by the Assessment of Spondyloarthritis International Society.**

23 Rudwaleit M, Sieper J. A case of axial undifferentiated spondyloarthritis diagnosis and management. *Nat. Clin. Pract. Rheumatol.* 3(5), 298–303 (2007).

▪▪ **An approach of the early diagnosis of axial spondyloarthritis in clinical practice is described.**

24 Rudwaleit M, Feldtkeller E, Sieper J. Easy assessment of axial spondyloarthritis (early ankylosing spondylitis) at the bedside. *Ann. Rheum. Dis.* 65(9), 1251–1252 (2006).

25 Rudwaleit M, van der Heijde D, Khan MA, Braun J, Sieper J. How to diagnose axial spondyloarthritis early. *Ann. Rheum. Dis.* 63(5), 535–543 (2004).

26 Brown MA, Kennedy LG, MacGregor AJ *et al.* Susceptibility to ankylosing spondylitis in twins the role of genes, HLA, and the environment. *Arthritis Rheum.* 40(10), 1823–1828 (1997).

27 Burton PR, Clayton DG, Cardon LR *et al.* Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. *Nat. Genet.* 39(11), 1329–1337 (2007).

28 Poddubnyy DA, Rudwaleit M, Listing J, Braun J, Sieper J. Comparison of a high sensitivity and standard C reactive protein measurement in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis. *Ann. Rheum. Dis.* 69(7), 1338–1341 (2010).

29 Poddubnyy D, Haibel H, Listing J *et al.* Rates and predictors of radiographic spinal progression over two years in patients with early axial spondyloarthritis. *Ann. Rheum. Dis.* 70(Suppl. 3), 327 (2011).

30 Lukas C, Landewe R, Sieper J *et al.* Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann. Rheum. Dis.* 68(1), 18–24 (2009).

31 van der Heijde D, Lie E, Kvien TK *et al.* ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. *Ann. Rheum. Dis.* 68(12), 1811–1818 (2009).

32 van Tubergen A, Heuft-Dorenbosch L, Schulpen G *et al.* Radiographic assessment of sacroiliitis by radiologists and rheumatologists: does training improve quality? *Ann. Rheum. Dis.* 62(6), 519–525 (2003).

33 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.* 68(10), 1520–1527 (2009).

▪▪ **A detailed definition of active sacroiliitis on MRI – a feature especially relevant for the early diagnosis of ankylosing spondylitis and axial spondyloarthritis.**

34 Song IH, Carrasco-Fernandez J, Rudwaleit M, Sieper J. The diagnostic value of scintigraphy in assessing sacroiliitis in ankylosing spondylitis a systematic literature research. *Ann. Rheum. Dis.* 67(11), 1535–1540 (2008).

35 Klauser A, Halpern EJ, Frauscher F *et al.* Inflammatory low back pain high negative predictive value of contrast-enhanced color Doppler ultrasound in the detection of inflamed sacroiliac joints. *Arthritis Rheum.* 53(3), 440–444 (2005).

36 Strobel K, Fischer DR, Tamborrini G *et al.* 18F-fluoride PET/CT for detection of sacroiliitis in ankylosing spondylitis. *Eur. J. Nucl. Med. Mol. Imaging* 37(9), 1760–1765 (2010).

37 Amor B, Dougados M, Mijiyawa M. Criteria of the classification of spondylarthropathies. *Rev. Rhum. Mal. Osteoartic* 57(2), 85–89 (1990).

38 Dougados M, van der Linden S, Juhlin R *et al.* The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum.* 34(10), 1218–1227 (1991).

39 Rudwaleit M, Landewe 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.* 68(6), 770–776 (2009).

40 Rudwaleit M, van der Heijde D, Landewe 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.* 68(6), 777–783 (2009).

▪▪ **The final set of the Assessment of Spondyloarthritis classification criteria for axial spondyloarthritis.**

41 Rudwaleit M, van der Heijde D, Landewe R *et al.* The Assessment of Spondyloarthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann. Rheum. Dis.* 70(1), 25–31 (2011).

▪ **Definition and classification criteria for peripheral spondyloarthritis.**

42 Sieper J, Rudwaleit M. Early referral recommendations for ankylosing spondylitis (including pre-radiographic and radiographic forms) in primary care. *Ann. Rheum. Dis.* 64(5), 659–663 (2005).

43 Brandt HC, Spiller I, Song IH, Vahldiek JL, Rudwaleit M, Sieper J. Performance of referral recommendations in patients with chronic back pain and suspected axial spondyloarthritis. *Ann. Rheum. Dis.* 66(11), 1479–1484 (2007).

▪▪ **Description and first validation of a referral strategy for patients with high probability of axial spondyloarthritis seen on the primary care level.**

44 Poddubnyy D, Vahldiek JL, Spiller I, Buss B, Rudwaleit M, Sieper J. Evaluation of 2 screening strategies for early identification of patients with axial spondyloarthritis in primary care. *J. Rheumatol.* doi:10.3899/jrheum.110070 (2011) (Epub ahead of print).

▪ **A multicenter study confirmed the good performance of a simple referral strategy with three referral parameters (inflammatory back pain, HLA-B27 and sacroiliitis on imaging) for patients with chronic back pain and suspected axial spondyloarthritis.**

45 Braun A, Saracbasi E, Grifka J, Schnitker J, Klein F, Braun J. Identifying patients with axial spondyloarthritis in primary care: how useful are items indicative of inflammatory back pain? *Arthritis Rheum. Dis.* 70(10), 1782–1787 (2011).

46 Hermann J, Giessauf H, Schaffler G, Ofner P, Graninger W. Early spondyloarthritis usefulness of clinical screening. *Rheumatology (Oxford)* 48(7), 812–816 (2009).

Website

101 Assessment in Ankylosing Spondylitis (ASAS) International Society. www.asas-group.org

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.					
	1	**2**	**3**	**4**	**5**
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1. Your patient is a 40-year-old African American man with 3 months of low back pain not related to any history of trauma or overuse. You consider whether this patient has spondyloarthritis.
You realize that spondyloarthritis is closely associated with the presence of the HLA-B27 antigen. HLA-B27 is most likely to be encountered in which of the following populations?

- ☐ **A** African Americans
- ☐ **B** Inuits
- ☐ **C** Japanese Americans
- ☐ **D** Mexican Americans

2. You take a more extended history. Which of the following findings is most suggestive of spondyloarthritis in this patient?

- ☐ **A** The absence of enthesitis
- ☐ **B** The absence of dactylitis
- ☐ **C** The absence of psoriasis
- ☐ **D** A substantial reduction in pain after taking full-dose NSAIDs

3. Which of the following clinical presentations is most consistent with a diagnosis of ankylosing spondylitis?

- ☐ **A** A peak intensity of pain in the late afternoon
- ☐ **B** Pain substantially improved with rest
- ☐ **C** Onset after age 50
- ☐ **D** Morning stiffness

4. What should you consider as you initiate a diagnostic workup for spondyloarthritis?

- ☐ **A** The presence of the HLA-B27 antigen alone is virtually diagnostic for ankylosing spondylitis
- ☐ **B** Erythrocyte sedimentation rate is universally elevated in cases of spondyloarthritis
- ☐ **C** Plain radiographs should not be used in the evaluation for possible spondyloarthritis
- ☐ **D** MRI of the sacroiliac joints allows for early identification of patients with axial spondyloarthritis