Indonesian Journal of Rheumatology
Journal Homepage: https://journalrheumatology.or.id/index.php/IJR

Indonesian Rheumatology Association (IRA) Recommendations for Diagnosis and Management of Axial Spondyloarthritis 2021

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ARTICLE INFO

Keywords:
Axial Spondyloarthritis
levels of evidence (LOE)
grades of recommendation (GOR)
NSAIDs
anti-TNF
anti-IL-17A (Secukinumab, Ixekizumab).

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/IJR.v13i1.174

ABSTRACT

Objective. Recommendations for spondyloarthritis are made to provide guidelines in diagnosis establishment, therapy, and monitoring of axial spondyloarthritis cases.
Method. Literature searches were conducted online. The drafting team determines the levels of evidence (LOE) and grades of recommendation (GOR). After conducting a discussion, each recommendation that has been agreed upon by the drafting team is then classified based on the levels of evidence and grades of recommendation. The final step in the preparation of these recommendations is to determine the level of agreement (LOA) on each recommendation carried out by a team of panelists who have been appointed by IRA.
Results. Twenty recommendations regarding axial spondyloarthritis were established. Strong recommendations or GOR A include: Ax-SpA diagnosis can be made according to the 2010 ASAS criteria, or the 1984 modified New York criteria specifically for the US; conventional radiographic examinations and MRI of the sacroiliac joints and vertebrae may be used as evaluators of disease activity and predictors of therapeutic response, as well as patients who do not respond to NSAIDs (within 4 weeks) can be administered a combination of NSAIDs and anti-TNF, and if it is not possible, a combination of NSAIDs and anti-IL-17A (Secukinumab, Ixekizumab).
Conclusion. These recommendations provide a direction for clinicians to diagnose and manage spondyloarthritis.

1. Preliminary

Spondyloarthritis, formerly known as spondyloarthropathy or seronegative spondyloarthritis, is a group of inflammatory rheumatic diseases that have a similar clinical picture in terms of inflammation of the back pain (spondylitis), sacroiliac joints (sacroiliitis), peripheral arthritis, enthesitis, dactylitis, accompanied by extra-articular manifestations (uveitis, psoriasis, and inflammatory bowel disease) and is associated with the HLA-B27 antigen.[1,2]

Spondyloarthritis is a group of autoimmune rheumatic diseases that are increasingly being encountered in daily practice, so health practitioners need to be more vigilant. Globally, the prevalence of spondyloarthritis is 0.5%-2% of the population.[3] The prevalence of spondyloarthritis in each continent varies, such as in Southeast Asia as much as 0.20%, in the North Pole 1.61%, in America by 1.35%, in Europe about 0.54% of the population, and in South Asia as much as 0 ,22% of the population experience this condition.4 This variable number is influenced by various things such as health problems that occur, the definition that is used as the basis for diagnosis, classification criteria that change from time to time, as well as fundamental differences in genetic and environmental factors that play a role in the onset of the disease.[3]

Spondyloarthritis is divided into several subgroups, with the ankylosing spondylitis (AS) subgroup has the greatest prevalence. The US prevalence in continental Europe is 0.24%, in North America 0.31%,[2] in Sub-Saharan Africa 0.02%, and in the Arctic about 0.35% of the population. The prevalence of psoriatic arthritis is the second highest in the spondyloarthritis subgroup. The distribution in the Middle East is 0.01%, and in Europe 0.19%. The prevalence of reactive arthritis varies from 0.0%-0.2%. Meanwhile, based on existing research data, the incidence of spondyloarthritis associated with IBD can be said to be small, namely 0.0% - 0.1%, and 0.0-0.7% in cases of spondyloarthritis that cannot be classified.[4]

Spondyloarthritis can lead to various unwanted complications if not treated properly. In axial spondyloarthritis, bone deformities can occur due to damage and deformity of bone formation, which can occur simultaneously or alternately. Osteoproliferation results in the formation and growth of syndesmophytes that trigger structural damage. The development of syndesmophytes varies greatly in patients with axial spondyloarthritis, but in severe cases, it can lead to complete fusion of the axial joint and even the peripheral joint.[5] In psoriatic arthritis, systemic inflammation can lead to atherosclerosis, increased morbidity from cardiovascular disease, and mortality in severe disease.[6]

2. Methods

The spondyloarthritis recommendation drafting team was formed by the Indonesian Rheumatology Association (IRA) to conduct literature review and formulate recommendation questions for diagnosis, therapy, and monitoring of SpA cases. The panel team consisted of specialists in internal medicine, sub-specialists in rheumatology from various branches of IRA and institutions in Indonesia. The panelist team then gave individual opinions regarding the level and strength of the recommendations that have been prepared by the drafting team. In the drafting team and the panelist team, there are no representatives from pharmaceutical companies.

In preparing these recommendations, literature searches were conducted online. After the drafting team determines the recommendation questions, the drafting team then determines the levels of evidence (LOE) and grades of recommendation (GOR) which refers to the provisions listed in Table 1. Levels of evidence is a hierarchical system of classification of evidence based on the quality of the design methodology, validity, as well as its application to patient care. Meanwhile, the grades of recommendation are based on the levels of evidence which consider the overall degree of evidence as well as the judgement by the drafting team. GOR was developed based on several considerations, namely cost, preference, value, feasibility, risk-benefit assessment, as well as quality assessment of available scientific evidence.[5]

Table 1 Levels of Evidence and Grades of Recommendation

	Levels of Evidence (LOE)		Grades of Recommendation (GOR)
I.	High quality meta-analyses or systematic reviews of randomized clinical trials (RCTs) or individual RCTs with low risk bias	A.	Strong recommendation: refer to degree I. studies
II.	High quality systematic review of observational studies (case control/cohort) or individual observational studies	B.	Medium recommendation: refer to degree II studies or extrapolation from degree I studies
III.	Non-analytic studies (case reports or case series)	C.	Weak recommendation: refer to degree III studies or extrapolate to degree II studies
IV.	Expert opinion	D.	Consensus recommendation: expert opinion based on limited strength of evidence

Each recommendation that has been agreed upon by the drafting team is then classified based on the levels of evidence and grades of recommendation. The final step in the preparation of these recommendations is to determine the level of agreement (LOA) on each recommendation carried out by a team of panelists who have been appointed by PB IRA.

The panel of panelists formed consisted of 46 people consisting of specialists in internal medicine, subspecialist rheumatology, who had more than 5 years of work experience. Members of the panelist team play a role in providing a score for each recommendation point using a scale of 0-10, where 0 means completely disagree and 10 means full agreement. Each recommendation point with a value below 8 will be discussed and reviewed by the drafting team to be revised. An assessment related to the LOA will then be conducted by the panelist team.

3. Recommendations

Recommendations 1. Axial spondyloarthritis (Ax-SpA) consists of two subtypes: nonradiographic (nrAx-SpA); and radiographs (rAx-SpA) which alsocalled ankylosing spondylitis (AS).

According to ASAS and NICE, as listed in Table 3, axial spondyloarthritis (Ax-SpA) is classified into two subtypes namely:[7,8]

- Radiographic axial spondyloarthritis (r-axSpA), proven by the presence of sacroiliitis on pelvic radiography. The term is synonymous with ankylosing spondylitis (AS) according to the modified New York criteria.[9,10,11,12,13]
- Nonradiographic axSpA(nr-axSpA), proven by no evidence of sacroiliitison conventional pelvic radiographs.

Recommendation 2. The diagnosis of Ax-SpA can be made by the 2010 ASAS criteria, or the modified 1984 New York criteriaexclusively for US

The diagnosis of AS can be made using the New York criteria that have been modified in 1984 as listed in Table 1.[8]

Table 1. AS Diagnosis According to Modified New York Criteria[8]

A. Diagnosis According to Modified New York Criteria (1984)
Clinical Criteria
• Low back pain for at least 3 months, which improves with activity, but does not improve with rest
• Limited movement of the lumbar vertebrae in the sagittal and frontal directions
• Decrease in chest cavity expansion relative to normal values, according to age and sex

Radiological Criteria

- Bilateral sacroiliitis grade 2 or unilateral sacroiliitis grade 3 – 4

Definitive ankylosing spondylitis

- If the criteria for sacroiliitis are obtained, add one clinical criterion

According to the 2010 ASAS classification criteria (Table 2 or Figure 1), the early stages of the disease are characterized by active sacroiliitis on MRI and at least one SpA or HLA-B27 feature with two or more SpA features.[10,14]

Table 3. ASAS Classification Criteria for Ax-SpA

Patients with low back pain 3 months (with or without peripheral manifestations) with onset of patient age <45 years, with the following criteria:		
Sacroiliitis on radiograph* plus >1 SpA picture	*or*	**HLA-B27 plus 2 more SpA pictures****
** SpA overview: • Inflammatory back pain Nyeri • Arthritis • Enthesitis (heel) • Uveitis • Dactylitis • Psoriasis • *Crohn's disease*/ulcerative colitis • Responds well to NSAIDs • Historyfamily with SpA • HLA-B27 • CRP Boost		*Sacroiliitis on radiograph: - Active (acute) inflammation on MRI is suspected strong as sacroiliitis associated with SpA or - Definitive radiographic sacroiliitis according to modified New York criteria

Sensitivity 82.9%, specificity 84.4%; n = 649 patients with chronic low back pain and age at onset <45 years. Imaging arm (sacroiliitis) itself has a sensitivity of 66.2% and a specificity of 97.3%.

**Note: elevated CRP is considered a feature of SpA in the context of chronic low back pain. (adapted from Rudwaleit M, et al. Ann Rheum Dis 2009;68:777–783

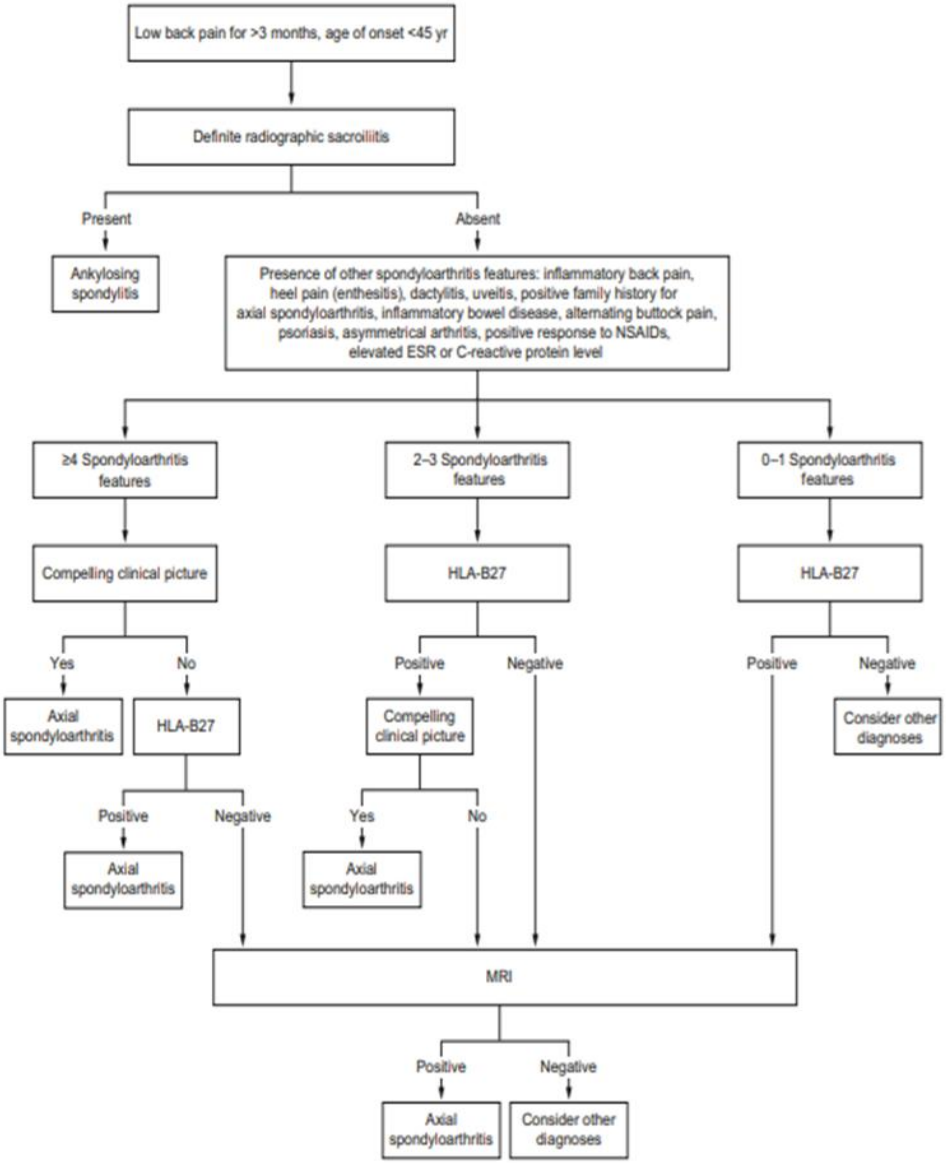
Recommendation 3. The diagnosis of rAx-SpA is made if sacroiliitis is found by conventional radiographic examination; and if sacroiliitis is found only by MRI examination or a positive HLA-B27 examination, then it is classified as nrAx-SpA

Radiological examination plays an important role in the diagnosis of axial spondyloarthritis as listed in the algorithm for the diagnosis of axial spondyloarthritis in Figure 2. In axial spondyloarthritis, sacroiliitis is found in 70-80% of patients (AS).[15,16] The appearance of inflammation in the peripheral and axial joints can be evaluated from conventional radiographs as well as by MRI and musculoskeletal ultrasound examinations.[17]

Radiological features that can be found include sclerosis and erosion to the occurrence of ankylosing or total fusion, especially in the sacroiliac joints. While in the spine, a syndesmophyte image is obtained, namely the annulus fibrosus bone which can then connect each vertebral column so that it gives a "bamboo spine" image.[17]

Conventional radiographic examination of the

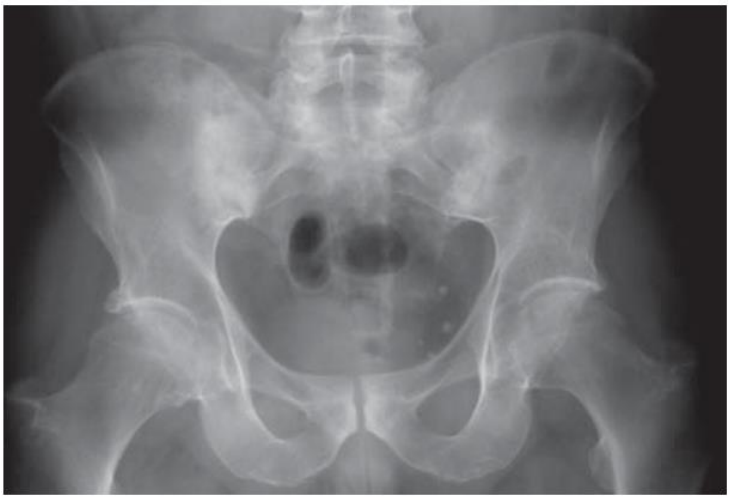
Sacro Iliac Joint (SIJ) is the first modality recommended for the diagnosis of ax-SpA and remains the mainstay of choice for the assessment of structural changes in the spine and SIJ. 3. Examples of the results of conventional radiographs of patients with AS can be seen in Figure 2, Figure 3, and Figure 4



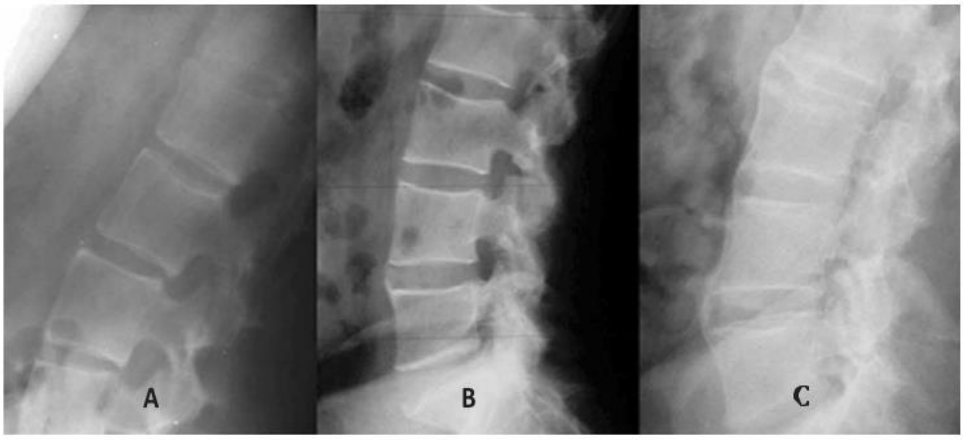
Picture 1. Axial Spondyloarthritis Diagnostic Algorithm[19]

Table 4. Degree of Sacroiliitis based on Radiology (1966)[17]

Level	Definition / Changes in the radiological picture
0	Normal
1	Suspicion of abnormalities
2	Minimal abnormalities in the form of erosion or mild sclerosis (minimal), without joint space narrowing
3	Significant abnormalities of moderate or severe sacroiliitis accompanied by one or more of the following features: erosion, evidence of sclerosis, widening, narrowing of the joint space or partial ankylosis
4	Severe abnormality - total ankylosis

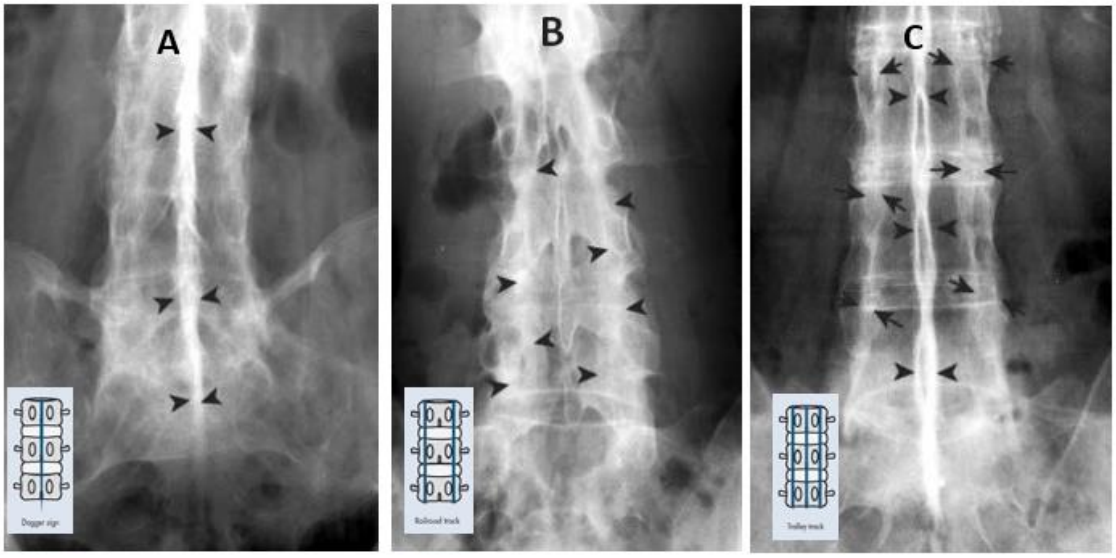


Picture 2. Conventional Radiography of the Pelvic Patient with AS Indicating Grade III Bilateral Sacroiliitis [20]



A) Shiny corners and erosions B) Early syndesmophytes C) Spinal fusion or ankylosis

Picture 3. Lumbar Vertebrae Changes in AS[21]



A) Dagger sign B) Railroad track sign C) Trolley track sign

Picture 4. Conventional Radiography Showing Ossification in the Spine [22]

In AS, ossification of the supraspinous and interspinous ligaments was also found to form a thin radio-opaque line in the midline, vertically downward, known as the dagger sign. Fusion of the posterior joint capsular ligaments forms a bilateral radio-opaque appearance similar to that seen in the antero-posterior projection, a feature known as the railroad track sign. If both images are found on conventional radiographs, it is calledas a trolley track sign (Figure 4).[22]

Meanwhile, in nonradiographic spondyloarthritis (nrAx-SpA), conventional pelvic and lumbosacral radiographs were found to be normal or there is a unilateral grade I or grade II sacroiliitis.[15,23] In nrAx-SpA, sacroiliitis can be seen only by MRI.[15]

Magnetic resonance imaging (MRI) should be performed in the pelvic and vertebral region. Pelvic MRI was performed primarily using short T1 inversion recovery (STIR) and T1 weighted sequences of the whole spine (sagittal section) and sacroiliac joints (coronal oblique view) with intravenous gadolinium contrast. An MRI scan of the semicoronal T1W sequence and either the short tau inversion recovery (STIR) or fat-saturated T2-weighted (T2FS) sequence, is performed in routine MRI examinations for evaluation of the sacroiliac joint.[23] The definition of abnormality on MRI follows the definition of a positive MRI according to ASAS, which is either an inflammatory lesion or a structural lesion.[15,23]

Some patients with axial spondyloarthritis will develop spondylitis before sacroiliitis and some patients do not even have sacroiliitis, so that MRI of the spine is required.[24] MRI is also capable of detecting bone marrow edema (BME) or osteitis and erosions before they are detected by conventional radiographs. Thus, MRI is very useful for the early diagnosis of AS.[25] The findings of other cases of axial spondyloarthritis on MRI can be seen in Table 5.[16]

In addition to conventional radiography and MRI, other radiological modalities such as CT scan and ultrasound can also be used to assess disease activity in axial spondyloarthritis as listed in Table 5.[16]

Table 5. Characteristics of Lesions in the Sacroiliac Joints and Spine of Ax-Spa Patients as Depicted by MRI[16]

Inflammatory Disorders	Structural Abnormalities
SIJs	
Sacroiliitis—good bone marrow edema (osteitis)itis unilateral or bilateral of the sacroiliac joints	Subchondral sclerosis
Synovitis	Erosion
capsulitis	Backfill/subchondral fat metaplasia
	Bony bridges
Enthesitis	Ankylosis
Spine	
Anterior/posterior spondylitis—bone marrow edema (osteitis) especially in the vertebrae	Fat metaplasia
Spondylodysitis	Erosion
Arthritis of the costovertebral joints	Sindesmofit
Facet joint arthritis	Ankylosis
Enthesitis of the spinal ligament	

Table 6. Assessment of Imaging Techniques Available for Use on AS[16]

Technique	Inflammation/Acute Disorder	Structural/Chronic Disorder
Conventional radiographs	-	+
CT Scan	-	++
ultrasound	+	(+)
MRI T1w	(+)	+
STIR/T2FS/T1Gd	++	+

*– no diagnostic value; + with diagnostic value; (+) limited diagnostic value; ++, with diagnostic value, the gold standard.

If the MRI meets the ASAS criteria, the diagnosis of non-radiographic axial spondyloarthritis can be made. If the MRI does not meet the ASAS criteria, it still does not rule out axial spondyloarthritis, so other tests such as HLA-B27 or repeat MRI are required.[23,24]

Recommendation 4. Conventional radiographic examination and MRI of the sacroiliac joints and vertebrae can be used as the indicators of disease activity, as well as predictors of therapeutic response

In addition to playing a role in diagnosis, radiological examination, especially conventional radiography and MRI, also plays a role in the management and monitoring of axial spondyloarthritis because it can assess disease activity and predictor of response to therapy. Disease activity depicted on conventional radiographic examinations is appropriate.[17]

Recommendation 5. Assessment of disease activity can be done by using ASDAS or BASDAI assessment.

Monitoring of disease activity is carried out at the time of initial diagnosis and during evaluation of therapy using the appropriate instruments in Table 7. If disease activity is in doubt after the patient has received therapy with biologic agents, spinal or sacroiliac joint MRI should be performed.[26]

Table 7. Core Domain of Assessment of Spondyloarthritis International Society (ASAS)/Outcome Measures in Rheumatology (OMERACT) for AS

Criteria	Rating
Functional	BASFI
Pain	NRS/VAS (previous week/spinal/night due to AS)
Spinal mobility	Modified Schober Test chest wall development*Occiput to wall* cervical rotation Lateral spinal flexion or BASMI
Peripheral joints	Number of swollen joints (44 joints)
Enthesis	Validated enthesis scores such as MASES, San Francisco and Berlin
Joint stiffness	NRS/VAS (duration of stiffness and pain/spinal/previous week)
Acute phase reactants	*C-reactive protein* (CRP), erythrocyte sedimentation rate (ESR)
Fatigue	BASSAI

*AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; MASES, Maastricht Ankylosing Spondylitis Enthesis Score; NRS, numerical rating scale 0–10;

VASE,visual analogue scale0–100.

(Adapted from Sieper J, et al 2009. Ann Rheum Dis, 68: ii1-ii44)

However, in general, the assessment of AS disease activity can be assessed using the ASDAS (Appendix 6) or the BASDAI (Appendix 5), with the interpretation of the results as follows:[27]

- ASDAS :
  - <1.3 : not active
  - 1.3 – 2.1 : light activity (ASAS)/moderate activity (ASDAS)
  - 2.1 - 3.5 : activity high
  - >3.5 : very activity high

- BASDAI:
  - : not active
  - Cut off4: active
  - 4 : high activity
  - 10 : very active
- Repair:
  - : clinically important improvement
  - 2.0 : major improvement

Recommendation 6. Assessment of osteoporotic fracture risk with BMD examination is recommended in every patient with axial spondyloarthritis

Based on a meta-analysis, it was found that the prevalence of osteoporosis in axial spondyloarthritis varied from 11.7 to 34.4% of cases and the prevalence of fracture was found to be 11 to 24.6%.[28] Thus, it is necessary to screen for osteoporosis in patients with axial spondyloarthritis. Osteoporosis screening can be performed using BMD DXA on the spine and pelvis.[26]

Recommendation 7. The goal of Ax-SpA treatment is to achieve the target of remission (ASDAS <1.3) or at the minimum, low disease activity (ASDAS <2.1)

Monitoring of axial spondyloarthritis disease activity is carried out at least 2 times in 1 year or every 6 months using ASDAS or BASDAI instruments (according to US therapeutic targets).[29.30] In patients on biologic therapy, if disease activity is in doubt, spinal or pelvic MRI is recommended.[26] The target of therapy in Ax-SpA cases is to reduce disease activity by achieving an ASDAS value <1.3 (remission) or at least an ASDAS <2.1 (low disease activity).[17] In addition, other targets of axial spondyloarthritis therapy are controlling the pain (a decrease of at least 2 points on VAS) and improving functional impairment.[26,30,32]

Recommendation 8. NSAIDs are the first choice of treatment for SpA (no particular choice of NSAID is preferred)

In the management of SpA cases, the first line therapy given continuously is NSAIDs, as described in Figure 5 for the active Ax-SpA algorithm and Figure 6 for stable Ax-SpA. In the selection of NSAIDs, no particular NSAID option is preferred.[26]

Recommendation 9. Conventional DMARDs such as methotrexate and sulfasalazine can be given for peripheral joint manifestations

If additional manifestations are found to be predominantly peripheral, local glucocorticoid injections may be administered, particularly if the arthritis involves two joints. If there are manifestations in more than two joints, sulfasalazine (first choice) or methotrexate can be preferred.[26]

Recommendation 10. Patients who do not respond to NSAIDs (within 4 weeks) can be given a combination of NSAIDs and anti-TNF , and if this is not possible, alternative combination of NSAIDs and anti-IL-17A (Secukinumab, Ixekizumab) may be administered

If axial spondyloarthritis remains active despite taking NSAIDs (after 4 weeks), the choice is a combination of NSAIDs and anti-TNF . In patients with moderate to severe heart failure comorbidities, the use of anti-TNF is not allowed. If under certain conditions anti-TNF is not possible, a combination of NSAIDs and anti-IL-17A (Secukinumab, Ixekizumab) can be recommended as an alternative.[26]

Recommendation 11. In patients with IBD or uveitis, treatment with monoclonal antibodies is recommended over other biologic agents.

In patients with comorbid IBD or uveitis, the

treatment recommendation is to use anti-TNF monoclonal antibodies instead of other biologic agents. One consideration of these recommendations is that the use of etanercept may lead to an increased risk of IBD exacerbations and episodes of uveitis compared to monoclonal antibodies such as infliximab or adalimumab.[26]

Recommendation 12. If there is no response to NSAIDs and anti-TNF (primary non-response) then it is recommended to replace with anti-IL-17A, while if anti-TNF responds well at first but the response decreases (secondary non-response) then it is recommended to replace the drugs with other anti-TNF, or in certain circumstances, with anti-IL-17A (Secukinumab, Ixekizumab).

If axial spondyloarthritis disease activity is still active despite receiving NSAIDs and anti-TNF , then the patient's response to therapy can be divided into:[26]

a. Primary non-responder (not responding with anti-TNF)
    - In this case, the patient's treatment of choice is anti-IL-17A (Secukinumab, Ixekizumab).

b. Secondary non-responders (anti-TNF α respond well at the start of treatment, but the response disappears over time)
    - In this case, the patient's treatment options are other anti-TNF or in certain circumstances can use anti-IL-17A (Secukinumab, Ixekizumab).

Recommendation 13. Sulfasalazine can be used as an alternative if the patient is unable to receive anti-TNF or anti-IL-17A (Secukinumab, Ixekizumab).

In patients who are unable to receive anti-TNF or anti-IL-17A (Secukinumab, Ixekizumab), a single conventional DMARD, especially Sulfasalazine, or a combination with close monitoring may be tried.[26]

Recommendation 14. Evaluation of the effectiveness of a single NSAID was assessed after 4 weeks of therapy, the effectiveness of anti-TNF was assessed after 3 months of therapy and the effectiveness of anti-IL-17A (Secukinumab, Ixekizumab) was assessed after 4 months of therapy.

Monitoring the effectiveness of pharmacological therapy is carried out in different time periods. In the use of NSAIDs, the effectiveness of the drug was assessed after 4 weeks of therapy. In the use of anti-TNF , the effectiveness of the drug was assessed after 3 months of therapy. Meanwhile, the assessment of the effectiveness of anti-IL-17A (Secukinumab, Ixekizumab) was assessed after 4 months of therapy.[31]

Recommendation 15. If disease activity is stable, anti-TNF or anti IL-17 can be continued, and NSAIDs are given only if necessary

In cases of stable axial spondyloarthritis with the use of biologic agents (anti-TNF or anti-IL-17A), it is recommended to continue with biologic agents. In patients with persistent remission, discontinuation or gradual reduction (frequency or dose) may be considered, noting that only one third of these patients will not relapse. This decision is taken after discussion and agreement with the patient. In patients whose disease activity is stable on combination therapy of anti-TNF and NSAIDs, it is strongly recommended to continue anti-TNF alone and discontinue NSAIDs.[26]

Recommendation 16. It is not recommended to replace anti-TNF therapy or original anti-IL-17 with the other biosimilar products

In patients with disease controlled with original anti-TNF or anti-IL-17, it is not recommended to change therapy with biosimilar products.[31] This is related to the risk of differences in the therapeutic response of the original product with biosimilar products in terms of efficacy, safety, and tolerability in patients.[32]

Recommendation 17. In patients with persistent remission, DMARD reduction should be considered with caution.

In patients with axial spondyloarthritis on

persistent remission, DMARD administration may be reduced, but this decision must be carefully considered.[26]

Recommendation 18. In patients with spinal fusion or advanced osteoporosis, spinal manipulation is not recommended

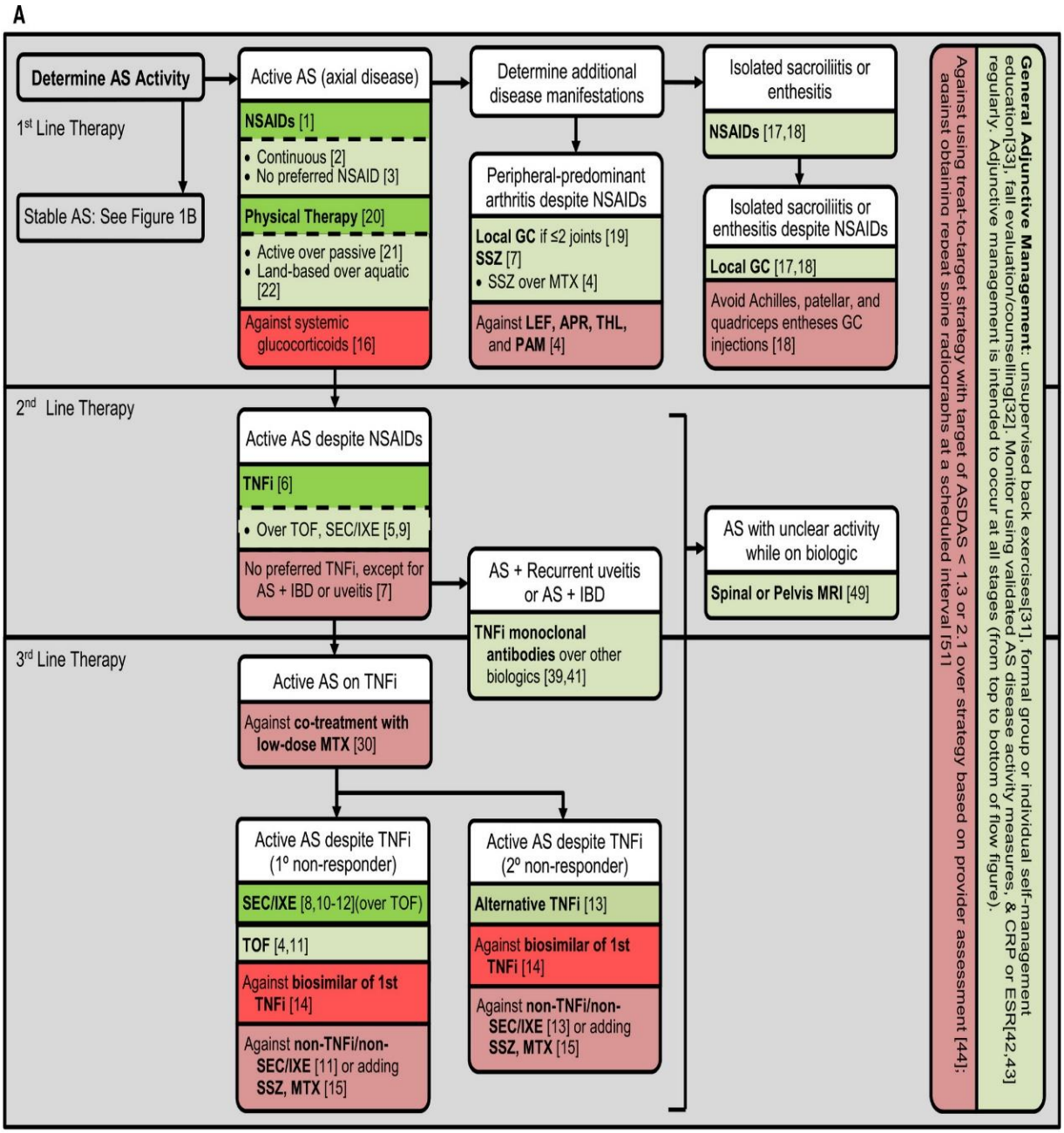
Surgery is the last treatment modality of choice if the patient's complaints have not improved with pharmacological therapy. However, there are some conditions in which surgery should be avoided, one of which is the patients with spinal fusion or advanced osteoporosis. In spinal fusion or advanced osteoporosis, spinal manipulation should be avoided.[26]

Recommendation 19. In patients with advanced hip arthritis, it is recommended to perform Total Hip Replacement

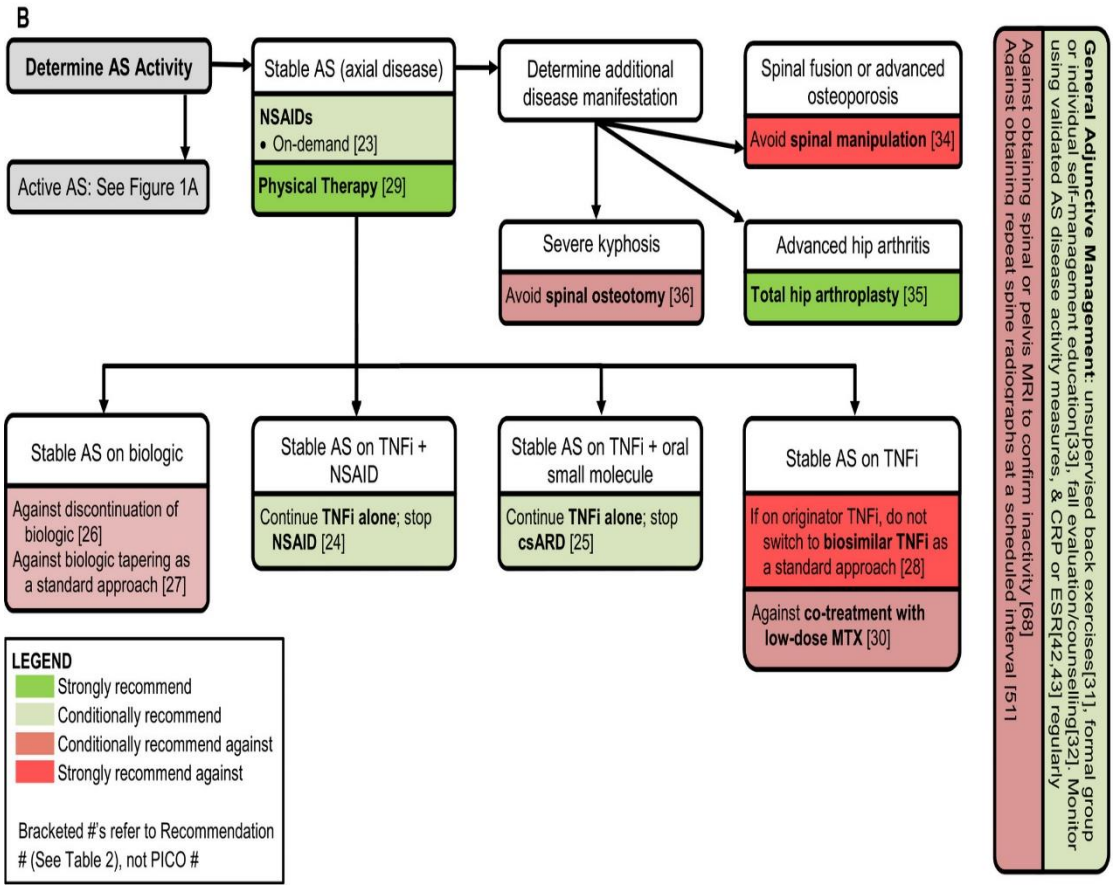
In patients with advanced hip arthritis, it is recommended to perform a hip arthroplasty (total hip replacement) procedure.[26]

Recommendation 20. In patients with severe kyphosis, an elective spinal osteotomy is not recommended

Apart from spinal fusion or advanced osteoporosis, surgery should also be avoided in severe kyphosis. In severe kyphosis, spinal osteotomy should be avoided.[26]



Picture 5. Medical Treatment Options for Active Axial Spondyloarthritis[26]
(adapted from Ward MM, et al. Arthritis & Rheumatology. 2019; 71(10): 1599-613.)



Picture 6. Medical Treatment Options for Stable Axial Spondyloarthritis[26]
(adapted from Ward MM, et al. Arthritis & Rheumatology. 2019; 71(10): 1599-613.)

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