Indonesian Journal of Rheumatology

Journal Homepage: <https://journalrheumatology.or.id/index.php/IJR>

Indonesian Rheumatologist Association (IRA) Recommendations for Diagnosis and Management of Peripheral Spondyloarthritis 2021

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ARTICLE INFO

Keywords:

Peripheral Spondyloarthritis
levels of evidence (LOE)
grades of recommendation (GOR)
level of agreement (LOA)

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

<https://doi.org/10.37275/IJR.v13i1.175>

ABSTRACT

Objective. Spondyloarthritis recommendations are made to provide guidance in diagnosis, treatment, and monitoring of peripheral 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.

Result. Thirty five recommendations regarding peripheral spondyloarthritis were compiled. There are 6 strong recommendation or GOR A for psoriatic arthritis and 8 recommendations for enteropathic arthritis.

Conclusion. These recommendations provide directions for clinicians to diagnose and to manage peripheral spondyloarthritis.

1. Preliminary

Spondyloarthritis, formerly known as spondyloarthropathy or seronegative spondyloarthritis, is a group of inflammatory rheumatoid diseases that have a similar clinical picture in terms of inflammatory low 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 that 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 Arctic 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 has this condition.⁴ This variable figure is influenced by various things such as health problems that occur, the definition on which the diagnosis is based, classification criteria that change from time to time, as well as fundamental differences in genetic and environmental factors that play a role in the emergence of disease.³

Spondyloarthritis is divided into several subgroups, with the ankylosing spondylitis (AS) subgroup being the spondyloarthritis group that has the greatest prevalence. US prevalence in the European continent 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, there can be abnormalities in the bone due to damage and deformity of bone formation, which can occur simultaneously or alternately. Osteoproliferation results in the formation and growth of syndesmophytes that lead to structural damage. The development of the syndesmophyte varies widely in patients with axial spondyloarthritis, but in severe cases, it can lead to complete fusion of

the axial joints and even the peripheral joints.⁵ In psoriatic arthritis, systemic inflammation can lead to atherosclerosis, increased morbidity due to cardiovascular disease, and mortality in severe disease.⁶

2. Methods

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

In preparing these recommendations, literature searches are carried out 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 refer to the provisions listed in Table 1. Levels of evidence is a hierarchical system of evidence classification based on the quality of the design methodology, validity, as well as its application to patient care. Meanwhile, grades of recommendation are based on levels of evidence which take into account the overall level of evidence and also consider the judgement by the drafting team. GOR was developed based on several considerations, namely cost, preference, value, feasibility, risk-benefit assessment, as well as the quality assessment of available scientific evidence.⁷

Table1. Levels of Evidence and Grades of Recommendation

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

After conducting discussions, each recommendation that has been agreed upon by the drafting team is then determined the levels of evidence and grades of recommendation. The final step in the preparation of this recommendation is to determine the level of agreement (LOA) for each recommendation made by a panel of panelists who have been appointed by PB IRA.

The panelist team that was formed consisted of 46 people consisting of internal medicine specialists, rheumatology subspecialists who have more than 5 years of work experience. The members of the panelist team have a role to score each recommendation point using a scale of 0-10, where 0 means no agreement at all and 10 means full agreement. If a member of the panelist team gives a score below 8, that member will comment. Each recommendation point with a value below 8 will be discussed and reviewed again by the drafting team to be revised and subsequently asked for another LOA-related assessment by the panelist team.

3. Recommendations

Table2. CASPAR Criteria

Criteria	Explanation	Score
1. Evidence of psoriasis		
Psoriasis today	Psoriasis of the skin or scalp is described by a subspecialist in rheumatology or dermatology.	2

Psoriatic Arthritis

Recommendations 1. Any articular inflammatory disease (joints, spine, or entheses) in psoriasis patients should be suspected as psoriatic arthritis.

Some conditions that need to be suspected towards a diagnosis of psoriatic arthritis, among others, are:

1. Oligoarthritis and polyarthritis with forms of peripheral arthritis, spondylitis, dactylitis, enthesitis.⁸
2. Patients with psoriasis or a family history of psoriasis, accompanied by symptoms of articular inflammation as mentioned in number 1.⁹
3. Uveitis and conjunctivitis without any obvious cause.

Recommendation 2. The CASPAR criteria can be used to guide the diagnosis of psoriatic arthritis.

The diagnosis of PsA is based on the Classification Criteria for Psoriatic Arthritis (CASPAR) in 2006 which is detailed in Table 2 below.¹⁰

History of psoriasis	History obtained from patient or doctor.	1
Family history with psoriasis	Family history of psoriasis (first generation or second).	1
2. Psoriatic nail disorders	Onycholysis, nail pitting, and hyperkeratosis found on physical examination.	1
3. Negative RF	Based on local laboratory reference ranges (recommended by the ELISA or nephelometric method)	1
4. Dactylitis		
Current dactylitis	Evidenced by physical examination	1
History of dactylitis	Based on information doctor subspecialtyrheumatology	1
5. Radiographic evidence of new bone formation in the juxta articular area	Appears as ossification of the joint margin area (not osteophyte) on conventional radiographs of the hand or foot	1

* Psoriatic arthritis is confirmed if there is inflammatory articular disease (joints, spine, or entheses) with a score of ≥ 3 from the five criteria.

- The CASPAR criteria have a specificity of 98.7% and a sensitivity of 91.4%
- RF: rheumatoid factor

(adapted from Ritchlin, et al. N Engl J Med 2017; 376: 957-70)

Recommendation 3. HLA-B27 is a laboratory examination which can aid diagnosis establishment.

If possible, the HLA-B27 examination can aid psoriatic arthritis diagnosis. HLA-B27 is often positive in cases of PsA with axial joint involvement.¹⁰

Recommendations 4. Conventional radiographs, musculoskeletal ultrasound, and / or MRI are necessary for diagnosis of PsA.

Radiological examinations that can support the diagnosis of psoriatic arthritis include conventional radiography, musculoskeletal ultrasound (USG), and / or MRI examinations.^{10,12}

On conventional radiographs, the case findings of psoriatic arthritis were intermediate others can be:

- a. Radiological evidence in the form of a juxtaarticular new bone formation.¹⁰
- b. Radiology of peripheral joints: loss of bone mass with eccentric erosions, narrowing of the joint space, formation of new bone

characterized by periostitis, ankylosing bone, and entesophyte.¹⁰

- c. In axial joints: unilateral sacroiliitis, paramarginal and vertical syndesmophytes.¹⁰
- d. Dactylitis (sausage finger).¹²
- e. Periarticular osteoporosis.¹²
- f. Resorption of the distal finger bones.¹²

On the ultrasound examination of musculoskeletal cases of psoriatic arthritis, the possible features include synovitis, tenosynovitis, subcutaneous soft tissue thickening, enthesitis, and erosion of the entheses area.¹² Meanwhile, on MRI examination, the results found can be in forms of focal erosions, synovitis, and bone marrow edema in peripheral and axial structures, especially at entesis. Bone marrow edema is best observed on the T2-weighted, fat-suppressed, short tau inversion recovery (STIR) sequence.¹⁰ We also found features of cartilage

degeneration, bone erosion, synovial proliferation, synovitis, tenosynovitis, and spinal edema.¹²

Recommendation 5. Assessment of disease activity can be conducted using DAPSA scoring

Activity monitoring in PsA patients can be done using several instruments, such as Minimal Disease Activity (MDA), Psoriatic Arthritis Response Criteria (PsARC), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI) which identifies joint pain, softening, damage, psoriasis, dactylitis, enthesitis, and the effect of disease on quality of life.¹³

The Indonesian Rheumatology Association recommends disease activity assessment using the DAPSA instrument. Interpretation of disease activity based on the DAPSA score is divided into four, namely remission (score 0-4), low disease activity (5-14), moderate disease activity (score 15-28), and high disease activity (score > 28).¹⁴

Recommendation 6. The goal of management is to achieve a remission target (DAPSA ≤4), or a low disease activity (DAPSA ≤14)

The targets of PsA therapy are achieving remission (DAPSA ≤4) or improvement of complaints and disorders from the clinical domain (peripheral arthritis, skin involvement, dactylitis enthesitis, spinal involvement), and prevention of structural damage in early-stage PsA or preventing disease progression at an advanced stage.^{14,15} If clinical

improvement cannot be achieved due to several factors, such as persistent deformity, side effects of therapy, and patient response to given therapy, low disease activity (DAPSA ≤14) can be an alternative therapeutic target.¹⁴

Recommendation 7. A single NSAID can be used to relieve symptoms and signs of inflammation, especially in patients with mono / oligoarthritis, or enthesitis, or predominantly axial involvement. Evaluation regarding effectiveness was assessed at least after 4 weeks of therapy.

Nonsteroidal anti-inflammatory drugs (NSAIDs) alone are used to reduce the symptoms and signs of PsA, especially in patients with manifestations of mono / oligoarthritis, enthesitis, or predominantly axial involvement. It is necessary to weigh the benefits and risks carefully, especially in the population with cardiovascular disorders. The effectiveness of NSAID treatment was assessed after 4 weeks of therapy. The provisions for NSAID use are listed in Figure 8 with the conclusion that NSAID use includes:¹⁶

- a. Mild cases: NSAIDs and local glucocorticoid injection
- b. Peripheral arthritis: NSAIDs in combination with DMARD, preferably not more than 1 month.
- c. Axial or entesal: NSAIDs can be given over 12 months.

Picture 1. Pharmacological and Non-pharmacological Therapeutic Algorithms for Psoriatic Arthritis according to EULAR 2019.

bDMARDs, biological disease-modifying antirheumatic drugs; EULAR, European League Against Rheumatism; IL-12 / 23i, interleukin-12/23 inhibitors; IL-17i, an interleukin-17 inhibitor; JAKi, Janus kinase inhibitor; NSAIDs, nonsteroidal anti inflammatory drugs; PDE4i, phosphodiesterase-4 inhibitor; PsA, psoriatic arthritis; TNFi, tumor necrosis factor inhibitor.

(Adapted from Gossec et al. Ann Rheum Dis 2020; 79: 700-712)

Recommendation 8. Local glucocorticoid injection is considered as adjunct therapy, whereas systemic glucocorticoid is given at the lowest effective dose.

Giving glucocorticoids in cases of PsA may provide benefits. Local glucocorticoid injection can be considered as an adjunct therapy. Meanwhile, systemic glucocorticoid administration is not given for PsA with axial manifestations and it is recommended to be given short term with the lowest effective dose.¹⁶

Recommendation 9. In polyarthritic patients, or mono / oligoarthritis patients with poor prognostic factors, conventional DMARD should be initiated immediately, with methotrexate preferable for cutaneous manifestations.

PsA patients with polyarthritis after NSAID therapy as well as patients with mono / oligoarthritis with poor prognostic factors (structural damage, high ESR / CRP, dactylitis, nail involvement) should immediately be given conventional DMARD (csDMARD) as the first choice.¹⁶

Methotrexate is more recommended for patients with skin manifestations, with the methotrexate dose can be increased gradually from 7.5 - 25 mg per week with folic acid supplementation. Other csDMARD options are leflunomide and sulfasalazine. The target of therapy is improvement of more than 50% in 3 months and the target is achieved within 6 months. If this is not achieved, then csDMARD therapy is discontinued. In patients with mild PsA activity and no adverse risk factors, a different class of csDMARD may be tried before changing therapy to bDMARD.¹⁶

Recommendation 10. Patients with peripheral arthritis who do not respond to conventional DMARD, biological DMARD therapy should be initiated (anti TNF- α , anti IL-17, anti IL 12/23); if there is prominent skin involvement, anti IL-17 or IL-12/23 is preferred.

PsA patients with peripheral arthritis who respond inadequately to at least one csDMARD are advised to replace therapy with biological DMARD (bDMARD) such as anti-TNF- α , anti IL-17, anti IL 12/23. If there is prominent skin involvement, the IL 17i and IL12 /23i groups are preferred. If there is enthesitis and dominant axial manifestations, administration of bDMARD is recommended earlier.¹⁶

Recommendation 11. Patients who cannot be given biological DMARD can be given JAKi or PDE4i (especially in mild cases).

In PsA with peripheral arthritis and an inadequate response to at least 1 type of csDMARD and 1 type of bDMARD, or if bDMARD is unsuitable, administration of JAKi should be considered. Tofacitinib is preferred over other JAKi.¹⁶

In mild manifestations of PsA and an inadequate response of at least 1 csDMARD, bDMARD, and JAKi, PDE4i should be considered. Apremilast is preferred over other PDE4i.¹⁶

Recommendation 12. Patients with enthesitis or with predominant axial manifestation that does not respond to NSAIDs or local glucocorticoid injection, biological DMARD therapy should be given (anti-TNF- α , anti IL-17); if there is skin involvement, IL-17i is recommended.

In PSA with nonspecific enthesitis or active axial manifestations that are less responsive to NSAIDs or local glucocorticoid injections, biological DMARD (bDMARD) therapy should be considered. In general, TNFi and IL17i have the same efficacy, but in predominant axial manifestations, administration of TNFi is preferred. Meanwhile, if there is skin involvement, IL17i administration is recommended.¹⁶

Recommendation 13. Patients who fail to respond, or have contraindications to bDMARD, are replaced with bDMARD or another tsDMARD

In patients who do not respond to bDMARD therapy or have contraindications to bDMARD, treatment options may be changed to another bDMARD or another targeted synthetic DMARD (tsDMARD).¹⁶

Recommendation 14. Patients with persistent remission, reduction of DMARD should be considered with caution.

In persistent remission PsA, the dose of DMARD can be reduced with caution. Permanent remission is a status of complete remission for a minimum of 6 months.¹⁶

Recommendation 15. Criteria for referral to rheumatology based on the results of Psoriasis Epidemiology Screening Tool.

The referral criteria from non-rheumatology services to rheumatology refers to the results of screening with the Psoriasis Epidemiology Screening Tool which contains five questions (Appendix 13). If there is skin involvement, collaboration with a dermatologist is required. If uveitis is suspected, the patient should be referred to an ophthalmologist or if there is a suspicion of inflammatory bowel disease, the patient should be referred to a gastroenterohepatologist.¹⁷

4. Reactive Arthritis

Recommendation 16. Reactive arthritis is a sterile arthritis that is triggered by an infection outside the joints, especially the gastrointestinal tract and genitourinary tract.

Reactive arthritis is inflammation of the sterile joints that occurs several weeks (1-6 weeks)

after infection of the extra-articular organs / system, most commonly gastrointestinal and genitourinary tract infections.^{18,19} It is estimated that 4-8% after Chlamydia infection of the urinary tract and 1-1.5% after gastrointestinal infections due to Campylobacter, Yersinia, Shigella, Salmonella,

Clostridium difficile, and Escherichia coli causing reactive arthritis.^{20,21}

Reactive arthritis was previously known as Reiter's syndrome with a triad of clinical manifestations, namely arthritis, urethritis or cervicitis, and conjunctivitis or uveitis. Reactive arthritis has genetic risk factors in common with other spondyloarthritis because it is closely related to the HLA-B27 gene.^{18,19}

Reactive arthritis can affect both men and women. Most cases are found in men aged 20-40 years. The incidence of Caucasians is higher than other ethnicities, possibly due to the HLA-B27.^{20,21} Based on an epidemiological study in India, out of 36 reactive arthritis patients, there were 4: 1 male versus female and 24-28 years onset.

Recommendation 17. Inflammation of the joints that occurs several weeks after infection, especially gastrointestinal and / or urinary tract, needs to be thought of as reactive arthritis.

Reactive arthritis should be considered in cases of joint inflammation occurring several weeks (1-6 weeks), either mono or oligoarthritis of the lower limb, which occurs after gastrointestinal or urinary tract infection. In addition, reactive arthritis also needs to be considered in cases of conjunctivitis or uveitis that appear several weeks after gastrointestinal or urinary tract infection.²³

Recommendation 18. The diagnosis of reactive arthritis is based on ACR 1999 criteria consisting of major and minor criteria.

The diagnostic criteria according to the 1999 ACR were divided into definite and probable. A definite diagnosis is established if the patient's manifestations meet two major criteria and at least one minor criterion that is relevant as listed in Table 6.1. Meanwhile, a probable diagnosis is enforced if the patient's manifestations meet two major criteria without a minor criterion or one major criterion and ≥ 1 minor criterion.²³

Table 3. Criteria for Diagnosis of Reactive Arthritis according to ACR 199923

Major criteria	1. Arthritis with the following 2 of 3 characteristics: • asymmetric • monoarticular or oligoarticular • lower limb 2. There is a history of previous infection with the following 1 of 2 characteristics: • enteritis (diarrhea for a minimum of 1 day and occurring 3 to 6 weeks before arthritis) • urethritis (minimal dysuria or discharge from the genitals 1 day and occurs 3 days to 6 weeks before arthritis)
Minor criteria	At least one of the following two symptoms: 1. Evidence of infection as a trigger • evidence of Chlamydia trachomatis infection from a urethral swab examination / cervix or biochemical (ligase) examination of urine. • evidence of gastrointestinal infection from the results of the relevant pathogen cultures 2. Evidence of Chlamydia infection in the synovium from PCR (polymerase chain reaction) or immunohistochemistry

Recommendations 19. Investigations to make the diagnosis include inflammatory markers (ESR and CRP), joint fluid analysis, conventional radiographic examinations, sonography, urethral / cervical swab, pathogen cultures, and HLA-B27 whenever possible.

There are no specific laboratory tests or biomarkers to diagnose reactive arthritis. However, investigations that can be done to support the diagnosis of reactive arthritis include:^{18,20}

a. Examination for inflammatory markers

The sedimentation rate and CRP (C-reactive protein) test can be done to check for inflammation.

b. Joint fluid analysis

Analysis of joint fluid in monoarthritis obtained a leukocyte count of 10,000 to 50,000, predominantly polymorphonuclear (PMN) cells, especially neutrophils.

c. Conventional radiography

Conventional radiographs are performed to find sacroiliitis, periostitis, syndesmophytes, erosion of

the bones around the joints, narrowing of the joints and edema of the bone marrow.

d. Sonography

On sonographic examination, found effusion, synovitis, bone erosion, tendinitis, tenosynovitis, tendon rupture and enthesitis.

e. Urethral / cervical swab, pathogen culture

This examination is intended to look for pathogens that have the potential to trigger or trigger reactive arthritis.

f. HLA-B27 examination

HLA-B27 examination can be done if possible. A positive HLA-B27 examination result was associated with recurrent manifestations of chronic arthritis, uveitis, aortitis, sacroiliitis and spondylitis.

Recommendation 20. Most cases are self-limiting. NSAID is the first choice of therapy for controlling inflammation.

Most (about two-thirds) cases of reactive arthritis have a self-limiting clinical course, so that in the acute phase the symptoms will improve with rest.

Non-steroidal anti-inflammatory drugs are the drugs of first choice if symptoms do not improve with rest. Pharmacological therapy aims to address the source of infection that precipitates arthritis and extra-articular manifestations. Thus, antibiotics can be considered to address the source of infection in cases where there is evidence of infection (which acts as a trigger for reactive arthritis).^{24,25}

Recommendation 21. In cases that last more than 6 weeks and do not improve with NSAID administration, it is recommended to administer Conventional DMARD.

Conventional disease modifying antirheumatic drugs (cDMARD) is indicated in cases of severe arthritis, tend to be chronic (lasting more than 6 weeks), do not respond to NSAIDs, and predominantly affect peripheral joints. cDMARDs that can be administered are methotrexate and sulfasalazine. If the clinical condition is still refractory to cDMARD, a biological DMARD can be given where anti-TNF- α , anti-IL6 or anti-IL7 administration is reported to give good results.

5. Enteropathic Arthritis

Recommendation 22. In cases of spondyloarthritis, there are gastrointestinal complaints such as chronic diarrhea, anemia and fever. These conditions can be suspected as enteropathic arthritis.

Enteropathic arthritis is a group of spondyloarthritis associated with inflammatory bowel disease (IBD) which includes Crohn's disease and ulcerative colitis.²⁶ Approximately 50% of patients with SpA have microscopic intestinal inflammation and 7% develop IBD. In US patients, the prevalence of IBD is 4–14%. The risk of developing IBD increases 3-5 times in US patients compared to healthy people. The prevalence of IBD occurred with the same frequency between the nr-axSpA and AS groups. Inflammatory bowel disease occurs frequently in male AS patients and decreases in prevalence in the elderly.²⁷

Enteropathic arthritis needs to be considered in

spondyloarthritis patients with:²⁸

- Family history of IBD
- Chronic diarrhea for more than 4 weeks accompanied by weight loss
- Chronic abdominal pain
- Rectal bleeding without an obvious cause
- Prolonged weight loss and fever
- History of perianal fistula or abscess
- Anemia
- Malabsorption symptoms
- Extraintestinal symptoms such as erythema nodosum, pyoderma gangrenosum, oral thrush and cholangitis and perianal diseases (fissures, fistulas, abscesses)
- Marks on the skin in the form of lacerations or macerations

In patients with SpA who do not have the above signs, enteropathic arthritis needs to be

considered if the patient meets at least 2 symptoms as follows:²⁹

- Chronic abdominal pain for more than 4 weeks, persistent or diminished
- Iron deficiency with or without anemia
- Extraintestinal manifestations
- Fever for more than 1 week for no apparent reason
- Weight loss for no apparent reason
- Family history of IBD

Recommendation 23. In the case of IBD, if there are symptoms of spondyloarthritis both axial and / or peripheral, enteropathic arthritis can be suspected.

Enteropathic arthritis can be suspected in IBD patients who experience symptoms of back pain for more than 3 months, pain or swelling in peripheral joints, enthesitis, and dactylitis. ²⁸ Spondyloarthritis occurs in 10–39% of patients with IBD as an extraintestinal manifestation. spondyloarthritis is more common in Crohn's disease than in ulcerative colitis. The manifestation of axial arthritis accounts for 20%, with an estimated AS of 2-16% and sacroiliitis of 12-46%. Patients with IBD and AS as

well as patients with IBD and sacroiliitis, respectively, had a positive HLA-B27 of 25–78% and 7–15%. Peripheral SpA manifestations in IBD range from 0.4–34.6%, and are higher in young people.²⁸

Recommendation 24. The diagnosis of enteropathic arthritis is based on clinical findings of spondyloarthritis based on ASAS criteria and laboratory investigations, radiological imaging and gastrointestinal biopsy.

There is no gold standard for diagnosing enteropathic arthritis. Enteropathic arthritis was diagnosed based on clinical correlation of spondyloarthritis with ASAS criteria (Figure 1), biochemistry (laboratory examination), radiology, endoscopy, and histology. Supporting examinations that can be done for assisting diagnostic process are as follows:^{28,30}

1. Inflammation markers (ESR (ESR), C-reactive protein (CRP))^{28,30}
2. Stool culture and microscopy^{28,30}
3. Fecal Calprotectin (FC)^{28,30}
4. Endoscopy and colonoscopy
Ileocolonoscopy remains the primary diagnostic evaluation for IBD, assessing the entire lower gastrointestinal tract including the terminal ileum. Mucosal biopsy should be evaluated for all visible macroscopic abnormalities.²⁹
5. Conventional radiography of the spine and sacroiliac joints³¹
6. Musculoskeletal ultrasound³¹
7. MRI / abdominal (lumbosacral) computed tomography It is useful for additional examinations in assessing the degree of Crohn's disease.³⁰
8. Video capsule endoscopy (VCE), conducted to assess difficult networks
affordable by endoscopy and colonoscopy.³⁰
9. Bowel biopsy examination to support the diagnosis (gold standard) of ulcerative colitis and Crohn's disease.²⁹

Recommendation 25. Laboratory tests of

complete blood count LED, CRP and fecal calprotectin serve as diagnostic tools and monitoring disease activity.

Complete blood laboratory tests of LED, CRP, and fecal calprotectin can be useful to support the diagnosis of enteropathic arthritis as well as a tool to monitor disease activity.^{28,30}

Disease activity and quality of life in enteropathic arthritis such as SpA in general, are assessed using the Ankylosing Spondylitis Disease Activity Score (ASDAS - CRP or ASDAS-LED), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), fecal calprotectin, count the number of swollen and painful joints, the Leeds Enthesitis Index (LEI) and the Health Assessment Questionnaire (HAQ). Close monitoring of disease activity is required to achieve the desired therapy.³²

Recommendation 26. A positive HLA-B27 test can aid diagnosis

As with spondyloarthritis in general, the HLA B-27 examination can help to diagnose enteropathic arthritis, if it is able to be conventionally managed.³³

Recommendations 27. Recommended radiological examinations are conventional radiographs of the spine and sacroiliac joints, as well as ultrasound musculoskeletal or lumbosacral MRI.

Recommended radiological examinations to support the diagnosis of enteropathic arthritis include conventional radiographs of the spine and sacroiliac joints, musculoskeletal ultrasound, or lumbosacral MRI if necessary.

Recommendation 28. Management is aimed at controlling both axial and peripheral IBD and spondyloarthritis with sulfasalazine, and the use of biological agents (anti-TNF- α) as soon as possible if indicated or conventional DMARD for refractory conditions.

Based on the pathogenetic mechanisms underlying SpA and IBD, the approach to

enteropathic arthritis therapy is almost the same, but there are some differences in safety and effectiveness of the treatment modalities used.³⁰ Detailed recommendations for treatment options can be seen in Table 4. The use of biological agents (anti-TNF- α) is given as soon as possible if there are indications or after refractory conditions using a conventional DMARD.^{24,25}

Table 4. Management of Patients with IBD and SpA.²⁸

Peripheral SpA (≤ 4 joints, enthesitis, dactylitis) and active IBD
• Systemic steroids and / or sulfasalazine based on indications for IBD   • NSAIDs should be avoided   • Anti-TNFα based on IBD guidelines   • Consider discontinuation of anti-TNF α only after complete remission of IBD
Peripheral SpA (> 4 joints) and active IBD
• Systemic steroids and / or sulfasalazine based on indications for IBD   • NSAIDs should be avoided   • Anti-TNF based on IBD guidelines   • Consider discontinuation of anti-TNF α only after complete remission of IBD
Peripheral SpA and IBD remission
• Local injection of steroids, short-term (≤ 15 days) NSAIDs and oral sulfasalazines are present appropriate choice in peripheral oligoarthritis (≤ 4 joints, enthesitis, dactylitis)   • Short-term (≤ 15 days) NSAIDs / systemic steroids may be considered with sulfasalazine in peripheral polyarthritis (> 4 joints)   • Anti-TNFα based on rheumatological indications   • Anti-TNF α can be gradually discontinued based on rheumatological opinion in cases with prolonged remission
Axial SpA and IBD are active
• Therapy rehabilitation based on ASAS recommendations   • Anti-TNF based on IBD guidelines   • Long-term anti-TNF α treatment based on axial SpA treatment recommendations can only be given after complete IBD remission
Axial SpA and IBD remission
• Therapy rehabilitation based on ASAS recommendations   • NSAIDs can be given short term (≤ 15 days)   • Anti-TNFα based on ASAS guidelines   • Long-term anti-TNF α treatment according to ASAS guidelines

Several treatment modalities that can be used for axial SpA and IBD can be seen in Table 5.

Table 5. Modality of Treatments for Axial Spondyloarthritis and IBD

Treatment Modality	Axial SpA	IBD
NSAIDs	+	-

Sulfasalazine	Advantage on peripheral arthritis only	+
Monoclonal antibodies (adalimumab, infliximab)		+
<i>Soluble receptor antibodies</i> (etanercept)		-
Secukinumab (IL-17 inhibitor)		-
Ustekinumab (IL-12/23 inhibitor)		+
Vedolizumab (integrin inhibitor)		+
Tofacitinib (JAK inhibitor)		+

(Adapted from Kiwalkar et al. Axial Spondyloarthritis; 2019)

Recommendation 29. The use of systemic corticosteroids is not recommended for long term, and local injectable corticosteroids can be used in cases of peripheral arthritis.

Steroid class drugs can be given in cases of enteropathic arthritis. However, the use of systemic corticosteroids is not recommended for long-term use due to the risk of causing adverse side effects in various organs such as musculoskeletal, cardiovascular, endocrine metabolic, and so on.³⁴ Corticosteroids in forms of local injection can be used in cases of peripheral arthritis.²⁸

Recommendation 30. The use of NSAIDs is not recommended for long-term because it can worsen the condition of IBD.

Administration of NSAIDs in cases of enteropathic arthritis should be given in the short term (≤ 15 days) because long-term use can worsen the condition of IBD.²⁸

Recommendation 31. Clinical monitoring of disease activity with the ASDAS and BASDAI indices for spondyloarthritis, and for IBD can be seen clinically.

Disease activity and quality of life in enteropathic arthritis such as SpA in general, are assessed using the Ankylosing Spondylitis Disease Activity Score (ASDAS - CRP or ASDAS-LED), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), fecal calprotectin, count the number of swollen and

painful joints, the Leeds Enthesitis Index (LEI) and the Health Assessment Questionnaire (HAQ).³² Meanwhile, monitoring of IBD disease activity can be seen in general through clinical patients.²⁸

6. Non-Specific Spondyloarthritis

Recommendation 32. Any joint disorder in the form of mono-, oligo- or non-specific polyarthritis, which does not meet specific clinical, serological and radiological features to meet specific diagnostic criteria (ankylosing spondylitis, psoriatic arthritis, reactive arthritis, juvenile spondyloarthritis, or enteropathic arthritis), a diagnosis of undifferentiated spondyloarthritis / undifferentiated arthritis can be considered.

Some clinicians do not recognize nonspecific spondyloarthritis as a specific terminology / diagnosis, but are associated with other spondyloarthritis diseases, namely ankylosing spondylitis, psoriatic arthritis, arthritis associated with inflammatory bowel disease and reactive arthritis. Non-specific or undifferentiated spondyloarthritis (uSpA) has clinical symptoms that are consistent with the spondyloarthritis disease group (mono-, oligo- or polyarthritis), but does not meet the diagnostic criteria (clinical, serological, and radiological symptoms) for specific / specific spondyloarthritis diseases. Symptoms of uSpA can be so atypical as accompanied by systemic complaints that patients can be diagnosed as having an anxiety or depression disorder, or suffering from

fibromyalgia.

The prevalence of uSpA disease is about ~ 1% of the population, with females being affected more frequently than males (3: 1) .35,36 The onset of uSpA age ranges widely, with a peak around 50 years of age. Nonspecific spondyloarthritis tends to affect the patient's older age and shorter duration of disease compared with AS and psoriatic arthritis. Approximately 20-25 percent of patients with uSpA have a positive result for HLA-B27. Those factors, particularly older age, female predominance, and low positive value of HLA-B27, showed the distinction of uSpA from AS and the other classical spondyloarthropathies.

Recommendation 33. The clinical manifestations of uSpA can be a combination of two phenotypes: axial SpA clinical symptoms (inflammatory low back pain) and peripheral symptoms (peripheral arthritis).

The clinical manifestations of uSpA can be a combination of two phenotypes, namely axial SpA clinical symptoms (inflammatory back pain in 87.5% of cases) and peripheral symptoms (peripheral arthritis in 62.5% of cases).37 The clinical manifestations of uSpA include inflammatory low back pain, buttock pain. enthesitis, peripheral arthritis, dactylitis, swelling of the knee joint, general stiffness in the body that gets worse on waking and decreases after exertion and fatigue (see Table 6). Extraarticular manifestations are rare, occurring in less than 10% of patients. Extraarticular manifestations of uSpA include acute anterior uveitis or conjunctivitis, oral ulcers, skin rash, nonspecific IBD, pleurisy, and pericarditis. In addition, anxiety and depression for several years, along with fibromyalgia, should make the clinicians aware of uSpA diagnosis.35

Table 6. USpA Clinical and Laboratory Overview

Clinical and / or Laboratory Abnormalities	Frequency
Inflammatory back pain	90%
Butt pain	80%
Enthesitis	75%
Peripheral arthritis	40%
Dactylitis	20%
Acute anterior uveitis	1-2%
Fatigue	55%
Increased LED (LED = sedimentation rate)	32%
HLA-B27 positive	25%

(Adapted from Paramarta et al. Rheumatology (Oxford) 2013; 52 (10): 1873-1878)

The onset of uSpA disease is often insidious. Over time, some patients with uSpA show more characteristic clinical symptoms for specific spondyloarthritis diseases such as ankylosing spondylitis (US).35

In general, there are no specific criteria for the diagnosis of uSpA. However, the use of modified Amor criteria can help in confirming the clinical diagnosis of uSpA (see Table 7).38

Table 7. Diagnostic Criteria for uSpA Using Modified Amor Criteria

Inclusion Criteria	Score	Exclusion Criteria
Inflammatory back pain	1 point	Specific spondyloarthritis diagnosis
Unilateral / asymmetric buttock pain	1 point	Sacroiliitis on radiology = grade 2
Bilateral / symmetrical buttock pain	2 points	Post genitourinary infection / gastrointestinal

Enthesitis	2 points	Psoriasis
Peripheral arthritis	2 points	<i>Keratoderma blennorrhagicum</i>
Dactylitis	2 points	Inflammatory bowel disease (Crohn's disease or ulcerative colitis)
Acute anterior uveitis	2 points	Positive rheumatoid factor
HLA-B27 positive or family history of spondyloarthritis	2 points	Positive antinuclear antibody, titer > 1:80
Good response to anti drugs nonsteroidal inflammation	2 points	

* USpA diagnosis is enforced if it meets 6 points or more.

(Adapted from Dougados, et al. Arthritis Rheum 1991; 34: 1218–1227)

Recommendation 34. HLA-B27, LED and CRP checks can helpmake the diagnosis.

As with other cases of spondyloarthritis, laboratory tests can help to diagnose uSpA. The HLA-B27 test can help confirm the diagnosis if possible, with a positive result rate of 20-25% in uSpA cases. In addition, the LED and CRP examinations can also support the diagnosis of uSpA, which results in 50% of cases experiencing an increase in both markers.³⁵

Recommendation 35. The first choice of pharmacologic therapy is NSAIDs, and if they do not respond, corticosteroids or DMARD can be given according to clinical manifestations.

Most of the patients with uSpA have active chronic disease and require long-term therapy. For ongoing

symptoms, some patients have mild and intermittent symptoms requiring only symptomatic therapy intermittent. These episodes can last from 1-2 weeks to several months, with long asymptomatic periods requiring no therapy.³⁵

The first choice of pharmacologic therapy in uSpA is NSAIDs. If the patient does not show a response after using NSAIDs, then corticosteroids or DMARD can be given according to the patient's clinical manifestations. In addition, in the case of uSpA, anti-TNF α may also be considered as an alternative therapy.³⁵

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