Axial spondyloarthritis

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Abstract

Axial spondyloarthritis (axSpA) is a chronic inflammatory condition that predominantly involves the axial skeleton. The term describes a disease spectrum including patients with radiographic axSpA (also called ankylosing spondylitis), which have established (chronic) sacroiliitis on radiographs, and a further subgroup of 'non-radiographic axSpA', which typically shows evidence of active sacroiliitis on magnetic resonance imaging (MRI) in the absence of definite radiographic changes. The association between axSpA and HLA-B27 has been known for some time, and newer genetic links have been found with *IL23R* and *ERAP1*. Animal studies also support a link between the gut microbiome, gut inflammation and axSpA, and biomechanical stress may play a role. Chronic back pain, often with inflammatory features, is the cardinal manifestation, with enthesitis being the key pathological lesion. Many patients develop peripheral features such as enthesitis, arthritis or dactylitis, and some develop extra-articular manifestations (also called extra-musculoskeletal manifestations), namely uveitis, psoriasis or inflammatory bowel disease. Diagnosis of early-stage disease can be challenging, and MRI plays a key role in detecting subtle inflammatory changes. Non-steroidal anti-inflammatory drugs and physical therapy are cornerstones of management, with tumour necrosis factor and interleukin (IL)-17 inhibitors vastly improving clinical outcomes. Newer treatments include new IL-17 inhibitors and JAK inhibitors.

Keywords

Ankylosing spondylitis; axial spondyloarthritis; biologics; diagnosis; enthesitis; inflammatory back pain; MRI; treatment

Key points

- Axial spondyloarthritis (axSpA) is part of the spondyloarthritis group of diseases and includes radiographic and non-radiographic axial spondyloarthritis.
- There is a well-known association with HLA-B27, and more recent genome-wide association studies have implicated *ERAP1* and *IL23R*. *IL23R* supports the role of the interleukin (IL)-23–IL17 pathway in disease.
- Hypotheses for pathogenesis include involvement of the gut microbiome influencing host susceptibility to different diseases, and biomechanical stress involved in triggering entheseal inflammation.
- Inflammatory back pain is the cardinal symptom, with morning stiffness and nocturnal pain. Enthesitis is the key peripheral, pathological lesion and represents active disease.
- MRI is the only imaging technique capable of detecting both active (inflammatory) and chronic (structural) lesions as well as their anatomical distribution, contributing to the early diagnosis of axSpA.
- The diagnosis of axSpA is based on clinical, laboratory and imaging findings. Early diagnosis is key to preventing structural damage and morbidity.
- Contextual interpretation of MRI is required and clinicians must keep in mind MRI's limitations, therefore not excluding or making a diagnosis solely based on MRI findings.

- There are several disease activity scoring measures, both physician and patient reported, to monitor progression of disease and response to treatment.
- The mainstay of treatment is non-steroidal anti-inflammatory drugs and physiotherapy.
- Anti-tumour necrosis factor drugs are used in severe axSpA. Anti-IL-17 drugs such as secukinumab and ixekizumab are highly effective, and JAK inhibitors are emerging as an effective treatment approach.

Introduction

Spondyloarthritis (SpA) is a heterogenous group of chronic, immune-mediated, inflammatory disorders that share a common pathophysiological pathway. Historically, SpA was divided in several subsets including ankylosing spondylitis (AS),[1] psoriatic arthritis, inflammatory bowel disease (IBD)-related arthritis (or enteropathic arthritis), reactive arthritis, arthritis associated with acute anterior uveitis (AAU), undifferentiated SpA and juvenile SpA (enthesitis-related arthritis) (Figure 1).[2] These groups share major clinical and imaging features, as well as genetic predispositions, leading to the unified concept of SpA. The Assessment of SpondyloArthritis International Society (ASAS) simplified the classification of SpA by dividing the group into axial SpA (axSpA) and peripheral SpA (pSpA), depending on the cardinal phenotypic manifestations (Figure 2).[3]

axSpA is characterized by chronic inflammation primarily affecting the entheses and synovial joints of the spine and the sacroiliac joints (SIJs). It encompasses radiographic (r-axSpA, or AS) and non-radiographic axSpA (nr-axSpA); the nr-axSpA category was created because of the recognition of early axial disease, characterized by a constellation of signs, symptoms, laboratory and imaging features that allow the diagnosis of axSpA to be made in the absence of definite SIJ changes on radiographs. These patients often have evidence of SIJ changes on magnetic resonance imaging (MRI), particularly bone marrow oedema (BMO)/osteitis (Figure 3).[4]

axSpa can lead to chronic pain, structural damage and progressive spinal stiffness. It is a life-long condition that can impair quality of life and reduce functional capacity and mobility.[5]

Epidemiology

The prevalence of axSpA varies significantly among different ethnic populations, being higher in white and certain Native American populations and lower in African American and Asian populations. It is correlated to the population frequency of human leukocyte antigen B27 (HLA-B27), which varies markedly with a north–south gradient. The estimated prevalence of axSpA in the USA is 0.9–1.4% of the adult population, and that of AS is 0.52–0.55%. In the UK, the prevalence of axSpA in a primary care population was estimated to be 0.3% using ASAS axSpA criteria, and 0.15% using modified New York criteria for AS (Table 1).

Aetiology

The exact aetiology of axSpA is unknown but is likely to be a complex interplay between genetic and environmental factors.

Genetic factors

The association between the major histocompatibility complex (MHC) HLA-B27 and SpA was first reported in the early 1970s and represents one of the strongest associations with common human diseases. In white patients with AS around 90% carry HLA-B27, while in African American patients with AS only 50% carry HLA-B27. The estimated prevalence of HLA-B27 in the white population is 8%, while in Scandinavian/Eastern European and in the Black African populations it is reported to be 10–16% and 4%, respectively. Approximately 1–2% of people who are positive for HLA-B27 develop AS.

Epidemiological data suggest that HLA-B27 does not explain all genetic susceptibility. The first genome-wide association study conducted in AS in 2007 led to the identification of two non-MHC susceptibility regions: *ERAP1* and *IL23R*. *ERAP1* encodes the endoplasmic reticulum aminopeptidase, an enzyme that behaves like a molecular ruler, cleaving proteins into segments of 10–16 residues in length, which are later presented by HLA-B27 on the cell surface. Associations with variants in three other genes of the same family have subsequently been identified. *IL23R* encodes the receptor for interleukin (IL)-23, which promotes the survival of T helper 17 CD4+ T cells. These play an important role in the inflammatory response in axSpA.

Environmental factors

Animal models strongly support a link between the gut microbiome and SpA pathogenesis, and the role of dysbiosis influencing susceptibility of the host to different diseases. Different studies have incriminated different bacterial species, and it is currently therefore not possible to define a gut microbiome signature for axSpA.

There is evidence that biomechanical stress could play a role, with patients with SpA needing a lower threshold of mechanical overloading to trigger entheseal inflammation. Further research in both these areas is needed.

Clinical features

The typical age of onset is during the second decade, with currently a mean delay of 6–8 years between symptom onset and definite diagnosis. Historically, AS has been shown to be more common in male patients, with a male:female ratio of 2:1 to 3:1. However, in recent axSpA cohorts, considering nr-axSpA, the gender ratio is close to 1:1 because of the lower tendency of female patients to develop radiographic sacroiliitis.

Increased disease awareness and earlier diagnosis will allow avoidance of unnecessary diagnostic procedures, especially when a patient consults many different specialists, and earlier initiation of adequate treatment. This will lead to the improvement of symptoms and patient-reported outcomes, positive impact on work productivity with direct and indirect healthcare cost savings, and potential prevention of the development of structural damage. Moreover, shorter disease duration has been associated with better response to treatment with biologic disease-modifying anti-rheumatic drugs (DMARDs), and early achievement of remission is a predictor of future sustained remission.

Musculoskeletal symptoms

Inflammatory back pain is the first clinical manifestation in 75% of patients. It is usually insidious at onset, worsens with inactivity and improves with exercise and non-steroidal anti-inflammatory drug (NSAID) use. There is often morning stiffness and nocturnal pain during the second half of the night. Sacroiliitis can cause alternating buttock pain that radiates down the thighs, but not past the knee.

Enthesitis is the key peripheral, pathological lesion of axSpA and occurs in approximately one-third of patients. Entheses are the sites of attachment of tendons, ligaments, fascia or joint capsules to bone and act to transmit tensile load from soft tissue to bone. The sites commonly involved in the spine are the attachments of joint capsules around facet joints and SIJs, disco-vertebral junctions, and the attachments of the interspinous ligaments. Peripheral enthesitis most commonly involves the Achilles tendons, plantar fascia, iliac crests, great trochanters, ischial tuberosities and tibial tubercles. These lesions are tender to palpate, which may be associated with swelling of the tendon or ligament insertion. Enthesitis can be inflammatory or mechanical, and therefore enthesitis alone should be viewed with caution.

Dactylitis is characteristic of SpA and involves the swelling of a whole digit. It is a combination of synovitis, enthesitis, tenosynovitis and soft tissue swelling. Dactylitis is generally associated with pSpA, but 15% of all patients who had a diagnosis of dactylitis were shown to have axSpA.

Peripheral arthritis can affect up to one-third of patients and is typically asymmetrical, oligoarticular and predominantly seen in the lower limbs. Synovitis is histologically non-specific, but MRI may demonstrate extensive entheseal lesions within the joint.

Extra-articular manifestations (also called extra-musculoskeletal manifestations)

Acute anterior uveitis: AAU is the most common extra-articular manifestation, occurring in 20–30% of patients with AS and 15% of those with nr-axSpA. The incidence is higher in HLA-B27-positive patients. It typically presents acutely with unilateral eye pain, redness, photophobia, increased tear production and blurred vision. Prompt treatment is critical to prevent visual loss. Attacks normally resolve over 2–3 months with treatment and recurrence is common. AAU is asynchronous with the clinical activity of other lesions. In most cases topical corticosteroids are adequate but anti-tumour necrosis factor (TNF) agents can be used in refractory cases.

Psoriasis: around 10–25% of patients with AS have concomitant psoriatic lesions, and involvement of the SIJs and spine occurs in 5% of patients with psoriasis. The latter is often termed ‘psoriatic spondylitis’ and tends to be asymmetrical.

Inflammatory bowel disease: the prevalence of IBD in SpA ranges from 6% to 15% with up to 60% of AS patients having subclinical inflammation on colonoscopy. There is a clear overlap between these conditions, probably linked by dysbiosis of the gut as described above.

Fatigue: this is a common complaint that can occur in 65% of individuals with AS. Increased levels of fatigue are associated with increased pain and stiffness and reduced functional capacity. This can have both personal and societal costs, and many sufferers have significant difficulties with personal relationships and reduced work capacity.

Co-morbidities

Cardiovascular complications are rare, affecting <10% of AS patients. Heart block is the most frequent, caused by fibrosis of the conduction system. Aortic insufficiency, resulting from aseptic endocarditis and aortitis, can lead to aortic valve insufficiency. There is elevated cardiovascular morbidity from the combination of chronic inflammation, NSAID consumption, high blood pressure and smoking.

Restrictive lung disease can be seen in end-stage disease, with limited chest expansion because of fusion of the thoracic wall. Apical fibrosis can occur in severe disease.

Renal disease is seen in 10–35% of individuals with AS and can be linked to long-term use of NSAIDs. Immunoglobulin A nephropathy has been reported, and amyloidosis is a rare complication in severe, active, long-standing disease.

Osteoporosis is commonly seen in long-standing axSpA, with increased fracture risk. Spinal fractures are typically horizontal and usually the result of hyperextension injuries. Acute spinal pain in axSpA should suggest a spinal fracture.

Investigations

Laboratory

C-reactive protein (CRP) is an important component and can be increased in up to 40% of patients with axSpA. It is one of the associated risk factors for radiographic progression and is more frequently present in r-axSpA than nr-axSpa. It predicts a good response to anti-TNF treatment and is one of the ASAS classification features.

Imaging

Imaging is an integral part of the diagnosis and management of axSpA. The modified New York criteria, published in 1984 (Table 1), required the presence of radiographic changes at the SIJ. However, it can take several years for changes to be evident on radiographs and a proportion of patients never develop changes, leading to delayed and missed diagnosis.

In 2009, ASAS created the ASAS classification criteria, which included the use of MRI for the detection of pre-radiographic changes in early axial disease. MRI can be used both as a predictor of and to monitor the response to therapy. MRI findings of axSpA can be divided into active changes, which include BMO/osteitis, synovitis, enthesitis, capsulitis and intra-articular effusion, and structural changes, which include erosions, sclerosis, bone fatty infiltration, fat deposition in an erosion cavity (‘backfill’) and bone bridging or ankylosis. T1-weighted sequences are more suitable to show structural changes, and fat-suppressed, fluid-sensitive sequences (including short tau inversion recovery, fat-saturated T2 and Dixon methods) are more suitable to assess inflammatory changes.

Challenges arise as BMO/osteitis is not unique to inflammatory conditions and distinction from degenerative changes can be difficult. In addition, up to 27% of lesions suggestive of SpA in the spine and SIJ have been found in healthy controls. In general, axSpA tends to have higher levels of inflammation, with BMO/osteitis typically located in subchondral bone marrow and associated with the presence of erosions, ankylosis and fat infiltration.

Radiographic changes in the spine, such as syndesmophytes or complete bony bridging, occur late and are highly specific, while MRI changes are detected earlier but are less specific. Corner inflammatory lesions and fatty lesions of the spine may predict progression of structural damage.

Ultrasonography has been highlighted for use in the assessment of entheseal inflammation in axSpA and may reduce the number of false positives of clinical identification of pain (i.e. localised pain on physical examination driven by non-inflammatory mechanisms such as biomechanical stress or fibromyalgia).

Diagnosis

The diagnosis of axSpA is based on a pattern of clinical, laboratory and imaging findings. Notably, contextual interpretation of the changes detected on MRI is critical. Ultimately, this information needs to be combined with clinical information, and clinical judgement remains the mainstay for diagnosing axSpA. This exercise includes the exclusion of other diagnoses, namely clinical and imaging mimickers of axSpA. A diagnosis (and classification) can sometimes be made on a purely clinical basis. It is important to note that classification criteria are only intended to be used for research purposes, after a diagnosis has been made, and they should not be used as a checklist to make a diagnosis. Adequate clinical judgement will prevent mis-, under- or over-diagnosis.

Assessment

There are several tools available to assess disease activity, function, metrology, and quality of life.

The Bath Ankylosing Spondylitis Disease Index (BASDAI) is a patient-reported outcome measure including six questions assessing the symptoms of fatigue, spinal pain, peripheral joint pain, enthesopathy and stiffness using a 10 cm visual analogue scale or an 11-point (0 to 10) numerical rating scale. A score ≥4 reflects high disease activity warranting escalation in treatment.

The Ankylosing Spondylitis Disease Activity Score (ASDAS) includes objective measures of inflammation, either CRP concentration or erythrocyte sedimentation rate, in addition to four patient-reported outcome questions (back pain, duration of morning stiffness, peripheral pain/swelling, and patient global assessment). ASDAS cut-offs for disease activity states are 1.3, separating 'inactive disease' from 'low disease activity', 2.1, separating 'low disease activity' from 'high disease activity', and 3.5, separating 'high disease activity' from 'very high disease activity'.

The Bath Ankylosing Spondylitis Functional Index (BASFI) is a patient-reported outcome on physical function. It contains 10 items about everyday tasks and the ease of undertaking them. The assessment of spinal mobility is done using the Bath AS Metrology Index (BASMI), which incorporates information on five different assessments (four spinal assessments - cervical rotation, tragus-to-wall distance, modified Schober's test and lumbar lateral flexion, and one hip mobility measurement - intermalleolar distance) and can define clinically significant changes in spinal movements.

The Health Assessment Questionnaire for SpA (HAQ-S) is used to assess physical disability and pain, and is a good predictor of future disability. The Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire includes 18 items that address the impact of SpA on several aspects of quality of life. The ASAS Health Index (ASAS-HI) is a new tool to assess the health status of patients with SpA; it consists of a 17-question self-questionnaire with binary agree/do not agree response options, and a score range from 0 to 17, with 0 indicating the best state of health. The 17 questions of this self-report questionnaire cover different International Classification of Functioning, Disability and Health domains (pain, emotion, sleep, sexual function, mobility, self-care, social life).

Treatment

The goals of treatment are to reduce disease activity to prevent disability and structural damage, and to maintain work productivity and health-related quality of life.

NSAIDs, physical therapy and patient education remain the mainstays of treatment. These can improve pain and stiffness, and NSAIDs can also be effective in reducing the concentrations of acute-phase reactants. Patients should be encouraged to exercise on a regular basis and stop smoking. Intermittent physiotherapy can correct or minimize deformity, while smoking is associated with higher disease activity and radiographic progression.

Patients with pain and stiffness should use an NSAID as first-line drug treatment up to maximum dose if there are no contraindications. Both non-selective cyclooxygenase inhibitors, such as diclofenac and naproxen, and selective cyclooxygenase-2 inhibitors, such as etoricoxib and celecoxib, can be helpful. There is some controversy over the use of NSAIDs in preventing radiographic progression, with contradictory results seen in studies.

Conventional synthetic DMARDs, such as sulfasalazine, methotrexate and leflunomide, have little or no effect on axial disease but are sometimes used if peripheral involvement is present. However, evidence for the efficacy of conventional synthetic DMARDs in controlling peripheral manifestations associated with SpA is only available for sulfasalazine.

Glucocorticoid injections directed to the site of musculoskeletal inflammation can be considered in patients with axSpA with peripheral involvement. Analgesics can be considered for residual pain if recommended treatments have failed, are contraindicated or are poorly tolerated.

Biologics

The availability of biologic therapies has vastly improved clinical outcomes for axSpA patients who have not responded to NSAID therapy. There are currently five licensed anti-TNF drugs (adalimumab, certolizumab, etanercept, golimumab, infliximab) for the indication of AS, and four (adalimumab, etanercept, certolizumab, golimumab) for nr-axSpA. These have all been shown to reduce symptoms and improve function and quality of life.

No anti-TNF agent is preferred, but anti-TNF monoclonal antibodies should be used in individuals with IBD or recurrent uveitis. Non-TNF-blocking agents are also used. IL-17 blockers, such as secukinumab and ixekizumab, have been shown to be highly effective. These are particularly advised for patients who have heart failure or demyelinating disease as a contraindication to anti-TNF and in primary non-responders to anti-TNF. Together with etanercept, they are not preferred options in patients with IBD

or recurrent uveitis. Patient preferences regarding the frequency of dosing and route of administration should also be considered when selecting a biologic agent (Table 2).

Recent advances in biologic and targeted synthetic DMARD treatment

The efficacy of secukinumab and ixekizumab, monoclonal antibodies against IL-17A, has been demonstrated in both biologic-naive and anti-TNF-experienced patients with axSpA and both drugs are now approved for treatment in both AS and nr-axSpA. Other drugs in this class that have shown positive results in clinical trials include bimekizumab (IL-17A and IL-17F blocker), brodalumab (IL-17RA antagonist) and netakimab (IL-17A blocker).

Janus kinase (JAK) inhibitors are emerging as effective therapeutic agents in axSpA. Upadacitinib (a selective JAK-1 inhibitor) has been shown to be efficacious and well tolerated in active AS that had not responded to NSAIDs, and recently received European Medicines Agency approval for use in AS. Tofacitinib (a non-selective JAKi that mainly inhibits JAK1 and JAK3) and filgotinib (a selective JAK-1 inhibitor) have also shown promising results.

Biosimilars

Biosimilars are biotherapeutic products that are similar in terms of quality, safety and efficacy to an already licensed biotherapeutic product (also called the originator drug or bio-originator). They offer substantial savings, enabling more patients to access treatment. Switching from bio-originators to biosimilars is now widely accepted, but switching should be based on shared decision-making between patients and physicians. There are now biosimilars to adalimumab, etanercept and infliximab.

'Treat-to-target' (T2T) approach

The concept of T2T was imported from diseases such as hypertension and diabetes where well-defined, objective measures are maintained below a certain threshold to lead to better long-term health. In axSpA it is thought that intensive T2T approaches may contribute to better clinical outcomes and to decreasing the rate of radiographic progression, particularly in high-risk groups.

This approach is indirectly supported by associations between levels of disease activity (e.g. ASDAS) and future radiographic progression, but there is little direct evidence. T2T can be burdensome to the patient and providers, and can lead to 'over-treatment' with rapid cycling through all treatments. Furthermore, controversy remains over what the target should be for axSpA patients, with ASDAS inactive disease suggested as the most adequate target.

Prognosis

The course of axSpA is highly variable, from mild disease with intermittent symptoms to severe disease, with structural changes and ankylosis of the spine. Predictors for potentially severe disease have been suggested but not validated. These include hip involvement, age of onset before 16 years, peripheral arthritis, dactylitis or psoriasis. There is a trend towards treating patients as early as possible to prevent irreversible structural damage, and MRI use has facilitated this strategy.

The improvement in treatment options for axSpA in the last few years means that the future remains exciting for patients and the physicians treating them. However, more head-to-head studies are needed to help determine the optimal sequencing of treatments, and establishing which individuals benefit the most from each drug is a challenge for the future.

Figure 1. The spondyloarthritis spectrum. U-SpA, undifferentiated spondyloarthritis. Reproduced from Hayward et al. (2020) with permission.[2]

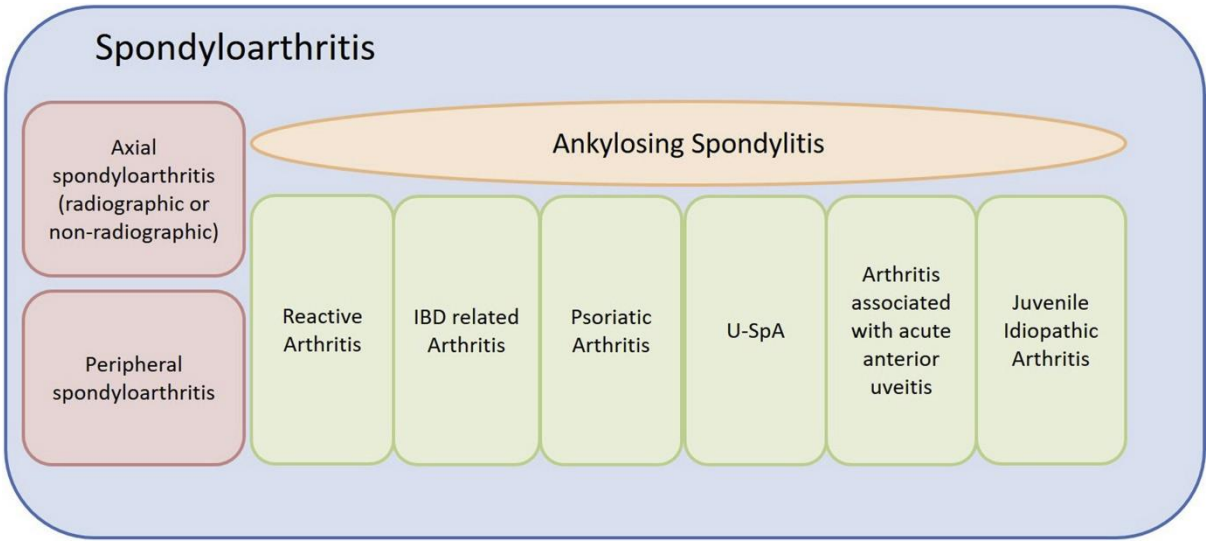

Figure 2. ASAS classification criteria for SpA. See text for abbreviations. Adapted from Rudwaleit et al. (2011).[3]

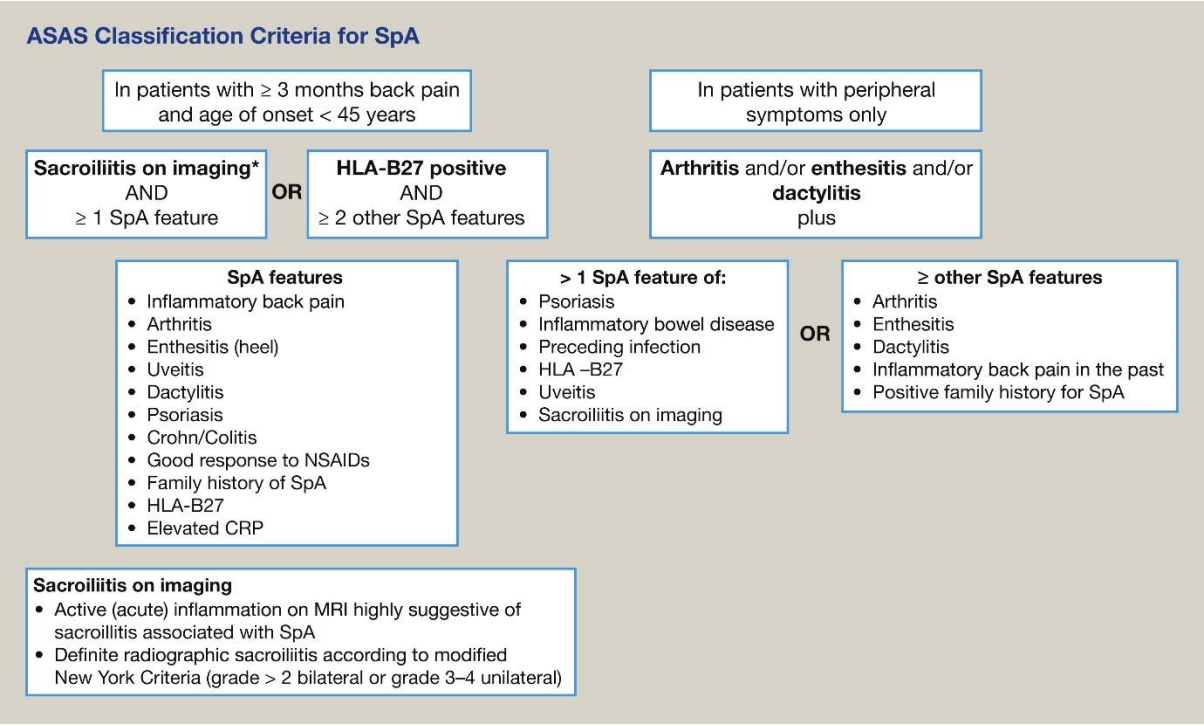

Figure 3. The axial spondyloarthritis continuum.

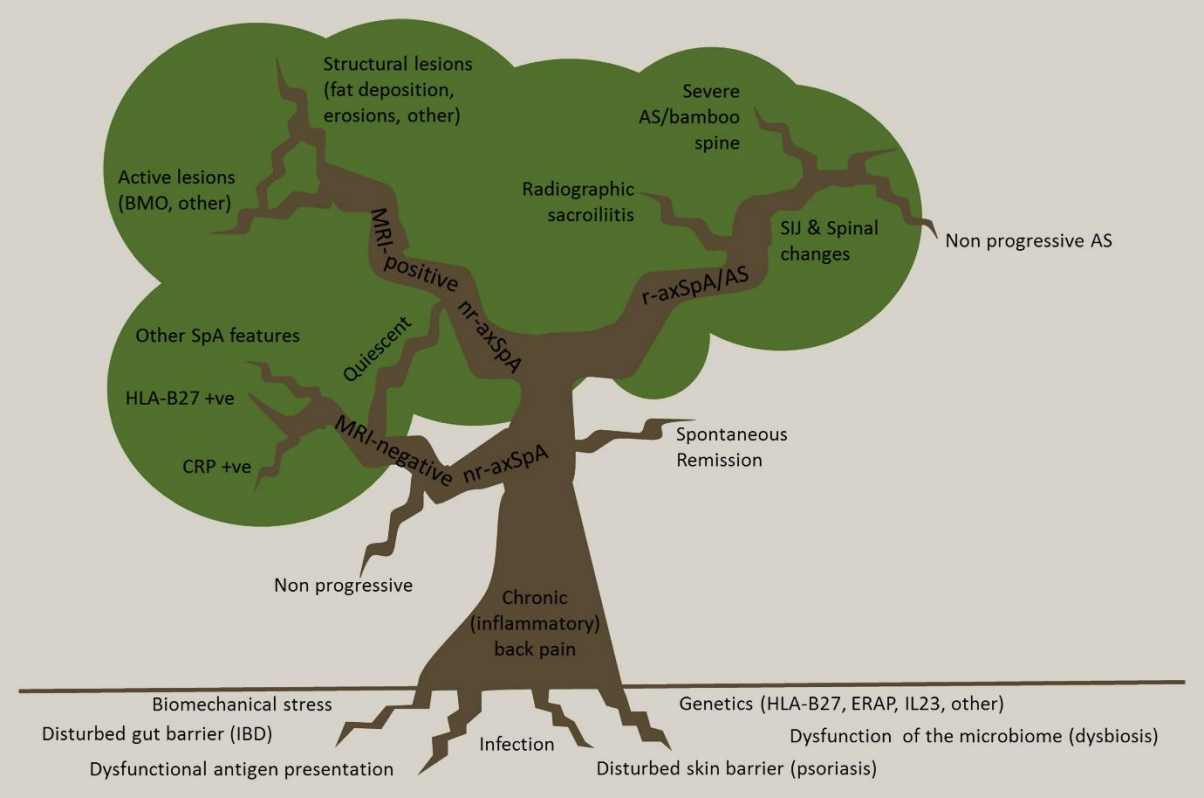

Table 1

Modified New York criteria for ankylosing spondylitis

Clinical criteria:

1) Low back pain and stiffness for >3 months which improves with exercise, but is not relieved by rest.
2) Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
3) Limitation of chest expansion relative to normal values corrected for age and sex.

Radiological criterion:

1) Sacroiliitis grade ≥2 bilaterally or sacroiliitis grade 3 to 4 unilaterally.

Grading:

1) Definite ankylosing spondylitis if the radiologic criterion is associated with at least 1 clinical criterion.
2) Probable ankylosing spondylitis if:
    a. Three clinical criteria are present.
    b. The radiologic criterion is present without any signs or symptoms satisfying the clinical criteria (other causes of sacroiliitis should be considered).

Source: van der Linden et al. (1984).[1]

Table 2

Standard dosing regimens of biologic and targeted synthetic DMARDs currently available for axSpA

Target	Drug	Mechanism of action	Dosing regimen
TNF	Adalimumab	Monoclonal antibody to TNF	*By subcutaneous injection* 40 mg every 2 weeks
	Certolizumab	Monoclonal antibody to TNF	*By subcutaneous injection* Loading dose: 400 mg every 2 weeks for three doses Maintenance dose: 200 mg every 2 weeks, or 400 mg every 4 weeks
	Etanercept	Fusion protein against TNF	*By subcutaneous injection* 50 mg once weekly
	Golimumab	Monoclonal antibody to TNF	*By subcutaneous injection* Body weight up to 100Kg: 50mg once a month on the same day each month Body weight 100kg and above: 50mg once a month for 3-4 doses on the same day each month. Can be increased to 100 mg once a month
	Infliximab	Monoclonal antibody to TNF	*By intravenous infusion alone* Initially 5 mg/kg, then 5 mg/kg to be taken at weeks 2 and 6 after the initial dose. Then 5 mg/kg every 6–8 weeks *Initially by intravenous infusion* Initially 5mg/kg followed by 5mg/kg after 2 weeks (intravenous infusion). Subcutaneous injection 120mg every 2 weeks to be started 4 weeks after the second intravenous dose. (Only for r-axSpA patients)
IL-17	Secukinumab	Monoclonal antibody to IL-17A	*By subcutaneous injection*

			Loading dose: 150 mg every week for 5 doses. Maintenance dose: 150 mg every month. (Can be increased to 300 mg in AS patients)
	Ixekizumab	Monoclonal antibody to IL-17A	*By subcutaneous injection* r-axSpA: Initially 160 mg for one dose then 80 mg every 4 weeks nr-axSpA: 80mg every 4 weeks
JAK	Upadacitinib	Selective JAK-1 inhibitor	*Orally* 15 mg, once daily

KEY REFERENCES

1. 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* 1984; **27:** 361–8.
2. Hayward RJ, Machado PM. Classification criteria in axial spondyloarthritis: what have we learned; where are we going? *Rheum Dis Clin North Am* 2020; **46:** 259–74.
3. 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* 2011; **70:** 25–31.
4. Michelena X, Lopez-Medina C, Marzo-Ortega H. Non-radiographic versus radiographic axSpA: what's in a name? *Rheumatology (Oxford)* 2020; **59**(Suppl 4): iv18–24.
5. Sieper J, Poddubnyy D. Axial spondyloarthritis. *Lancet* 2017; **390:** 73–84.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here

Question 1

A 30-year-old woman presented with a 4-month history of low back pain. She had morning stiffness and pain in the left heel. Two years previously she had had an episode of self-limiting, painful red eye. There was no history of injury or trauma and no significant family history.

Clinical examination was unremarkable.

Investigation

•Plain X-ray the pelvis was normal

Which of the following investigations should be prioritized to establish a diagnosis?

A. MRI of whole spine and sacroiliac joints

B. Genetic testing for HLA-B27

C. Assessment of response to physiotherapy

D. Assessment of response to NSAIDs

Correct answer: A. There are multiple clinical features suggestive of axSpA, namely morning stiffness, heel pain (suggests Achilles tendonitis), and history of painful red eye (suggests anterior acute uveitis). The presence of bone marrow oedema on MRI would significantly increase the likelihood of axial spondyloarthritis, more than any of the other suggested approaches, if only one investigation had to be prioritized.

Question 2

A 28-year-old man presented with increasing morning stiffness and fatigue from ankylosing spondylitis (radiographic axial spondyloarthritis). He also had bilateral swelling of the knees and two episodes of painful red eye that required topical corticosteroids. For the previous 2 years symptoms had been well controlled on regular non-steroidal anti-inflammatory drugs. The Bath Ankylosing Spondylitis Disease Index (BASDAI) score is now 5.2 and spinal pain score is 7.

What is the best step to take next?

A. Aspiration of the knees

B. Start adalimumab (anti-TNF monoclonal antibody)

C. Refer to physiotherapy for stretching exercises to improve morning stiffness

D. Start etanercept (anti-TNF fusion protein)

E. Continue current management

Correct answer: B. There are multiple indications that disease activity is currently poorly controlled (worsening of symptoms, active peripheral arthritis, uveitis flares). Therefore, this

patient requires escalation of treatment. Because of the history of uveitis, Adalimumab (anti-TNF monoclonal antibody) rather than Etanercept (anti-TNF fusion protein) is indicated.

Question 3

A 40-year-old man presented with increasing symptoms from both axial spondyloarthritis and Crohn disease. He had increasing abdominal pain and cramping, intermittent diarrhoea, blood in the stool, weight loss and anal fistula. Spinal pain and stiffness had also increased, together with swelling of his ankles and right knee.

A. Sulfasalazine

B. Methotrexate

C. Secukinumab

D. Adalimumab

E. Leflunomide

Correct answer: D. Both the axial SpA as well as the inflammatory bowel disease are poorly controlled. Therefore, this patient requires escalation of treatment. The most effective class of drugs capable of treating both conditions are anti-TNF monoclonal antibodies such as Adalimumab.

FURTHER READING

1. Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009; 68 Suppl 2: ii1-44.

2. van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, Regel A, Ciurea A, Dagfinrud H, Dougados M, van Gaalen F, Géher P, van der Horst-Bruinsma I, Inman RD, Jongkees M, Kiltz U, Kvien TK, Machado PM, Marzo-Ortega H, Molto A, Navarro-Compàn V, Ozgocmen S, Pimentel-Santos FM, Reveille J, Rudwaleit M, Sieper J, Sampaio-Barros P, Wiek D, Braun J. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017 Jun;76(6):978-991. doi: 10.1136/annrheumdis-2016-210770. Epub 2017 Jan 13. Review. PubMed PMID: 28087505.

3. Caetano AP, Mascarenhas VV, Machado PM. Axial Spondyloarthritis: Mimics and Pitfalls of Imaging Assessment. Front Med (Lausanne) 2021; 8: 658538.

4. Carvalho PD, Machado PM. How to investigate: Early axial spondyloarthritis. Best Pract Res Clin Rheumatol 2019; 33(4): 101427.

5. Smolen JS, Schols M, Braun J, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis 2018; 77(1): 3-17.