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REVIEW ARTICLE

Triple-negative axial spondyloarthritis: Navigating diagnostic uncertainty and justifying biologic therapy treatment

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ABSTRACT

Axial spondyloarthritis (axSpA) represents a spectrum of chronic inflammatory diseases with heterogeneous clinical presentations, ranging from radiographic ankylosing spondylitis (AS) to non-radiographic forms. The introduction of MRI and the ASAS classification criteria enabled earlier recognition, but significant diagnostic gaps persist, particularly in "triple-negative" patients who lack radiographic sacroiliitis, MRI-confirmed inflammation, and HLA-B27 positivity. These patients often display characteristic clinical features such as inflammatory back pain, enthesitis, and extra-articular manifestations, yet remain excluded from classification criteria and, consequently, from timely biologic access. Elevated inflammatory markers (CRP, ESR) are useful prognostic tools but lack sensitivity, leaving clinical pattern recognition central in many cases. Therapeutic dilemmas arise where international guidelines require objective inflammatory markers for biologic initiation, despite evidence that some patients without such markers may benefit from early intervention. The decision to initiate biologic DMARDs in triple-negative axSpA raises complex clinical, ethical, economic, and medico-legal challenges. Physicians must balance the risks of overtreatment with immunosuppressive therapy against the harms of undertreatment and disease progression. Shared decision-making, rigorous documentation, and consideration of pragmatic diagnostic labels such as "probable axSpA" may help bridge the gap. A structured clinical algorithm integrating clinical features, inflammatory markers, re-imaging, and therapeutic trial approaches is proposed to guide management in the absence of definitive biomarkers.

Keywords: Axial spondyloarthritis; diagnostic delay; triple-negative; classification criteria; biologic DMARDs.

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1. INTRODUCTION

Spondyloarthropathies (SpA) comprise a group of chronic inflammatory rheumatic diseases affecting the spine, sacroiliac (SI) joints, peripheral joints, and entheses. They are defined serologically by the absence of rheumatoid factor, distinguishing them from other inflammatory arthritides such as rheumatoid arthritis. The conceptualization of SpA has evolved markedly over the past century through advances in imaging, genetics, and classification frameworks. (1,2) Historically, ankylosing spondylitis (AS) was the prototypical entity. First described in 1904, AS was characterized as a progressive inflammatory disorder that could ultimately lead to fusion of the axial skeleton. For decades, diagnosis relied on radiographic evidence of sacroiliitis, formalized in the modified New York criteria of 1984. (3) These criteria emphasized structural damage on X-ray in conjunction with features such as inflammatory back pain

and limited spinal mobility. By the 1980s, however, research revealed that many relatives of AS patients displayed symptoms of inflammatory back pain in the absence of radiographic changes, suggesting a wider disease spectrum. (4) This prompted the development of the modern concept of axSpA, which encompasses both ends of the continuum: **r**adiographic axSpA (r-axSpA): synonymous with AS, defined by sacroiliitis on plain radiographs. (5); and non-radiographic axSpA (nr-axSpA): defined by clinical symptoms of axSpA without definitive radiographic sacroiliitis, but often with active inflammation visible on MRI. (6)

The introduction of MRI was pivotal, allowing detection of early inflammatory changes in SI joints years before structural damage became visible on X-rays. This recognition emphasized that inflammatory activity often precedes structural progression, a stage during which patients may already experience significant pain and disability. (1) Consequently, early recognition and timely treatment are crucial to prevent irreversible damage and optimize outcomes. (7)

2. THE ASAS CLASSIFICATION CRITERIA: FRAMEWORK AND LIMITATIONS

The Assessment of SpondyloArthritis International Society (ASAS) introduced classification criteria for axSpA in 2009 to enable earlier recognition and research standardization. (4) These criteria apply to patients with chronic back pain lasting ≥3 months and onset before 45 years of age. Classification can be achieved through two pathways. (8)

- Imaging arm. Requires radiographic sacroiliitis or active sacroiliac inflammation on MRI, plus ≥1 SpA feature such as inflammatory back pain, arthritis, enthesitis, uveitis, psoriasis, inflammatory bowel disease (IBD), family history, HLA-B27 positivity, or elevated C-reactive protein (CRP). (8) MRI is particularly valuable for detecting bone marrow edema prior to radiographic changes. (9, 10)

- Clinical arm. Requires HLA-B27 positivity and ≥2 additional SpA features. (8, 11) This acknowledges the strong genetic contribution of HLA-B27 and allows classification without imaging evidence. (11)

- Classification vs. diagnosis

Although designed as research tools rather than diagnostic standards (7, 8) the ASAS criteria are often used in clinical practice, and even for insurance approval of biologics, as de facto diagnostic requirements, potentially excluding patients with high clinical suspicion who do not fit either arm. (12)

3. THE DIAGNOSTIC VOID: TRIPLE-NEGATIVE PATIENTS

A subset of patients presents with characteristic features of axSpA but fails to meet ASAS criteria because they lack imaging and genetic hallmarks, so-called “triple-negative” cases. (1,13) These are defined by the absence of radiographic sacroiliitis, negative MRI for sacroiliac inflammation, and negative HLA-B27, despite clinical features such as inflammatory back pain, enthesitis, or dactylitis, often accompanied by elevated CRP or ESR. (13)

- Limitations of HLA-B27. While highly associated with axSpA (14), absence of HLA-B27 does not exclude the disease. Prevalence varies by ethnicity (85–95% in Caucasians versus ~50% in African Americans). (15) Up to half of non-radiographic axSpA (nr-axSpA) patients are HLA-B27 negative (16), and a negative result is linked to delayed diagnosis. (12)

- Fallibility of MRI. MRI, though sensitive, is imperfect. False negatives may result from intermittent inflammation. (10) Studies have shown that a single negative MRI is not conclusive. In one study, 27% of HLA-B27 positive patients with a negative baseline MRI developed a positive MRI during follow-up. (17) Another study found that among patients who were not responding to treatment, 6 out of 21 who had a negative pre-treatment MRI showed positive inflammation on a repeat scan. (18) Up to 30% of HLA-B27–positive patients with typical features remain MRI negative. (19)

- Inflammatory markers. Elevated CRP or ESR provides important objective evidence in triple-negative patients. (20) CRP is predictive of radiographic progression and favorable biologic response. (21) Although many axSpA patients have normal markers, their elevation strongly supports an inflammatory process. (20)

Clinical Features and Inflammatory Markers as Independent Indicators

In triple negative axSpA, clinical manifestations remain central to diagnosis.

1. **Inflammatory back pain (IBP)** is typically characterized by insidious onset before age 45, improvement with exercise, lack of improvement with rest, nocturnal pain, and alternating buttock pain. This pattern, although neither highly specific nor sensitive, raises clinical suspicion for axSpA in patients with non-diagnostic imaging or negative serological tests. (**22, 23)**

2. **Enthesitis**, the inflammation of tendon or ligament insertions, is frequently observed in axSpA, particularly in seronegative individuals. It may affect the Achilles tendon, plantar fascia, or costosternal junctions and may be detectable clinically or via imaging (e.g., ultrasound or MRI). (24)
3. **Dactylitis**, manifesting as a "sausage digit," is less common but highly specific when present, pointing toward a spondyloarthropathy spectrum disorder, even in the absence of serologic markers. (25)
4. **Extra-articular manifestations**, such as **uveitis**, **psoriasis**, and **IBD**, often serve as telling clinical clues. Acute anterior uveitis occurs in up to 40% of axSpA patients and significantly increases diagnostic likelihood when seen alongside back pain. (26–28) Psoriasis and IBD are likewise important comorbidities that strengthen suspicions of axSpA when serological and radiographic evidence is lacking. (26, 27)

4. ROLE OF C-REACTIVE PROTEIN (CRP) AND ERYTHROCYTE SEDIMENTATION RATE (ESR): VALUE AND LIMITATIONS

CRP and ESR are widely used as objective markers of systemic inflammation in axSpA, but both have significant limitations.

CRP, an acute-phase protein synthesized in the liver, is elevated in a subset of active axSpA patients and correlates with disease activity and imaging inflammation. (29) Notably, elevated baseline CRP is predictive of favorable response to TNF inhibitors and other biologics. (30)

ESR, another surrogate marker for inflammation, generally correlates with CRP, albeit with slower kinetics and less sensitivity in capturing acute inflammatory changes. (31)

However, both markers may be within normal ranges despite active disease:

1. A significant minority of nr-axSpA patients (ranging from 30% to 60% across cohorts) present with persistently normal CRP and ESR despite active disease as confirmed by MRI. (32)
2. False positivity can occur, such as elevated CRP due to infection or obesity rather than SpA, potentially confounding clinical interpretation. (33)
3. Elevated CRP at baseline is a criterion for regulatory approval of certain biologics in some jurisdictions, limiting access for patients with normal CRP despite compelling clinical indications, raising questions of equity in treatment access. (34)

Thus, while CRP and ESR remain valuable tools, their absence should not preclude consideration of biologic therapy when clinical suspicion is strong.

5. THE ROLE OF CLINICAL PATTERN RECOGNITION IN THE ABSENCE OF BIOMARKERS

Clinical intuition and pattern recognition often become central to decision-making when biomarkers fail to provide clarity. (Figure 1)

- A holistic clinical evaluation that integrates back pain features, peripheral manifestations, and extra-articular symptoms can be as informative as, if not more than, laboratory or imaging findings in certain contexts. (22,34)
- Expert consensus and classification criteria (e.g., ASAS criteria) emphasize the value of "clinical arm" evaluation, where characteristic features may justify diagnosis and management without radiographic or serological evidence. (4,23)
- Moreover, reliance purely on biomarkers may delay initiation of effective therapy, prolonging suffering and potentially allowing irreversible structural progression, a particularly salient concern in early disease where timely treatment can alter long-term outcomes. (31, 35)
- Several studies have demonstrated that even in the absence of elevated CRP, patients with active MRI findings and robust clinical signs achieve significant improvement when treated with biologics, underscoring that treatment decisions may be justified on clinical grounds alone. (32 ,36)

In total, while classification criteria, imaging, and biomarkers aid diagnosis, they are insufficient for all patients. Clinical expertise and pattern recognition remain indispensable, particularly for identifying and treating triple-negative axSpA where biologic therapy may still be justified

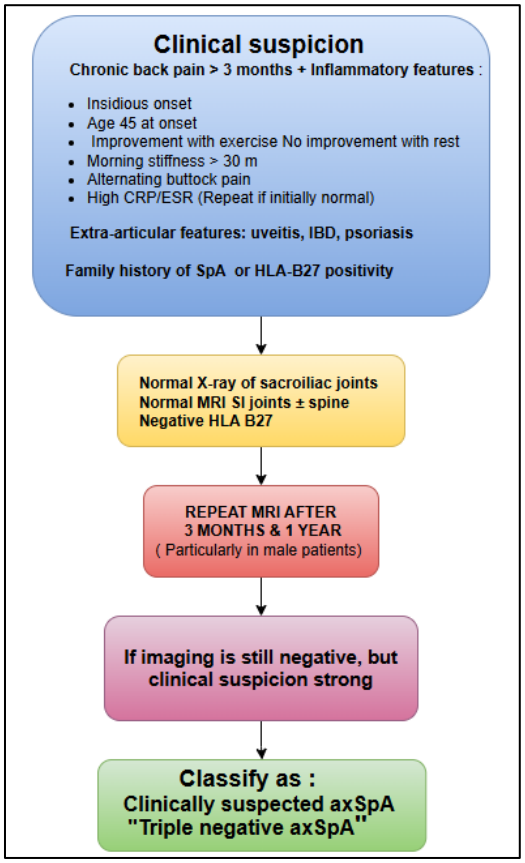

Figure 1. Clinical pattern recognition of triple negative ax-SpA in the absence of biomarkers algorithm.

6. THERAPEUTIC CONSIDERATIONS IN THE ABSENCE OF DIAGNOSTIC CERTAINTY

Managing axSpA when diagnostic confirmation is lacking presents a complex clinical challenge. Decisions around initiating biologic therapy must balance the potential benefits of early intervention against the risks of overtreatment. International guidelines provide a framework, yet significant gaps remain for patients who are seronegative, MRI-negative, or lack elevated inflammatory markers. In this context, therapeutic strategies must integrate evidence-based practice with clinical judgment, patient preferences, and broader ethical and economic considerations. (Figure 2)

1. Rationale for early treatment with biologics

Early intervention with biologic therapy in axSpA is increasingly supported by evidence suggesting that timely suppression of inflammation may prevent irreversible structural damage, improve quality of life, and reduce disability. (1.37) Although diagnostic uncertainty is more frequent in seronegative and non-radiographic cases, waiting for radiographic confirmation can delay effective treatment by several years, during which functional decline may occur. (4) Clinical trials have demonstrated that biologic agents such as TNF inhibitors and IL-17 inhibitors produce significant symptom relief and improved physical function even in patients without radiographic sacroiliitis, provided there is evidence of active disease. (36)

2. Risks and benefits of empirical treatment

Empirical use of biologics in seronegative or nr-axSpA remains a subject of debate. On one hand, biologics carry substantial benefits, including rapid pain reduction, improved mobility, and decreased extra-articular flares. (38) On the other hand, risks include potential immunosuppression, opportunistic infections, long-term malignancy concerns, and considerable financial burden. (39,40) The challenge is balancing the risk of overtreatment against the harm of undertreatment in patients who may otherwise progress silently. Cost-effectiveness analyses have highlighted the difficulty of justifying empirical biologic use in the absence of strong objective markers, but selective use in patients with high clinical likelihood remains defensible. (41)

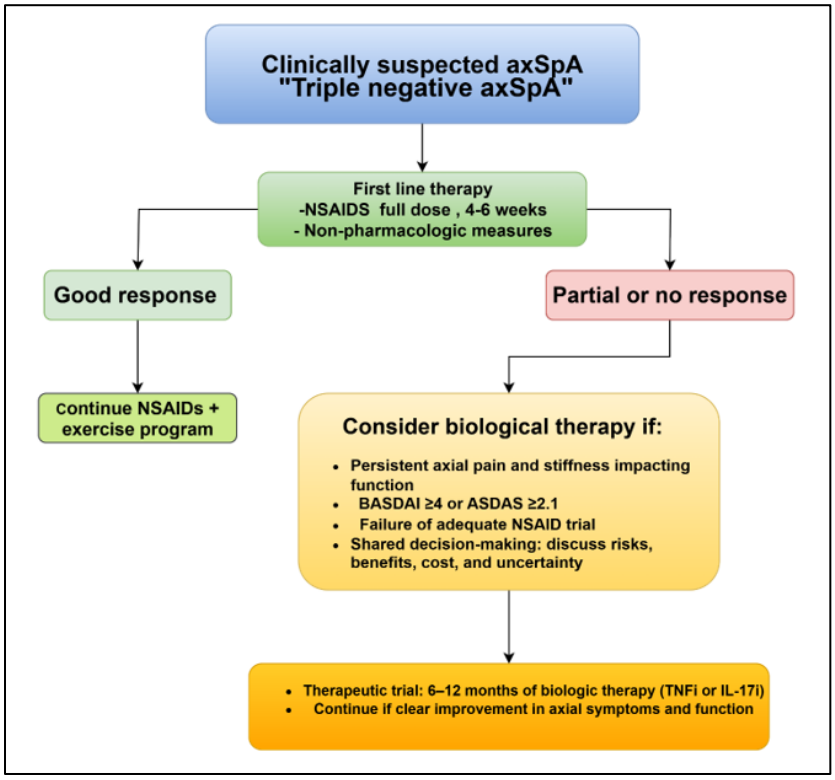

Figure 2. Therapeutic considerations algorithm.

3. Position of international guidelines

International guidelines, such as the **ASAS-EULAR recommendations**, emphasize the importance of objective signs of inflammation (elevated CRP or MRI-confirmed sacroiliitis) in guiding biologic initiation. (42) However, they acknowledge the role of clinical judgment where biomarkers are absent, but the clinical phenotype is compelling. For nr-axSpA, guidelines recommend biologics only if there is objective evidence of inflammation, which has created challenges for "triple-negative" patients (normal CRP, negative MRI, seronegative). (43) Recent expert discussions highlight the need for flexibility in applying these criteria, as rigid adherence may exclude patients who are clinically indistinguishable from those with clear biomarker evidence. (44)

4. Role of NSAIDs and DMARDs prior to biologics

NSAIDs remain the first-line pharmacologic therapy for axSpA due to their efficacy in controlling pain and stiffness, and some evidence suggests that continuous NSAID use may reduce radiographic progression (45). In contrast, conventional synthetic DMARDs (csDMARDs), such as methotrexate or sulfasalazine, show limited efficacy in axial disease but may provide benefit in peripheral arthritis or extra-articular manifestations (46). Current practice therefore dictates a trial of adequate NSAID therapy before advancing to biologics, although in patients with severe disease activity and rapid progression, early biologic initiation may be justified (42, 47). However, evidence indicates that biologic therapy is not effective in patients with triple-negative axial spondyloarthritis. In a randomized placebo-controlled trial, etanercept showed no significant benefit in suspected non-radiographic axSpA when inclusion did not require MRI positivity or elevated CRP, highlighting that patients without objective inflammatory findings derive little therapeutic gain from TNF blockade (48). Similarly, a bicentric retrospective study demonstrated poor efficacy of TNF inhibitors in nr-axSpA patients lacking objective signs of inflammation, reinforcing the limited value of biologics in this subgroup (49).

5. Shared decision-making and risk stratification

In the setting of diagnostic ambiguity, shared decision-making becomes crucial. Patients should be fully informed of the potential benefits, uncertainties, and risks of biologic therapy, as well as the limitations of available diagnostic tests. (50) Risk stratification tools that integrate clinical features, disease activity scores, comorbidities, and patient preferences can help tailor individualized treatment strategies. (51) Importantly, shared decision-making not only improves patient satisfaction and adherence but also ensures ethical justification for empirical biologic use in uncertain diagnostic scenarios. (52)

7. ETHICAL, ECONOMIC, AND HEALTH POLICY IMPLICATIONS

1. **Justification of high-cost biologics without objective criteria**

The deployment of expensive biologic therapies, often exceeding tens of thousands of dollars annually for patients lacking objective biomarkers, raises ethical questions around value, resource allocation, and societal benefit. (53) Cost–benefit analyses indicate that delayed or under-recognized axSpA diagnoses generate substantial economic burdens, with the UK alone estimating £3.1 to £12.5 billion annually due to diagnostic delay–related costs. (54)

2. **Insurance and payer resistance**

Insurers and payers often require elevated CRP or MRI-confirmed inflammation prior to approving biologics, placing seronegative/MRI-negative patients at a disadvantage, despite real-world benefit in symptomatic relief and function. (55) Resistance at the policy level can delay access and exacerbate disease progression. (56)

3. **Equity of access in low-resource settings**

Cost and infrastructure limitations in low-resource regions further restrict biologic access, disproportionately affecting patients in those areas. (58) Innovative low-cost diagnostic technologies and telemedicine may help reduce barriers, but structural policy support remains critical. (57)

4. **Medico-legal considerations**

Administering biologics in triple-negative patients falls outside established criteria and may therefore be regarded as off-label prescribing (48, 49). This carries heightened medico-legal implications. On one hand, offering biologics without conventional diagnostic confirmation may expose the prescribing physician to liability in the event of serious adverse effects, including opportunistic infections, malignancy, or paradoxical immune-mediated events, since treatment would not be aligned with guideline-based standards (50, 51). In this scenario, responsibility rests with the physician to document justification, obtain explicit informed consent, and discuss alternative therapies. (59) On the other hand, denying access to biologics solely due to the absence of imaging or laboratory confirmation, when clinical evidence of axSpA is compelling, may also present legal risks, as it could be construed as undertreatment or negligence if disease progression leads to irreversible disability (59). Ultimately, balancing these opposing responsibilities underscores the importance of shared decision-making, rigorous documentation, and adherence to both international recommendations and local regulatory frameworks to mitigate medico-legal exposure.

8. TOWARD A PRAGMATIC DIAGNOSTIC AND TREATMENT MODEL

1. **Proposal of a clinical algorithm or checklist for suspected SpA in seronegative/MRI-negative cases**

A practical, symptom-based algorithm is essential for guiding clinicians through weighted recognition of axSpA features in the absence of biomarkers. (55) Recent literature underscores the urgency of structured approaches to reduce diagnostic delay and guide efficient referral. (58)

2. **Consideration of “probable SpA” or “inflammatory disease of uncertain classification”**

Interim diagnostic labels, such as "probable axSpA" or "inflammatory disease of uncertain classification"allow for earlier empirical intervention when classical parameters are not yet met, without compromising future diagnostic clarity. (56)

3. **Role of follow-up, re-imaging, and therapeutic trial approach**

Serial monitoring, including clinical reassessment, repeat imaging, and a considered therapeutic trial of NSAIDs or biologics, can confirm diagnosis over time. (56) This pragmatic model acknowledges disease dynamics and supports dynamic treatment decisions. (56)

9. CONCLUSION

Axial spondyloarthritis illustrates the gap between rigid classification frameworks and the complexities of real-world practice. While the broadened concept of axSpA has advanced recognition beyond radiographic ankylosing spondylitis, a significant diagnostic void persists for “triple-negative” patients lacking HLA-B27, MRI-confirmed sacroiliitis, and elevated inflammatory markers. The frequent use of ASAS classification criteria as diagnostic and reimbursement thresholds risks delaying care, prolonging disability, and compounding economic burden. Yet, empirical use of biologic DMARDs without objective evidence remains contentious, given

uncertain efficacy, safety risks, high cost, and medico-legal implications. In this context, clinical expertise, holistic evaluation, and recognition of characteristic features such as inflammatory back pain, enthesitis, or extra-articular disease remain indispensable. A pragmatic model is needed, incorporating interim diagnostic categories (e.g., “probable axSpA”), structured clinical algorithms, repeat assessments, and judicious therapeutic trials. Shared decision-making, supported by explicit documentation and close monitoring, offers a balanced pathway that addresses patient needs while mitigating ethical and legal risks. Reducing diagnostic delay, refining classification criteria, and ensuring equitable access to effective therapies should remain central priorities. Bridging evidence-based standards with clinical judgment will be key to improving outcomes for patients excluded by current frameworks yet burdened by inflammatory disease.

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