South African Rheumatism and Arthritis Association 2024 guidelines for the management of axial spondyloarthritis

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Early diagnosis and prompt treatment initiation are essential in the management of axial spondyloarthritis (axSpA), also known as ankylosing spondylitis, remembering that underdiagnosis and overdiagnosis of axSpA are common. These South African guidelines offer screening tools and details of useful investigations, including imaging. Care of the axSpA patient requires a multidisciplinary holistic approach emphasising lifestyle interventions, particularly exercise, smoking cessation and psychosocial support. The ankylosing spondylitis disease activity score is recommended as a measure of disease activity, and a stepwise algorithm for therapy is provided. Screening for comorbidities and vaccination is advised.

Keywords: axial spondyloarthritis, South Africa

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Axial spondyloarthritis (axSpA) is a chronic inflammatory joint disease affecting the axial skeleton, and falls within the 'family' of spondyloarthritides. Within this family, conditions including psoriatic arthritis, reactive arthritis and inflammatory bowel disease (IBD)-associated arthritis, as well as the prototype of axial disease (also referred to as ankylosing spondylitis), are found.[1] The prevalence of axSpA usually parallels that of HLA-B_{27} positivity.[2-4] Prevalence and incidence data from Africa are sparse.[3,5]

The original classification of axSpA relied on the presence of radiographic (X-ray) evidence of sacroiliitis. With the use of magnetic resonance imaging (MRI) in patients with back pain since the 1990s, inflammatory sacroiliitis was identified in patients with no features of sacroiliitis on plain X-rays, known as non-radiographic axSpA (nr-axSpA).

Peripheral joint involvement and musculoskeletal features (dactylitis, enthesitis) and extra-articular features (psoriasis, IBD and uveitis) often co-exist with axSpA, and clinicians are referred to the peripheral SpA guidelines for details of management of these problems.

Diagnosis of axSpA and screening tools

Early diagnosis and prompt treatment initiation are essential in the management of axSpA. Delays can result in higher disease burden, progressive structural damage, decreased health-related quality of life (HRQoL) and substantial economic burden, and negative outcomes regarding employability.[6-9] Both underdiagnosis and overdiagnosis of axSpA are prevalent.[10,11]

Screening tools for axSpA have been developed (Table 1).[12,13] All patients with lower back pain, especially those with symptom onset aged ≤40 years, should be screened for inflammatory features. If present, imaging of sacroiliac joints (SIJ) and HLA-B27 antigen testing should be considered.[14]

A clinical diagnosis of axSpA, based on the clinical presentation in combination with laboratory and imaging tests, and excluding other potentially more likely diagnoses, is the starting point. The Assessment of SpondyloArthritis International Society (ASAS) has developed classification criteria (Fig. 1) that are highly specific and sensitive.[15,16]

Overdiagnosis of axSpA is often related to false positive MRI findings, poor awareness of the differential diagnosis of axSpA and widespread pain syndromes such as fibromyalgia.[17-19] Mechanical causes of sacroiliitis include previous back surgery with malalignment, hypermobility with scoliosis/kyphosis, pregnancy, athletes and participants in extreme sports. Infection, particularly tuberculosis and brucellosis, must be considered.[20]

Assessing disease activity and disability

The ankylosing spondylitis disease activity score (ASDAS) is calculated using an online calculator[21,22] (https://www.asas-group.org/instruments/asdas-calculator). Based on specific cut points, disease activity can be classified into inactive disease, low, high or very high disease activity (Table 2). The ASDAS cutoff for clinically important

Table 1. Screening approach to chronic back pain. Patients with chronic low back pain (duration ≥3 months) with back pain onset <40 years of age should be referred to a rheumatologist if ≥1 of the following parameters is present

Parameter	Details
Inflammatory back pain	Any set of criteria, preferably ASAS definition of inflammatory back pain: four out of the following five parameters: (*i*) age at onset <40 years; (*ii*) insidious onset; (*iii*) improvement with exercise; (*iv*) no improvement with rest; (*v*) night pain with improvement upon getting up
Peripheral manifestations (arthritis, enthesitis and/or dactylitis)	Past or present, diagnosed by a physician
Extra-articular manifestations (psoriasis, inflammatory bowel disease and/or uveitis)	Past or present, diagnosed by a physician
Positive family history of SpA	Presence in first-degree or second-degree relatives of any of the following: (*i*) axSpA; (*ii*) psoriasis; (*iii*) acute uveitis; (*iv*) reactive arthritis; (*v*) IBD
Good response to NSAID	24 - 48 hours after a full dose of a NSAID the back pain is not present any more or is much better
HLA-B27 test	Only 5% of the general population with HLA-B27 positivity have SpA 20 - 33% of persons with chronic back pain and HLA-B27 positivity have SpA Moderate cost: done once only
Sacroiliitis on imaging, if available (X-ray or MRI)	Only if imaging is available, not recommended as routine screening parameter
Elevated acute phase reactants	CRP serum concentration or erythrocyte sedimentation rate above upper normal limit after exclusion of other causes for elevation

ASAS = Assessment of SpondyloArthritis International Society; SpA = spondyloarthritis; axSpA = axial spondyloarthritis; IBD = inflammatory bowel disease; NSAID = non-steroidal anti-inflammatory drug; HLA-B27 = human leukocyte antigen B27; MRI = magnetic resonance imaging; CRP = C-reactive protein.

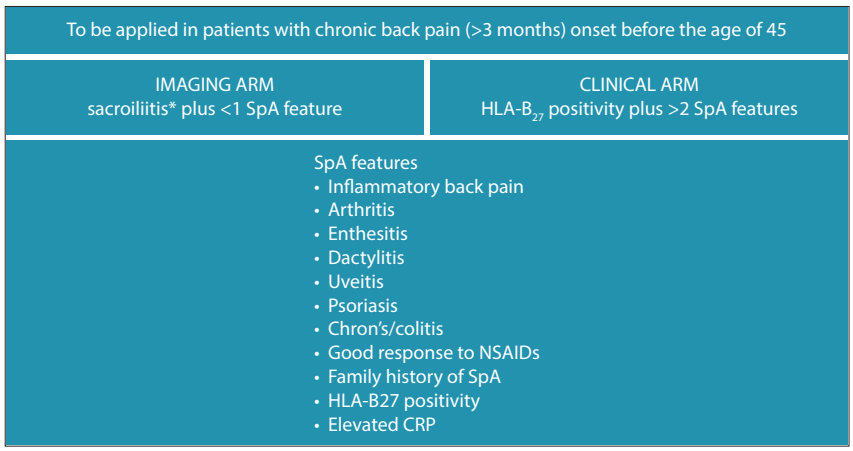

Fig. 1. Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axial spondyloarthritis (reproduced with permission). (SpA = spondyloarthritis; HLA-B27 = human leukocyte antigen B27; NSAIDs = non-steroidal anti-inflammatory drugs; CRP = C-reactive protein.)
**Sacroiliitis may be definite radiographically according to modified New York criteria, or by active inflammation on sacroiliac joint magnetic resonance imaging showing clear presence of bone marrow oedema or osteitis.*

improvement between examinations is ≥1.1, and the cutoff for a major improvement is ≥2.0. An alternative to the ASDAS is the Bath ankylosing spondylitis disease activity index (BASDAI),[23] with a score ≥4/10 considered 'active' disease, with a change of ≥50% in the BASDAI reflecting a clinically relevant improvement.[24] The Bath ankylosing spondylitis functional index (BASFI) measures functional disability in 10 different areas based on a visual analogue scale of 0 - 10.[25]

Radiography

Pelvic X-rays

The modified New York criteria describe the grading of the SIJ on pelvic X-rays.[26,27] Sclerosis, erosions, joint space widening or ankylosis of SIJ are features of established disease, and may take years to develop. Changes compatible with a classification of axSpA are grade 2 (or higher) changes bilaterally or grade 3 (or higher) unilaterally. Degenerative changes of SIJ are common.

Magnetic resonance imaging

A non-contrast MRI of the SIJs is key to diagnosing early disease, as it is more specific and sensitive than plain radiographs. Interpretation of MRI by a radiologist with expertise in axial imaging is recommended. A 'positive MRI' has the following requirements:

- bone marrow oedema (BMO) on a T2-weighted sequence sensitive for free water (such as short tau inversion recovery (STIR) or T2FS) or bone marrow contrast enhancement on a T1-weighted sequence (such as T1FS post-Gd)
- inflammation clearly present and located in a typical anatomical area (subchondral bone)
- MRI appearance must be highly suggestive of SpA.

Management principles

Patient information and decision-making

The aim of treatment is to maintain a good quality of life and function, including social participation. There is strong evidence that uncontrolled disease leads to radiographic progression, and that physical disability is a result of high disease activity and structural damage.[28-30] Importantly, there is now a choice of therapies to control inflammation in axSpA. Control of active disease can lead to improvements in physical function, HRQoL and work productivity.[31]

A management plan should be developed based on shared decision-making between patients and clinicians, according to the patient's values, goals, preferences and comorbidities. Patient education should offer information about axSpA and its complications, including disease assessment modalities, treatment goals, medications and adherence. A rheumatology nurse can offer patient education and support, with positive effects on adherence to therapy and on HRQoL.[32-34] Treatment should be individualised according to patient charac-

teristics, clinical features including extra-articular features, comorbidities and psychosocial factors.

Interventions including pharmacological therapy, physical activity, disease-related problem-solving, emotional wellbeing, communication skills and use of community resources, including patient support organisations, should be emphasised.

Referral to a rheumatologist and multidisciplinary team

All axSpA patients should ideally be seen by a rheumatologist, particularly those with diagnostic uncertainty, persistent moderate or high disease activity, functional impairment, or extra-articular disease. Care of the axSpA patient requires a multidisciplinary holistic approach that might include a dermatologist, gastroenterologist, ophthalmologist, occupational therapist, podiatrist, physiotherapist, biokineticist, pain specialist, clinical psychologist or social worker, as appropriate.

Lifestyle interventions and work participation

The importance of a healthy lifestyle, including smoking cessation, physical therapy and participation in patient support groups should be encouraged.[35-37] Exercise is a cornerstone in the management of axSpA, with demonstrated benefits on disease outcomes independent of pharmacological treatment.[35,38-40] Work participation may have positive effects on health outcomes, and SpA patients should be encouraged to continue formal or informal work.[41]

Comorbidities and extra-articular disease

The majority of axSpA patients have ≥1 comorbidity leading to premature mortality, functional impairment and reduced HRQoL.[42] Accelerated atherosclerosis and cardiovascular events, infections and osteoporosis are the major comorbidities in axSpA, and need regular screening and evidence-based management.[43] Additional comorbidities include chronic fatigue, depression, anxiety, degenerative joint disease, hypertension, dyslipidaemia, obesity and central pain sensitisation syndromes such as fibromyalgia syndrome.[44]

Screening for hepatitis B, hepatitis C, HIV and tuberculosis should be done at presentation, and repeated as clinically indicated. The vaccination status, pregnancy plans, contraception and lactational status (if relevant) of the patient should be regularly reviewed and discussed.

Therapy of axSpA

Goal of therapy

The goal of therapy is to achieve remission (ASDAS <1.3), or at least low disease activity (ASDAS <2.1).

Details of therapies

Disease-modifying antirheumatic drugs (DMARDs)

These agents are divided into three broad groups: conventional synthetic (cs) DMARDs, biologic (b) DMARDs and targeted synthetic (ts) DMARDs. The bDMARDs are either biologic original (bo) DMARDs or biosimilar (bs) DMARDs, and include:

- tumour necrosis factor inhibitors (TNFi): either receptor blockers (etanercept (original and biosimilar) or monoclonal antibodies (infliximab (original and biosimilar)); adalimumab (original and biosimilar) and golimumab
- IL-17 inhibitors (IL-17i) (secukinumab and ixekizumab).

The tsDMARDs include the Janus kinase (JAK) inhibitors tofacitinib and upadacitinib. Baricitinib, a JAK2 inhibitor, is not currently approved for axSpA therapy.

Glucocorticoids

Patients with axial involvement should not receive long-term systemic glucocorticoids (GCs). If required, local injections of GCs at sites of inflammation may be considered.[45] Of note, GC injections into the achilles or patella tendons is associated with a risk of tendon rupture.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are first-line therapy for axSpA, and the response is usually excellent. The toxicity of these drugs should not be underestimated, and all NSAIDs should be used with caution. Many axSpA patients have risk factors for NSAID-induced gastrointestinal tract events, including older age (>60 years), as well as co-prescription of aspirin. Hence, there should be a low threshold for co-prescribing a proton pump inhibitor for gastro protection, or for considering a cyclooxygenase-2 (COX-2) selective agent.[46] In addition, all NSAIDs, both non-selective agents and selective COX-2 inhibitors, confer an increased risk of thrombotic events, and should be used with caution in patients with cardiovascular (CV) risk factors, although the CV risk induced by NSAIDs in axSpA remains controversial. Other side-effects of NSAIDs, including hypertension, renal and liver dysfunction, should not be forgotten. Analgesics such as paracetamol or opioids might be considered if there is an incomplete response to NSAIDs, or NSAIDs are contraindicated.

Sequential therapy for axSpA (Table 3)

First-line therapy: NSAIDs

Patients with predominantly axial manifestations associated with pain and stiffness should be commenced on an NSAID as first-line therapy provided there are no contraindications. The maximum recommended/tolerated dose should be titrated to response, side-effect profile and patient risk factors. A 2 - 4-week trial is recommended. If the response is poor, an alternate NSAID should be prescribed. Whether NSAIDs can retard radiographic progression (growth of syndesmophytes in the spine) in axSpA patients is controversial.[47-50] For patients who respond well to NSAIDs, continuous treatment is advised with appropriate monitoring.

Second-line therapy (if peripheral arthritis): Conventional synthetic disease-modifying drugs

Patients with purely axial disease should not be treated with csDMARDs as there is no evidence to support their use in axial disease.[51,52]

Sulphasalazine may be considered for patients with peripheral arthritis.[53] While there is no evidence to support the use of methotrexate (MTX) or leflunomide in patients with peripheral manifestations, they may be used in exceptional situations where other pharmacological treatment options are not available.

For extra-articular manifestations of axSpA, including psoriasis, uveitis and inflammatory bowel disease, csDMARDs may be beneficial (see 'Guidelines for the management of peripheral SpA' for details).

Third- and fourth-line therapy: b/tsDMARD therapy

South African Rheumatism and Arthritis Association (SARAA) eligibility criteria for b/tsDMARD therapies for axSpA:

- A diagnosis of definite axSpA made by a rheumatologist according to ASAS criteria
- Objective evidence of inflammation:
  - elevated C-reactive protein (CRP), or
  - MRI evidence of active sacroiliitis, or

  - ultrasound evidence of inflammation in the joint/enthesitis/dactylitis.
- Sustained high disease activity for two visits at least 4 weeks apart defined by:
  - ASDAS score of >2.1
  - spinal pain visual analogue scale (1 - 10 cm) ≥4.
- Failure of standard treatment:
  - at least two NSAIDs during a 4-week period
  - if peripheral arthritis, failure of sulfasalazine.
- Refractory enthesitis, uveitis or other extra-articular manifestations.

Choice of b/tsDMARD

There are, to date, no validated biomarkers or head-to-head studies of b/tsDMARD in axSpA to guide choice of biological agent in axSpA. On a group level, there are no differences in the efficacy of various TNFi for axSpA itself, but there are differences on an individual patient level, which remain poorly understood.[54] The choice of b/tsDMARD therapy depends on which SpA domain is involved, extra-articular disease, patient preference, tuberculosis risk, comorbidities, route of administration and cost. Details are offered in the peripheral SpA guidelines.

If the patient has extra-articular manifestations of uveitis or IBD, then monocloncal TNFi is preferred, and the soluble receptor (etanercept) should be avoided. Similarly, IL-17i and JAKi have not been shown to be efficacious in uveitis. IL-17i should not be used in patients with active IBD.[55] IL 12/23 inhibitors are not effective for axSpA. Baricitinib, a JAK2 inhibitor, is not currently approved for axSpA therapy.

The use of combination b/tsDMARDs is not recommended.

In SpA (axial or peripheral), there is little evidence that co-prescription of MTX with b/tsDMARDs is necessary.

All b/tsDMARDs should be initiated by a rheumatologist. All patients with a rheumatic disease on b/tsDMARDs must be included, with patient consent, in the SARAA biologics registry (https://www.saraa.co.za). Before commencing b/tsDMARD, appropriate screening and treatment for latent tuberculosis, hepatitis B, hepatitis C and HIV, in addition to vaccination, should be done.

Response to therapy

The patient should be evaluated at 3 months to assess the response to treatment. If there is an improvement of the ASDAS ≥1.1 and/or BASDAI ≥2, treatment should be continued. In the case of inadequate response to therapy, the patient needs review in terms of diagnosis of axSpA, structural damage v. active disease-causing symptoms (consider CRP and/or MRI scan) and adherence to therapy.

Tapering of bDMARDs

If the patient has a good response to therapy with sustained remission for a period of 6 months (ASDAS <1.3 and normal CRP on three consecutive visits or for 6 months), tapering of the bDMARDs might be considered in a shared decision-making process.[56,57] Tapering should either be in the form of reduction of dose or increasing the interval of administration. Tapering should be done slowly and cautiously to prevent any flares in disease. Discontinuation is not advised, as the evidence shows that a high proportion of patients experience disease flares.[58]

Special notes on comorbidities

Osteoporosis and spinal fracture

Screening for osteoporosis is recommended as per local protocol, remembering that sclerosis of the axial skeleton may make dual X-ray absorptiometry (DEXA) scan interpretation difficult – therefore DEXA of the wrist and hip (if unaffected by ankylosis) is recommended. Alternatively, dual-energy quantitative computed tomography may be used to assess the patient. Recently, the trabecular bone score mapping of L1-L4 derived from the DEXA image has been shown to be related to bone micro-architecture and fracture risk.[59]

If any significant changes in the patient's pain/backache occur and the nature of the pain changes from inflammatory to mechanical, spinal fractures should be considered, and appropriate imaging and treatment are advised.[60] Risk factors for spinal fracture in axSpA include advanced age, higher BASFI, longer disease duration, low bone mineral density and osteoporosis.

Table 2. Disease activity assessment tools and cutpoints for axial spondyloarthritis

Cutpoint	Ankylosing spondylitis disease activity score (ASDAS)	Bath ankylosing spondylitis disease activity index (BASDAI)
Inactive disease	<1.3	<1.6
Low disease activity	<2.1	<2.9
High disease activity	<3.5	<3.8
Very high disease activity	≥3.5	≥3.8
Online calculator	https://www.asas-group.org/instruments/asdas-calculator	https://www.basdai.com/BASDAI.php

Table 3. Stepwise algorithm for therapy in axial spondyloarthritis

Step	Therapy	Inadequate response within 3 months
First-line therapy	NSAID	Proceed to second-line therapy
Second-line therapy (if peripheral arthritis)	Sulfasalazine 2 - 3 g/daily	Proceed to third-line therapy
Third-line therapy	b/tsDMARD (TNFi/IL-17i/JAKi)	Proceed to fourth-line therapy
Fourth-line therapy	Alternative b/tsDMARD (TNFi/IL-17i/JAKi)	
Tapering	Consider tapering if sustained remission × 6 months	Restart b/tsDMARD if flares

NSAID = non-steroidal anti-inflammatory drug; b/tsDMARD = biologic/targeted synthetic disease-modifying antirheumatic drug; TNFi = tumour necrosis factor inhibitor; IL-17i = interleukin-17 inhibitor; JAKi = Janus kinase inhibitor.

Summary points pertaining to the management of axSpA

Early diagnosis and prompt treatment initiation are essential in the management of axSpA, using the ASAS classification criteria as a reference. Both under-diagnosis and over-diagnosis are prevalent.

Management by a rheumatologist-led multidisciplinary team should include pharmacological therapy, physical activity and referral to a patient support organisation.

The goal of therapy is to achieve remission (ASDAS <1.3), or at least low disease activity (ASDAS <2.1). Sequential therapy should be offered until this goal is achieved.

Screening and management of comorbidities including cardiovascular disease, infections, osteoporosis and depression should be undertaken.

axSpA = axial spondyloarthritis; ASAS = Assessment of SpondyloArthritis International Society; ASDAS = ankylosing spondylitis disease activity score.

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