

Review Article

Axial Spondyloarthritis: Clinical Features, Classification, and Treatment

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ABBREVIATIONS

HLA-B27: human leukocyte antigen-B27; **SpA:** spondyloarthritis; **AS:** ankylosing spondylitis; **nr-axSpA:** non-radiographic axial spondyloarthritis; **ReA:** reactive arthritis; **PsA:** psoriatic arthritis; **IBD-SpA:** inflammatory bowel disease associated spondyloarthritis; **ASAS:** Assessment of SpondyloArthritis international Society; **NSAIDs:** nonsteroidal anti-inflammatory drugs; **CASPAR:** Classification Criteria for Psoriatic Arthritis; **DMARDs:** disease modifying anti-rheumatic drugs; **CD:** Crohn's disease; **UC:** ulcerative colitis; **ESR:** erythrocyte sedimentation rate; **CRP:** C-reactive protein; **TNFi:** tumor necrosis factor- α inhibitors; **X-ray:** plain radiography; **MRI:** magnetic resonance imaging; **CT:** computed tomography; **US:** ultrasonography; **wb-MRI:** whole-body MRI; **ESSG:** European Spondyloarthropathy Study Group; **IL-17i:** Interleukin-17 inhibitors; **JAKi:** Janus kinase inhibitor; **PDE4i:** phosphodiesterase 4 inhibitor

The spondyloarthropathy family is a group of rheumatologic disorders first described in the 1970s, unified by the association with human leukocyte antigen (HLA)-B27 [1,2], inflammation of the axial joints, and enthesitis [3]. The spondyloarthropathies (SpA) as a group include several distinct diseases, specifically ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), reactive arthritis (ReA), psoriatic arthritis (PsA), and inflammatory bowel disease associated spondyloarthritis (IBD-SpA). The spondyloarthropathies are considered distinct entities based on historical classification systems originally developed to describe a disease process in a certain group of patients. The classification systems have also been used as diagnostic criteria in clinical practice. Clinically, these disorders share many of the same features, including inflammatory back pain, sacroiliitis, peripheral arthritis, enthesitis, dactylitis, and anterior uveitis. Epidemiologically, the prevalence of SpA varies by region and is directly related to the prevalence of HLA-B27 in a given population. For instance, the highest prevalence of SpA is found in the Northern Arctic indigenous communities, where up to 50% of the population is positive for HLA-B27 [4,5]. In the United States, it is estimated that SpA affects up to 1% of adults, similar to the prevalence

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of rheumatoid arthritis [6]. AS affects men more than women 79.6%, whereas nr-axSpA affects men and women equally 72.4% [7], independent of HLA-B27. This article will discuss the clinical and diagnostic features of SpA, compare the classification criteria, and provide updates regarding treatment options, including the development of biologics and targeted synthetic agents.

CLINICAL FEATURES

Inflammatory back pain

Inflammatory back pain is the hallmark of SpA, present in 70-80% of patients [8]. Five major parameters have been proposed by the ASAS (Assessment of SpondyloArthritis international Society) criteria to characterize inflammatory back pain. These include improvement with exercise, pain at night, insidious onset, age of onset <40 years, and no improvement with rest [9,10]. Fulfilling four of five of these parameters had a sensitivity of 77% and specificity of 91.7% for inflammatory back pain. Other features of inflammatory back pain include duration >3 months, morning stiffness >30 min, alternating buttock pain, cervical and thoracic pain, and chest wall pain [11]. Anterior chest wall pain can be present in up to 40% of patients with SpA, prompting unnecessary diagnostic cardiovascular work ups [12]. Patients with inflammatory back pain often go undiagnosed for several years given the good response to over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs).

Peripheral SpA: arthritis, enthesitis, and dactylitis

ASAS defines peripheral SpA as the presence of peripheral arthritis or enthesitis or dactylitis, plus one or more of the following: uveitis, psoriasis, Crohn's disease/ulcerative colitis, preceding infection, HLA-B27, or sacroiliitis on imaging OR two or more of the following: arthritis, enthesitis, dactylitis, inflammatory back pain, or family history of SpA [13,14]. A higher percentage of working disability was noted in patients with peripheral SpA compared to axial SpA [15].

Peripheral arthritis typically affects the lower limbs and is asymmetric (86.6% of patients) [16]. Peripheral arthritis and enthesitis are often the predominant manifestations in children and early adolescents with SpA, whereas axial disease may be asymptomatic and only detected on MRI [17]. Peripheral joint arthritis or peripheral enthesitis is present in up to 50% of patients with AS [11].

Enthesitis, or inflammation of the connection of tendons, ligaments, or joint capsule to bone is a highly specific feature of SpA (36.5% sensitivity, 88.9% specificity) [18]. Clinically, patients experience pain and stiffness at the site of enthesitis. In a meta-analysis of eight studies totaling 2,236 patients, enthesitis was present in 28.8-35.4% of patients with SpA [7].

Dactylitis is swelling of the digits due to inflammation of the joint capsules, entheses, and tendon sheaths. In the meta-analysis described above, dactylitis was a relatively uncommon feature of SpA, present in only 6% of patients with SpA [7]. Dactylitis has also been described in other conditions, such as sickle cell anemia.

Extra-Articular Features: anterior uveitis, psoriasis, and inflammatory bowel disease

Anterior uveitis, or inflammation of the anterior middle layer of the eye, the uvea, is highly associated with HLA-B27 [19]. Presenting symptoms include acute onset unilateral redness, pain, photophobia, and visual impairment [11]. The prevalence of uveitis increases with disease duration [20]. In subsequent flares, the inflammation becomes recurrent, bilateral, and alternating [19]. These episodes may occur independently of musculoskeletal symptoms such as inflammatory low back pain, peripheral arthritis, and enthesitis. A systematic review found the prevalence of anterior uveitis to be approximately 26% in patients with AS [4]. Uveitis associated with AS and ReA is usually acute, unilateral, anterior, and recurrent while that associated with PsA and IBD-SpA is more chronic, bilateral, and often involving posterior elements.

Psoriasis is a disease of chronic skin inflammation which may occur alone or in association with other conditions. In association with SpA, it is known as psoriatic arthritis (PsA). Although clinical features are variable, arthritis is typically severe, with bone erosions observed in 47% of patients within the first two years [21]. PsA is considered highly heritable, with the risk of disease presence in siblings being higher than that in rheumatoid arthritis [22]. The Classification Criteria for Psoriatic Arthritis (CASPAR) published in 2006 is a scoring system used in clinical practice and clinical trials, given that no uniform diagnostic criteria currently exist. It includes current, history of, or family history of psoriasis, psoriatic nail dystrophy, negative test for rheumatoid arthritis, current or history of dactylitis, and radiographic juxta-articular new bone formation [22].

Patients with PsA have a number of unique X-ray findings including joint space narrowing, marked joint destruction and bone resorption causing "pencil-in-cup" deformities, ankylosis, acro-osteolysis, and periostitis in the small joints of the hands and feet [14,21]. Radiographic damage may persist in up to 47% of

PsA patients at a median interval of two years despite treatment with disease modifying anti-rheumatic drugs (DMARDs) [21].

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), has been identified as a major extra-articular feature of SpA. There is a postulated relationship between joint and gut inflammation, and HLA-B27 may be responsible for mediating this connection at least in patients with axial disease [23]. In patients with AS, the prevalence of IBD is approximately 5-10%, with CD occurring more commonly than UC [11]. IBD is often clinically quiescent; however, ileal inflammation is detected upon colonoscopy with a prevalence of 30-44% [23]. Patients may have progression of their disease from asymptomatic intestinal inflammation to overt clinical IBD with evidence of persistent macroscopic ulcerations or histological inflammation on colonoscopy [23].

LABORATORY FEATURES

Although there are no laboratory features with absolute specificity for SpA, strong associations have been noted between SpA, HLA-B27, and elevated acute phase reactants.

HLA-B27 is known to be strongly associated with SpA [1,2]. While the presence of HLA-B27 is non-diagnostic, it exists in 90-95% of patients with AS and in 50-75% of patients with other forms of SpA [24]. Over 160 subtypes of HLA-B27 have been recognized, with HLA-B*27:05 being the most common subtype worldwide [24]. The role of HLA-B27 in the pathogenesis of SpA still remains uncertain. The leading theory is implicated in the abnormal function of HLA-B27 in antigen presenting cells, thereby triggering an immune mediated inflammatory response either by presentation of arthritogenic peptide or direct stimulation of effector cells. Another theory is that HLA-B27 contributes to gut inflammation and drives the downstream activation of IL-17, IL-22, IL-23, TNF- α , and other proinflammatory cytokines. These proinflammatory cytokines have been directly associated with the development of clinical features seen in SpA, including enthesitis (IL-17, IL-23), osteoproliferation with bone formation (IL-22), synovitis, and bone destruction (TNF- α , IL-17) [11].

Acute phase reactants, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are elevated in 35-50% of patients with predominantly axial SpA. In early axial SpA, elevated ESR and CRP levels are independently associated with spinal radiographic progression [25]. Mean ESR and CRP levels are significantly higher in patients with AS than nr-axSpA [26]. An elevated CRP level has been associated with radiographic sacroiliitis and the presence of syndesmophytes, or ossification of the spinal ligaments, in patients with AS [26]. Higher levels of acute phase reactants have further been shown to correlate with better response to treatment with tumor necrosis factor- α inhibitors (TNFi) [27].

RADIOLOGICAL FEATURES

There are a number of characteristic imaging findings in patients with SpA. Imaging modalities include plain radiography (X-ray), magnetic resonance imaging (MRI), computed tomography (CT), ultrasonography (US), and bone scintigraphy.

Plain radiography (X-ray): When considering a diagnosis of SpA, a plain film of the pelvis should be obtained to assess for sacroiliitis. Specific sacroiliac views can be obtained but are often not necessary. Radiographic findings of sacroiliitis include erosions, which may appear as widening of the joint space, sclerosis of the joint margins, joint space narrowing, and ankylosis or fusion of the joints, progressing in this order (Figures 1-3). The presence of sacroiliitis is graded on a scale of 0 through 4 by the presence of characteristic radiographic findings (Table 1) [9]. A patient is considered to have evidence of radiographic sacroiliitis if the imaging study is Grade 2 or higher bilaterally or Grade 3 or higher unilaterally [8]. Radiological sacroiliitis was observed in all AS patients, with the majority having reported Grade 2 findings [28].

In patients with early axial SpA, the presence of syndesmophytes at baseline was found to be a strong independent predictor of further spinal radiographic progression [25]. X-ray is superior to MRI for detecting syndesmophytes (Figure 4) [8]. One limitation of X-ray is that it can fail to detect acute changes in early disease. Therefore, patients may have normal X-rays early in their course [10].

X-ray can also reveal changes in other joints, including the hips, knees, shoulders, and areas of enthesitis. Secondary osteoarthritis is seen in 31% of patients with SpA-related

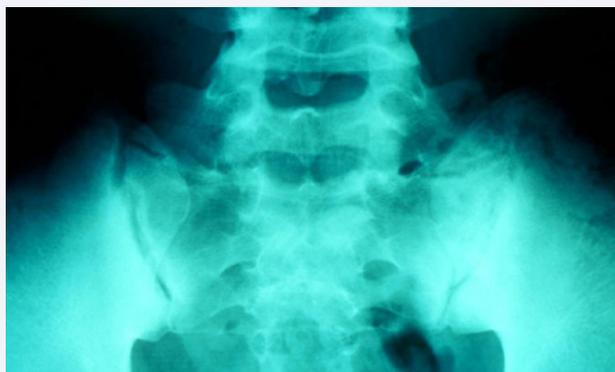


Figure 1 A patient with AS whose plain radiographs show bilateral, symmetric sacroiliitis, with sacroiliac joint narrowing and sclerosis (Grade 3).



Figure 2 A patient with AS whose plain radiographs show bilateral, symmetric sacroiliitis, with sacroiliac joint widening and sclerosis (Grade 3).



Figure 3 A patient with AS whose plain radiographs show bilateral, symmetric sacroiliitis with the sacroiliac joints being nearly fused (Grade 4).

Table 1: Radiographic grading of sacroiliitis, New York 1966.

Grade	Imaging Findings
0	Normal
1	Suspicious changes
2	Minimal abnormality <ul style="list-style-type: none"> • Small localized areas with erosion or sclerosis • No alteration in the joint width
3	Unequivocal abnormality Moderate or advanced sacroiliitis with >1 of: <ul style="list-style-type: none"> • Erosions • Evidence of sclerosis • Widening, narrowing, or partial ankylosis
4	Severe abnormality <ul style="list-style-type: none"> • Total ankylosis



Figure 4 Plain radiographs of a patient with longstanding AS showing a bamboo spine with fusion of the lumbar spine with marginal syndesmophytes.

oligoarthritis involving the knees [29]. Enthesitis of the Achilles tendon may be visualized as tendon thickening, erosions, or new bone formation at the attachment of the tendon on X-ray [30,31].

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) has been recognized as the most sensitive modality for discovering early active inflammation in the spine and sacroiliac joints. MRI can detect early findings of SpA, despite normal X-rays (Figure 5) [32]. Early abnormalities are present in both the anterior and posterior margins of the vertebral bodies (enthesitis, corner lesions), zygapophyseal

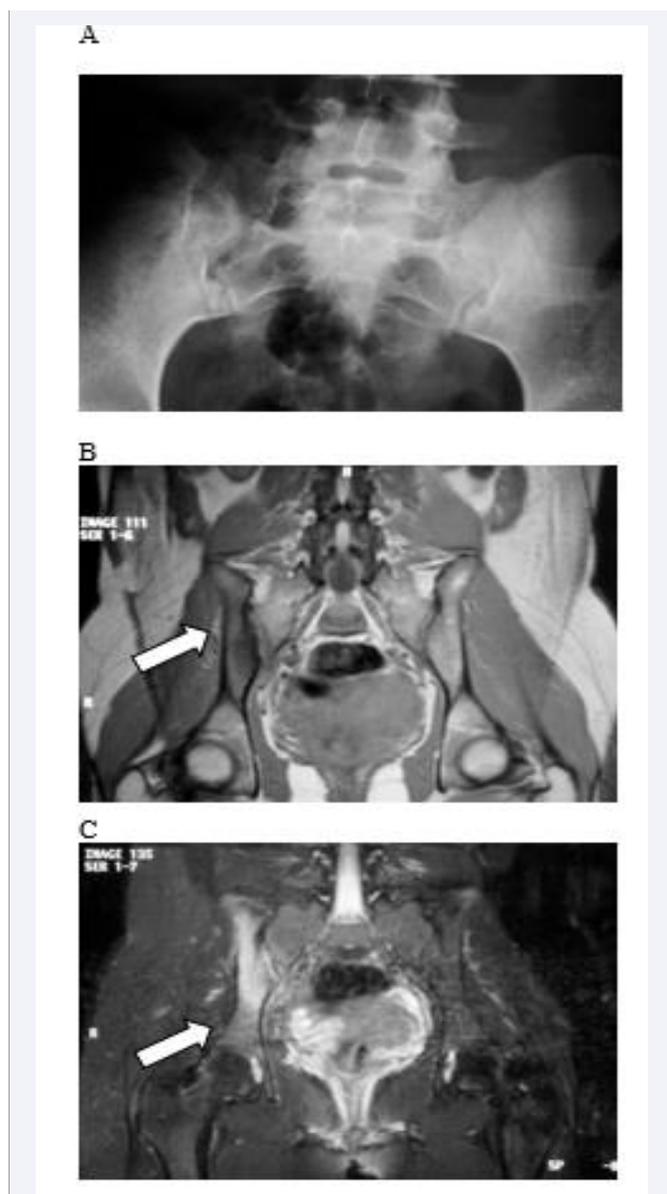


Figure 5 Non-radiographic axial SpA. The patient presented with pain in the right sacroiliac joint for about 3 months. A. X-rays of the pelvis showing normal sacroiliac joints. B. MRI T1 showing some irregularity of the right sacroiliac joint. C. MRI STIR showing inflammation of the sacroiliac with bone marrow edema.

joints, and peripheral joints and entheses, such as in the Achilles tendon and plantar fascia [33]. The early disease stages of active sacroiliitis can only be assessed using STIR or T1-weighted fat suppressed FSE sequence after administration of gadolinium contrast medium (T1/Gad) sequences. Active inflammatory lesions in SpA include bone marrow edema and osteitis, synovitis, enthesitis, and capsulitis (Figure 6A). Bone marrow edema and osteitis are integral for the quantification of active sacroiliac joint inflammation, appearing as hyperintense lesions on STIR images typically in the subchondral or periarticular bone marrow (Figure 6B) [26]. The presence of fatty changes at vertebral corners (fatty Romanus lesions) is a diagnostic imaging feature of axial SpA (Figure 7) [34]. Changes in bone marrow edema are

used to assess response to TNFi [26]. Chronic structural damage can be visualized both by X-ray and MRI [26]. However, a finding uniquely detected by MRI is periarticular fat deposition, which may be the first chronic lesion to indicate active inflammation.

Whole-body MRI (wb-MRI) has recently been evaluated as a tool to detect early disease manifestations of SpA throughout the entire skeleton, particularly in non-axial sites [32]. In patients

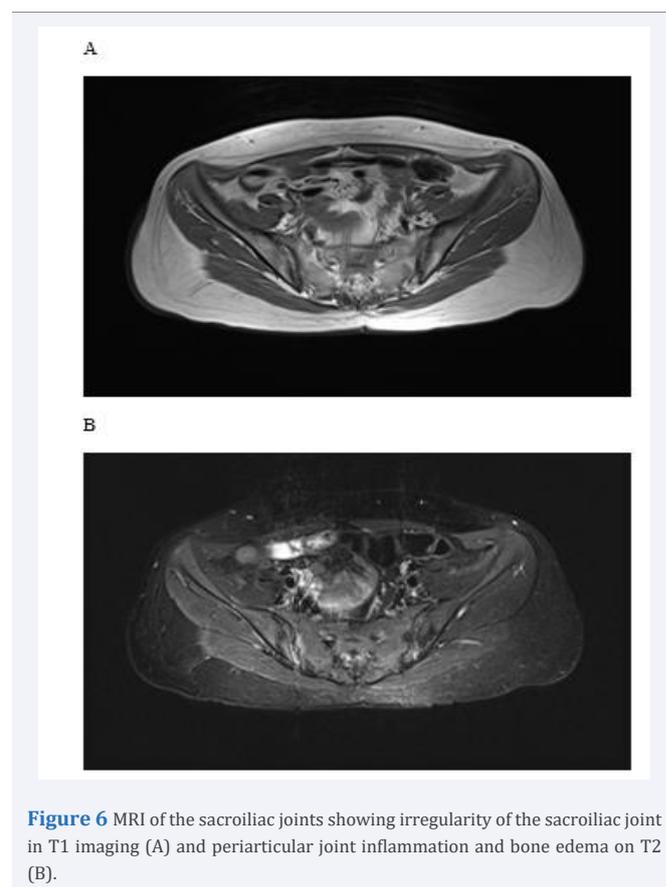


Figure 6 MRI of the sacroiliac joints showing irregularity of the sacroiliac joint in T1 imaging (A) and periarticular joint inflammation and bone edema on T2 (B).

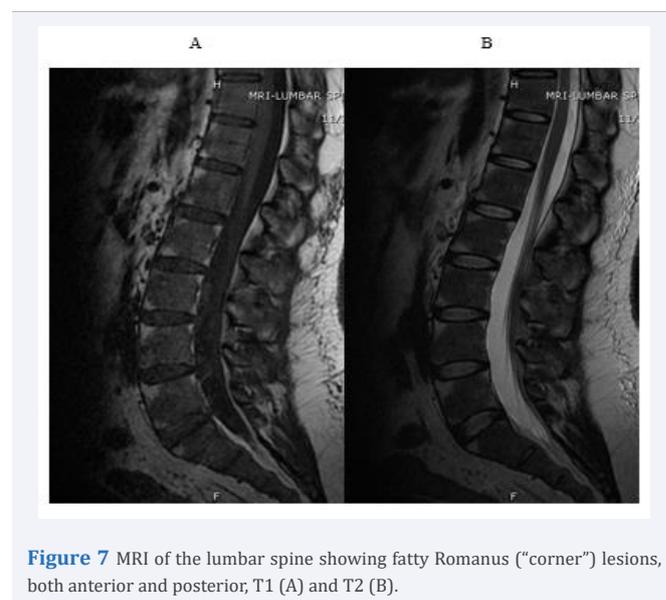


Figure 7 MRI of the lumbar spine showing fatty Romanus ("corner") lesions, both anterior and posterior, T1 (A) and T2 (B).

with SpA, wb-MRI was able to detect inflammation in non-axial sites in half of the study population [32].

Computed tomography (CT)

Computed tomography (CT) scanning has superior accuracy to conventional X-ray for detecting early sacroiliac abnormalities. This is largely attributable to the ability of CT to characterize the spatial configuration and bicompartamental anatomy of the sacroiliac joint [35]. CT and MRI have comparable efficacy in staging morphologic changes such as erosions and sclerosis [36]. However, CT is unable to detect inflammation, such as bone marrow edema and fatty changes, which often precedes structural changes [26,37].

Ultrasonography (US)

Ultrasonography (US) is a safe, noninvasive, cost-effective imaging modality without associated radiation exposure, which may be used in limited capacity to assess soft tissue inflammation. Its utility primarily lies in detecting enthesitis in patients with SpA, as it has been shown to have higher sensitivity than MRI in this context [38]. Power Doppler has proven utility in detecting response to TNFi therapy in SpA patients with enthesitis[38]. Duplex and color Doppler US can detect vascularization and thereby identify sacroiliac joint and spine inflammation in AS patients. However, evaluation of the sacroiliac joints is limited to the superficial surrounding soft tissue structures and posterior stabilizing ligaments [38]. Anterior chest wall involvement can also be assessed using Doppler US in patients with SpA. US can demonstrate sternoclavicular and manubriosternal joint erosions, margin narrowing, and ankylosis, although these findings may not always correlate clinically [39].

Bone scintigraphy

Bone scintigraphy is a nuclear imaging study used to detect areas of bone metabolism marked by increased radionuclide uptake [38]. Increased bone metabolism may occur secondary to malignancy, infection, fracture, and inflammation. Due to its ability to highlight areas of inflammation, bone scintigraphy has been evaluated as a method to detect acute sacroiliitis since the 1970s; however, in practice it has limited diagnostic utility [40]. In patients with established AS, scintigraphy only had a sensitivity of 52% for detection of active sacroiliitis [40]. Like CT, the use of scintigraphy is further limited by radiation exposure [38].

CLASSIFICATION

Rome, New York, and Modified New York

The first proposed classification criteria for SpA was the Rome Clinical Criteria for AS (1961) [41], which was subsequently revised in the New York Diagnostic Criteria for AS (1966) [42] and in the Modified New York Criteria for AS (1984) [43] due to limited sensitivity and specificity [44,45] (Table 2). In the Rome Criteria, the description of ‘low back pain’ was thought to be overly sensitive and non-specific, while ‘limited chest expansion’ was specific but insensitive [43]. The New York 1966 Criteria improved specificity by requiring the presence of at least one radiographic criterion for making a diagnosis. The Modified New York 1984 Criteria preserved this radiographic requirement. However, it modified the definition of back pain to be more consistent with what is now known as inflammatory back pain, i.e. ‘low back pain of at least 3 months’ duration improved by exercises and not relieved by rest’ [46]. Both the New York 1966 and 1984 Criteria improved specificity but made early diagnosis

Table 2: Rome, New York, and Modified New York Criteria.

Rome, 1961 Clinical Criteria for AS	New York, 1966 Diagnostic Criteria for AS	Modified New York, 1984 Diagnostic Criteria for AS
<p>Clinical Criteria</p> <ol style="list-style-type: none"> 1. Low back pain and stiffness for more than 3 months, not relieved by rest 2. Pain and stiffness in thoracic spine 3. Limited motion in lumbar spine 4. Limited chest expansion 5. History of evidence of iritis or its sequelae <p>Radiographic Criterion</p> <ol style="list-style-type: none"> 6. Radiograph showing bilateral sacroiliac changes characteristic of AS 	<p>Clinical Criteria</p> <ol style="list-style-type: none"> 1. Limitation of lumbar spine motion in all three planes: anterior flexion, lateral flexion, extension 2. Pain at dorsilumbar junction or in lumbar spine 3. Limitation of chest expansion to 2.5 cm or less measures at level of fourth intercostal space <p>Radiographic Criteria</p> <ol style="list-style-type: none"> 4. Grade 3 or 4 bilateral sacroiliitis 5. Grade 3 or 4 unilateral or grade 2 bilateral sacroiliitis 	<p>Clinical Criteria</p> <ol style="list-style-type: none"> 1. Low back pain of at least 3 months’ duration improved by exercises and not relieved by rest 2. Limitation of lumbar spine in sagittal and frontal planes 3. Chest expansion decreased relative to normal values for age and sex <p>Radiographic Criteria</p> <ol style="list-style-type: none"> 4. Bilateral sacroiliitis grade ≥2 5. Unilateral sacroiliitis grade 3 or 4
<p><i>Definite AS</i></p> <p>Grade 3 or 4 bilateral sacroiliitis with at least one clinical criterion OR At least four clinical criteria</p>	<p><i>Definite AS</i></p> <p>Grade 3 or 4 bilateral sacroiliitis with at least one clinical criteria OR Grade 3 or 4 unilateral or grade 2 bilateral sacroiliitis with clinical criteria 1 or criteria 2 and 3</p> <p><i>Probable AS</i></p> <p>Grade 3 or 4 bilateral sacroiliitis with no clinical criteria</p>	<p><i>Definite AS</i></p> <p>Bilateral sacroiliitis grade ≥2 or Unilateral sacroiliitis grade 3 or 4 and at least 1 clinical criterion</p> <p><i>Probable AS</i></p> <p>Three clinical criteria are present OR Radiographic criterion is present without any clinical criteria</p>
<p>Abbreviations: AS: Ankylosing Spondylitis</p>		

more difficult as radiological features are often absent early in the disease course.

1990 Amor Classification Criteria for Spondyloarthropathy

The Amor Classification Criteria for Spondyloarthropathy was developed in 1990 to better classify patients with features extending beyond those classically associated with SpA [47]. The Criteria include a variety of clinical, laboratory, and radiologic features that are compiled into a scoring system (Table 3). A grade of 1, 2, or 3 points is assigned to each finding, and a diagnosis of SpA is confirmed when the points combine to a composite of > 6. Diagnosis does not require evidence of radiographic sacroiliitis; however, presence of radiographic sacroiliitis is notably awarded the highest score. The sensitivity of the Amor criteria is 86.6% and its specificity is 90% [47].

1991 European Spondyloarthropathy Study Group (ESSG) Classification Criteria for Spondyloarthropathy

Like the Amor Criteria, the 1991 European Spondyloarthropathy Study Group (ESSG) Classification Criteria for Spondyloarthropathy expanded on clinical features. In the ESSG Criteria, the presence of inflammatory back pain and/or peripheral arthritis is required. These have been designated as entry criteria because they are considered the two leading symptoms of all types of SpA [48]. Patients who meet either of the major entry criteria and at least one of the minor criteria are considered to have SpA (Table 4). The ESSG Criteria has a sensitivity of 87% and specificity of 87%. Notably, like the 1990 Amor Criteria, the ESSG Criteria can be met without the presence of inflammatory back pain and radiographic sacroiliitis. Therefore, both systems are comprehensive in that they allow for diagnosis of early axial SpA and diagnosis of predominantly peripheral SpA.

ASAS Classification Criteria for Spondyloarthritis

The 2009 and 2011 ASAS Classification Criteria for Spondyloarthritis were developed out of a desire to increase the sensitivity for diagnosis of SpA by incorporating MRI to

detect early inflammatory disease in the sacroiliac joint, spine, and other parts of the axial skeleton [48,49]. Both the 2009 and 2011 ASAS Criteria use the leading clinical manifestation as a means to classify SpA. The term “axial SpA” is applied to patients with predominantly axial involvement, including the sacroiliac joints and spine. Those with predominantly peripheral joint manifestations, including peripheral arthritis, enthesitis, and dactylitis are considered to have “peripheral SpA.”

2009 ASAS Classification Criteria for Spondyloarthritis

The 2009 ASAS Criteria, which focuses on patients with predominantly axial SpA, is the first to make a key distinction between axSpA and nr-axSpA [26]. The radiographic diagnosis of axSpA requires the presence of sacroiliitis on plain radiographs, while the absence of these changes is considered nr-axSpA.

The 2009 ASAS Criteria has two entry criteria: back pain of any type for at least 3 months, and age of onset less than 45 years (Table 5). The set of criteria for radiographic axSpA has 2 arms, one imaging and one clinical. The imaging arm requires evidence of sacroiliitis on plain X-ray or MRI and at least 1 clinical SpA feature. The clinical arm requires HLA-B27 positivity and at least 2 other clinical SpA features.

Classification of nr-axSpA requires either MRI with evidence of sacroiliitis and at least 1 clinical SpA feature, or HLA-B27 positivity with at least 2 clinical features and no evidence of radiographic disease. The 2009 ASAS Criteria has a sensitivity of 82.9% and a specificity of 84.4%. The imaging arm alone has a sensitivity of 66.2% and a specificity of 97.3%.

2011 ASAS Criteria

The 2011 ASAS Criteria focuses on patients with predominantly peripheral SpA. The entry criterion is the presence of arthritis, enthesitis, or dactylitis (Table 6). Subsequent criteria include ≥1 extra-articular manifestation, HLA-B27, or sacroiliitis on plain radiographs or MRI, or ≥2 other musculoskeletal manifestations or family history of SpA. The sensitivity and specificity of the 2011 ASAS Criteria are 77.8% and 82.9%, respectively. Notably, the 2011 ASAS Criteria was found to perform better than

Table 3: 1990 Amor Classification Criteria for Spondyloarthropathy.

Clinical Features		Radiographic Feature		Laboratory/Other Features	
• Inflammatory back pain	1 pt	• Sacroiliitis on x-ray	3 pts	• HLA-B27+ or family history of SpA	2 pts
• Unilateral buttock pain	1 pt			• Good response to NSAIDs	2 pts
• Alternating buttock pain	2 pts				
• Enthesitis	2 pts				
• Peripheral arthritis	2 pts				
• Dactylitis	2 pts				
• Acute anterior uveitis	2 pts				
• Non-GC GU infection	1 pt				
• Acute diarrheal illness	1 pt				
• Psoriasis, balanitis, IBD	2 pts				

Abbreviations: Non-GC: nongonococcal; **GU:** genitourinary; **IBD:** inflammatory bowel disease; **HLA-B27:** human leukocyte antigen B-27; **SpA:** spondyloarthritis; **NSAIDs:** nonsteroidal anti-inflammatory drugs

Table 4: 1991 ESSG Classification Criteria for Spondyloarthritis.

Inflammatory back pain or Synovitis, and one of the following:
<ul style="list-style-type: none"> • Positive family history of SpA • Psoriasis • Inflammatory bowel disease • Urethritis, cervicitis, or acute diarrhea <1 month before arthritis • Alternating buttock pain • Enthesitis • Sacroiliitis by plain radiography
Abbreviations: SpA: Spondyloarthritis.

Table 5: 2009 ASAS Classification Criteria for Axial SpA.

In patients with back pain ≥3 months and age at onset <45 years		
Sacroiliitis on imaging* and ≥1 SpA feature**	OR	HLA-B27 and ≥2 other SpA features**
**SpA features: <ul style="list-style-type: none"> • Inflammatory back pain • Arthritis • Enthesitis (heel) • Uveitis • Dactylitis • Psoriasis • Inflammatory bowel disease • Good response to NSAIDs • Family history for SpA • HLA-B27 • Elevated CRP 		*Sacroiliitis on imaging: <ul style="list-style-type: none"> • Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA OR <ul style="list-style-type: none"> • Definite radiographic sacroiliitis according to mod. New York criteria
Abbreviations: SpA: Spondyloarthritis; NSAIDs: nonsteroidal anti-inflammatory drugs; HLA-B27: human leukocyte antigen B-27; CRP: C-reactive protein; MRI: magnetic resonance imaging.		

Table 6: 2011 ASAS Classification Criteria for Peripheral SpA.

In patients with peripheral manifestations only		
Arthritis or Enthesitis or Dactylitis		
≥1 SpA feature	OR	≥2 other SpA features
<ul style="list-style-type: none"> • Uveitis • Psoriasis • Inflammatory bowel disease • Preceding infection • HLA-B27 • Sacroiliitis on imaging 		<ul style="list-style-type: none"> • Arthritis • Enthesitis • Dactylitis • IBP ever • Family history of SpA
Abbreviations: SpA: Spondyloarthritis; HLA-B27: human leukocyte antigen B-27; IBP: inflammatory back pain		

versions of the ESSG and Amor Criteria which were modified by the addition of MRI [13]. The combined use of the 2009 and 2011 sets of ASAS Criteria yields a sensitivity of 79.5% and specificity of 83.3% [13].

TREATMENT

Smoking Cessation

All patients diagnosed with SpA should receive counseling for smoking cessation, as smoking is associated with higher disease activity. Smokers have worse functional outcomes and more severe structural damage on radiography [50]. Studies have shown a clear dose-response relationship between the number of pack-years and severity of BASDAI scores (functional outcomes) and mSASSS scores (radiologic findings) [50,51]. The

pathophysiology is thought to be related to the pro-inflammatory role of smoking, which increases cytokines including TNF- α , and IL-6. Consequently, it was observed that smokers have an impaired response to therapy with TNFi. One study demonstrated that smokers had significantly lower odds of achieving improvement in the BASDAI response at 1 year compared to non-smokers [51].

Physical therapy

A comprehensive review found that incorporating regular exercise improved overall pain, stiffness, chest expansion, spinal mobility, and cardiorespiratory function in SpA [52]. The 2019 ACR guidelines strongly recommend treatment with physical therapy over no physical therapy for both AS and nr-axSpA [53]. Land-based physical therapy was conditionally recommended over aqua therapy. Physical therapy should focus on improving four domains, including aerobics, flexibility, resistance, and neuro-motor. However, a standardized exercise protocol has yet to be developed [52].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are considered first-line therapy for treating pain and stiffness related to SpA [11]. Many clinical trials have demonstrated that NSAIDs are effective in improving symptoms when used continuously [53]. It is also acceptable to use on-demand NSAIDs when continuous use is limited by side effects [11]. The ACR 2019 guidelines do not recommend one particular NSAID over another, but rather suggest trying at least two different NSAIDs at maximal doses for at least one month. Currently, there is mixed data on whether NSAIDs have disease modifying effects [53].

Sulfasalazine

The use of sulfasalazine is recommended in limited circumstances. Sulfasalazine can be used for treatment of peripheral arthritis only when TNFi are contraindicated or not available [11,53]. The ACR formerly recommended sulfasalazine as an alternative to TNFi. However, in 2019 this recommendation was revised and IL-17i are now a preferred alternative to TNFi, followed by sulfasalazine. Studies show that sulfasalazine has little efficacy in axial-predominant symptoms [53,54].

Tumor Necrosis Factor- α Inhibitors (TNFi)

TNFi are considered first-line therapy after NSAID treatment failure for both AS and nr-axSpA [11,53]. The five TNFi are etanercept, infliximab, adalimumab, golimumab, and certolizumab. The ACR does not recommend one particular TNFi over another, except in patients with uveitis and IBD in which treatment with TNFi monoclonal antibodies is preferred [53]. Since the profound response to TNFi was first noted in the early 2000s, numerous open-label studies and over 24 randomized controlled trials have shown dramatic improvement in objective and subjective markers of disease [11,53]. Data suggests that early initiation of TNFi can inhibit development of new bony lesions and decrease the odds of disease progression by 50% in patients with AS [54]. A meta-analysis showed that the response to TNFi was similar in patients with AS and nr-axSpA [55].

Factors associated with a better response to TNFi are elevated acute phase reactants, young age, short disease duration, and low baseline disability [11,51]. TNFi can be used in both children and adolescents, but cautious use is recommended in pregnancy. Contra-indications to use are malignancy in the past 5 years, malignant melanoma, high risk of infection, advanced heart failure, systemic lupus erythematosus, and multiple sclerosis or other demyelinating disease. Prior to initiation of TNFi, all patients should be tested for hepatitis and tuberculosis [11].

Interlukin-17 inhibitors (IL-17i)

The ACR 2019 guidelines recommend using an IL-17i including secukinumab or ixekizumab after treatment failure with NSAIDs and TNFi in patients with AS and nr-axSpA. Large placebo-controlled trials favored the use of IL-17i in AS, and more recently, studies showed efficacy in patients with nr-axSpA. Greater familiarity with the long-term safety and toxicity of TNFi favors them over IL-17i [53]. Circumstances in which IL-17i are preferred over TNFi include patients with heart failure or demyelinating disease [53].

Other potential agents: JAKi and PDE4i

Tofacitinib, a Janus kinase inhibitor (JAKi), is currently being evaluated as a potential therapy for AS [53]. Tofacitinib is already approved for RA and PsA. A phase II clinical trial demonstrated improvement in spinal inflammation with tofacitinib [56]. The phase III trial ended in August 2020.

Apremilast, a phosphodiesterase 4 inhibitor (PDE4i), is currently not recommended by ACR [53]. The POSTURE trial, a phase III clinical trial, failed to show improvement in patients treated with apremilast over placebo in patients with AS [57].

Corticosteroids

Steroids are not currently recommended for treatment of SpA [53]. There is limited evidence that high-dose steroids may provide improvement in patients with AS [58].

Surgical interventions (total hip arthroplasty, spinal surgery)

Referral to Orthopedic Surgery may be warranted in patients with advanced disease. In patients with AS and advanced hip arthritis, the ACR recommends total hip replacement to improve quality of life [59]. However, in patients with AS and severe kyphosis, ACR does not recommend elective spinal osteotomy due to procedure-associated complications [59].

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