MAYO CLINIC

REVIEW

Recognizing Axial Spondyloarthritis: A Guide for Primary Care

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Abstract

Axial spondyloarthritis (axSpA) is an important cause of chronic low back pain and affects approximately 1% of the US population. The back pain associated with axSpA has a characteristic pattern referred to as inflammatory back pain (IBP). Features of IBP include insidious onset before age 45 years, association with morning stiffness, improvement with exercise but not rest, alternating buttock pain, and good response to treatment with nonsteroidal anti-inflammatory drugs. In patients with IBP, it is essential to look for other features associated with spondyloarthritis (SpA), such as enthesitis, dactylitis, peripheral arthritis, extra-articular manifestations (eg, psoriasis, uveitis, or inflammatory bowel disease), human leukocyte antigen B27 positivity, and a family history of SpA. Axial SpA is underrecognized, and a delay of several years between symptom onset and diagnosis is common. However, with new and effective therapies available for the treatment of active axSpA, early recognition and diagnosis are of critical importance. For this narrative review, we conducted a literature search of English-language articles using PubMed. Individual searches were performed to identify potential articles of interest related to axSpA (search terms: ["axSpA" OR "axial SpA" OR "axial spondyloarthritis" OR "ankylosing spondylitis"]) in combination with terms related to IBP ("inflammatory back pain" OR "IBP" OR "chronic back pain" OR "CBP" OR "lower back pain" OR "LBP"), diagnosis (["diagn*" OR "classification"] AND ["criteria" OR "recommend*" OR "guidelines"]), and referral ("refer*"). No date range was formally selected, as we were interested in providing an overview of the evolution of these concepts in clinical practice. We supplemented the review with insights based on our clinical expertise. Patients with chronic back pain should be screened for IBP and other SpA features; suspicion for axSpA should trigger referral to a rheumatologist for further evaluation.

 ■ Mayo Clin Proc. 2020;95(11):2499-2508

Back pain is a common health problem, affecting 80% to 85% of people at some point during their lifetime[1] and is the second leading symptom prompting a visit to a primary care physician (PCP).[2] Approximately 20% of people aged 20 to 59 years have chronic low back pain, and the prevalence increases with age.[3] One important but underrecognized cause of chronic low back pain is axial spondyloarthritis (axSpA), an inflammatory rheumatic disease that predominantly involves the spine and sacroiliac joints.[4,5] Axial spondyloarthritis is associated with a characteristic pattern of back pain features referred to as *inflammatory back pain* (IBP). The aims of this review are to (1) introduce the concept of IBP and other features salient to early detection of axSpA and (2) discuss strategies to identify patients with axSpA among patients with chronic back pain in a primary care setting. We hope that this review will raise awareness of axSpA as a cause of chronic back pain, particularly in young adults, and facilitate the timely referral of patients who may have axSpA for evaluation in a rheumatology clinic.

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MATERIAL AND METHODS

For this narrative review, we conducted a literature search of English-language articles using PubMed. Individual searches were

ARTICLE HIGHLIGHTS

- Inflammatory back pain is a key clinical symptom of axial spondyloarthritis (axSpA).
- Axial spondyloarthritis affects 1% of the US population but is widely underdiagnosed.
- With advances in current therapies, axSpA can be treated effectively; early treatment is associated with improved symptoms, physical function, and quality of life.
- Barriers to a timely diagnosis of axSpA include a lack of awareness about the disease, nonspecific findings on physical examination, and a lack of biomarkers for diagnosis.
- Improved awareness of axSpA among primary care physicians will likely increase timely referral to rheumatologists for early diagnosis and effective management, which will improve long-term outcomes.

performed to identify potential articles of interest related to axSpA (search terms: ["axSpA" OR "axial SpA" OR "axial spondyloarthritis" OR "ankylosing spondylitis"]) in combination with terms related to IBP ("inflammatory back pain" OR "IBP" OR "chronic back pain" OR "CBP" OR "lower back pain" OR "LBP"), diagnosis (["diagn*" OR "classification"] AND ["criteria" OR "recommend*" OR "guidelines"]), and referral ("refer*"). No date range was formally selected, as we were interested in providing an overview of the evolution of these concepts in clinical practice. After manually removing duplicates and articles deemed not relevant to the topic, the remaining articles of potential interest were reviewed and included for discussion and were supplemented with key insights from the authors as clinical experts in the field.

CLINICAL PICTURE

Axial spondyloarthritis is a disease predominantly of the axial skeleton, but peripheral joints, entheses, and extra-articular organs such as skin, eyes, and intestines are also frequently affected. Axial spondyloarthritis typically develops in individuals younger than 45 years and has a peak age at onset of between 20 and 30 years.[6] Chronic inflammation in the sacroiliac joints and the spine results in back pain and stiffness and can, over time, lead to pathologic new bone formation, structural damage, and, ultimately, fusion of sacroiliac joints and the spine in some patients—known as *bamboo spine*.[7]

Patients with axSpA who have obvious structural changes on radiographs of the sacroiliac joints indicating sacroiliitis are classified as having radiographic axSpA (r-axSpA), which is, for all practical purposes, the same as ankylosing spondylitis (AS).[8-10] Patients who have axSpA based on symptoms and other clinical features but lack obvious radiographic changes of sacroiliitis have nonradiographic axSpA (nr-axSpA). Although patients with nr-axSpA do not have definitive changes indicating sacroiliitis on radiographs, sacroiliitis is typically evident on magnetic resonance imaging (MRI) in these patients. In approximately 5% to 10% of patients, nr-axSpA will evolve to r-axSpA over 2 years; this rate increases to 5% to 30% over 10 years.[11-13] Because AS was a well-recognized entity for decades before the concept of nr-axSpA was introduced, much of the axSpA literature is based on only the subset of patients with AS. No diagnostic criteria exist for AS or axSpA. For research purposes, AS populations are typically defined using the modified New York classification criteria.[8] These criteria require definitive evidence of sacroiliitis on pelvic radiographs in combination with either IBP or limited range of motion in the spine, which typically occurs in later stages of the disease.[8,9]

The concept of axSpA (which includes AS) was first established by a set of classification criteria developed in 2009 by the Assessment of SpondyloArthritis international Society (ASAS)—a panel of rheumatology experts (Figure 1).[9] According to the ASAS classification criteria, patients who experience chronic back pain before the age of 45 years have axSpA if they (1) have imaging evidence of sacroiliitis (by MRI or radiography) plus 1 or more spondyloarthritis (SpA) feature or (2) are positive for human leukocyte antigen B27

Mayo Clin Proc. ■ November 2020;95(11):2499-2508 ■ https://doi.org/10.1016/j.mayocp.2020.02.007
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(HLA-B27) and have 2 or more other SpA features.[9] The SpA features include IBP, peripheral inflammatory arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn disease or ulcerative colitis, good response to nonsteroidal anti-inflammatory drugs (NSAIDs), family history of SpA, HLA-B27 positivity, and elevated C-reactive protein (CRP). Both AS (as determined by the modified New York criteria) and r-axSpA (as determined by the ASAS classification criteria) define the same patient population.[8-10] The modified New York criteria and ASAS classification criteria are mainly used for clinical research studies and should not be used as diagnostic criteria for AS or axSpA.[5,14] Clinician judgment is considered the criterion standard for a diagnosis of AS and axSpA.

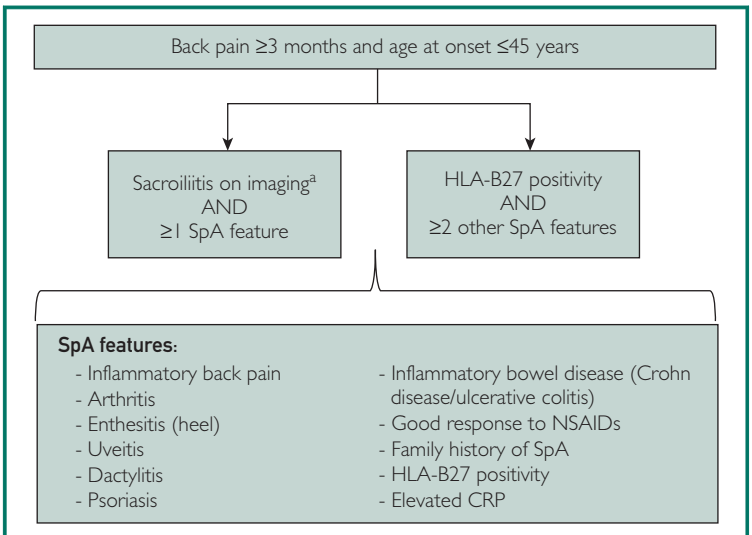

FIGURE 1. Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (SpA). [a]Imaging evidence of sacroiliitis includes active (acute) inflammation on magnetic resonance imaging highly suggestive of sacroiliitis associated with SpA or definite radiographic sacroiliitis according to the modified New York criteria for ankylosing spondylitis. CRP = C-reactive protein; HLA-B27 = human leukocyte antigen B27; NSAIDs = nonsteroidal anti-inflammatory drugs. Adapted from *Ann Rheum Dis*,[9] with permission from BMJ Publishing Group Limited.

EPIDEMIOLOGY

Worldwide estimates of axSpA prevalence range from 0.5% to 1.5%, which is comparable to that of rheumatoid arthritis.[15-17] In the United States, the prevalence rates of axSpA and AS were found to be 1.4% and 0.55%, respectively.[18] Ankylosing spondylitis is more common in men, with a male to female ratio of 2 to 3:1, but nr-axSpA is equally prevalent in men and women.[19,20] First-degree relatives of patients with AS have a 5.6- to 16-fold higher risk of development of AS. Ankylosing spondylitis is strongly associated with the genetic marker HLA-B27. Approximately 85% to 95% of white patients with AS are positive for HLA-B27.[21] Because HLA-B27 has a relatively high prevalence in the US population (6.1%) compared with the prevalence of axSpA (1.4%), the majority of HLA-B27−positive patients do not have axSpA.[22] The absolute risk of SpA in an HLA-B27−positive person is estimated to be between 2% and 10%.[23] Thus, HLA-B27 positivity has a moderate to high sensitivity but a low specificity for axSpA.

DISEASE MANIFESTATIONS AND COMORBIDITIES

The hallmark feature of axSpA is IBP, which is characterized by insidious onset of chronic (>3 months) back pain before the age of 40 to 45 years, waking up in the second half of the night due to back pain, improvement with physical activity but not with rest, morning stiffness persisting for more than 30 minutes, and a good response to NSAIDs (Table).[4,24-26] When describing their symptoms, many patients with axSpA report alternating buttock pain or hip pain; neck pain can be an early symptom in up to 50% of the patients with axSpA.[27] Other common clinical features in patients with axSpA include peripheral inflammatory arthritis, enthesitis, and dactylitis.[19,28,29] Approximately 30% of patients with axSpA have inflammation in peripheral joints, which is typically an asymmetric oligoarthritis (involving 2-4 joints)[19] that disproportionately affects joints of the lower extremities, such as the ankle, knee, and hip; however, joints of the upper extremities and the sternoclavicular or temporomandibular joints may also be affected. Peripheral arthritis is slightly more common in women. Enthesitis refers to inflammation of the enthesis, the

TABLE. Characteristics That Can Distinguish Inflammatory Back Pain From Mechanical Back Pain

Variable	Inflammatory back pain	Mechanical back pain
Age at onset	<40-45 y	Any age
Rapidity of onset	Insidious	Variable, may be acute
Chronicity	>3 mo	Variable duration
Night pain	Commonly worse at night; may cause awakening in the second half of the night due to back pain	Variable
Effect of physical activity or movement	Improvement with activity, not rest; minimally affected by position changes	Worsening with activity, improvement with rest; may improve or worsen with position changes
Morning stiffness	Persisting for >30 min; may be severe	Short-lived
Response to NSAIDs	Good	Variable
Location and characteristics of pain	Low back pain common but may affect any area of the spine; may cause alternating buttock pain; does not radiate into legs; does not cause numbness, burning, or tingling	Anywhere in spine; may radiate into legs; may cause numbness, burning, or tingling

NSAID = nonsteroidal anti-inflammatory drug.
Data from references 4 and 24-26.

structure where a joint capsule, ligament, or tendon inserts into the bone. Enthesitis presents as pain or stiffness with tenderness to palpation. Visible swelling at the entheses is uncommon. Common sites for enthesitis include the Achilles tendon and plantar fascia insertions into the calcaneus and the patellar and quadriceps tendon insertions into the tibial tubercle and patella.[29] Dactylitis is characterized by diffuse swelling of a whole finger or toe ("sausage digit"), which may be painful and is present in approximately 6% of patients with axSpA.[30] Dactylitis typically occurs in one or a few digits at a time. Diffuse swelling or puffiness of all digits in an extremity should trigger consideration of an alternative etiology.

Patients with axSpA frequently have extra-articular manifestations—including uveitis, psoriasis, and inflammatory bowel disease (IBD)—and additional comorbidities associated with axSpA such as fatigue, osteoporosis, cardiovascular disease, and sleep apnea.[19,31-36] The most common extra-articular manifestation in axSpA is anterior uveitis, which affects 25% to 35% of patients. Uveitis in axSpA is typically acute and unilateral and can be self-limited; recurrence is common and may occur in the alternate eye.[31] Patients present with acute unilateral eye pain, redness, photophobia, and blurred vision.[37] Occasionally, uveitis is the first manifestation of axSpA, even before the onset of IBP. Symptomatic IBD occurs in 4% to 6% of patients with axSpA,[19,20] but asymptomatic ileal and colonic mucosal inflammation is found in up to 50% of patients.[38,39] Psoriasis is seen in about 10% of patients with axSpA.[40]

Patients with AS often have reduced mobility in the spine due to disease activity and later also from syndesmophyte formation and bony fusion of vertebrae. However, findings on physical examination of the spine may be completely normal in patients with nr-axSpA; therefore, it is important to look for other features of SpA on examination. Tender or swollen joints, a tender Achilles tendon or plantar fascia insertion, sausage digits, or psoriatic skin lesions, if present, support a diagnosis of axSpA. No specific diagnostic laboratory tests exist for axSpA. Human leukocyte antigen B27 testing plays an important role, but HLA-B27

Mayo Clin Proc. ■ November 2020;95(11):2499-2508 ■ https://doi.org/10.1016/j.mayocp.2020.02.007
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positivity alone does not confirm a diagnosis of axSpA, and a negative HLA-B27 test result does not rule out an axSpA diagnosis. Serum CRP levels may be elevated in approximately 60% of patients with axSpA, but CRP elevation is neither sensitive nor specific for axSpA.[41]

A single anterior-posterior radiograph of the pelvis is the recommended initial imaging study in a patient with suspected axSpA. Findings of sacroiliitis include joint space narrowing, sclerosis, erosive changes, and, in late stages, fusion of the joint. An MRI of the sacroiliac joints is valuable because it can demonstrate active inflammation in early stages, which may or may not progress to structural damage visible on radiography. Typical MRI lesions include bone marrow edema on short tau inversion recovery sequences in subchondral and periarticular areas and erosions, fatty lesions, sclerosis, or ankylosis on T1-weighted images. Magnetic resonance imaging is recommended when the findings on sacroiliac joint radiographs are normal or equivocal.[42] Although the availability of MRI has revolutionized the diagnosis of axSpA, the sensitivity and specificity of MRI for axSpA are imperfect, and MRI findings need to be interpreted in the context of the entire clinical picture to make a diagnosis of axSpA. In most situations, it is appropriate to refer patients to a rheumatologist for further work-up when the findings on sacroiliac joint radiographs are normal and the clinical suspicion for axSpA remains high.[43]

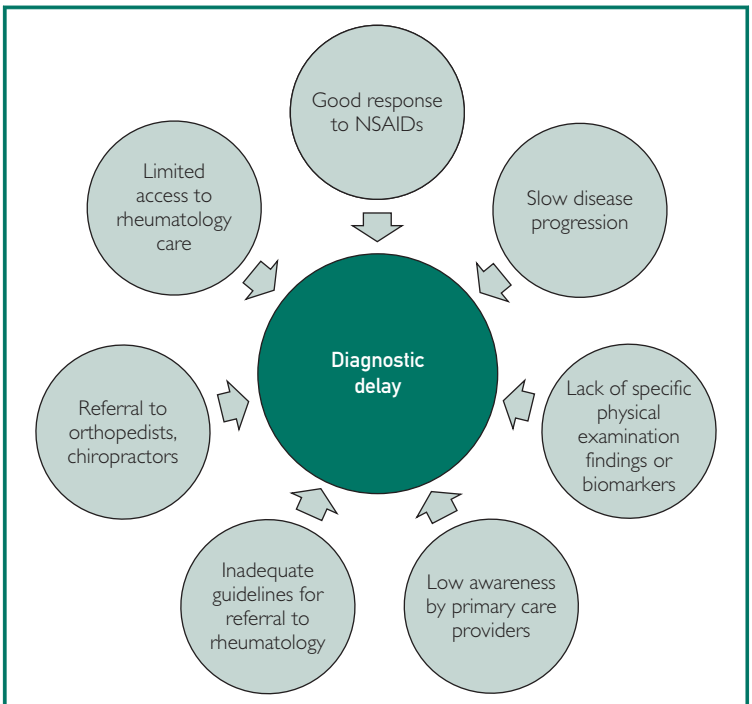

FIGURE 2. Factors contributing to delay in diagnosis of axial spondyloarthritis. NSAID = nonsteroidal anti-inflammatory drug. Data from *Clin Rheumatol.*[50]

BARRIERS TO A TIMELY DIAGNOSIS OF AXSPA

The true prevalence of axSpA is unknown, and large differences between diagnostic prevalence and population prevalence have been reported (2.6 vs 14 cases per 1000 US adults, respectively).[44,45] This discrepancy may reflect substantial underdiagnosis in routine clinical practice; in many cases, patients with possible axSpA were not referred to a rheumatologist.[45] The average delay between symptom onset and diagnosis of axSpA is estimated to be 5 to 7 years, with evidence that the delay can be significantly longer in women than in men.[46-49]

Several factors may contribute to the delay in diagnosis (Figure 2),[50] including the high prevalence of back pain—most commonly due to mechanical etiologies—in the general population (19% based on National Health and Nutrition Examination Survey data[51]). The lack of specific physical examination findings in patients with early axSpA and absence of extraspinal manifestations has been reported to impair early diagnosis.[52] The lack of biomarkers unique to axSpA, younger age at onset, and gradual disease onset may also contribute to delayed referral for evaluation by a rheumatologist.[21,53,54] Instead, patients may be referred to and treated by orthopedists, physiatrists, chiropractors, and other providers in an attempt to relieve symptoms.[53] Paradoxically, a good response to NSAIDs may contribute to a delay in diagnosis because further evaluation may not be pursued when patients report improved symptoms

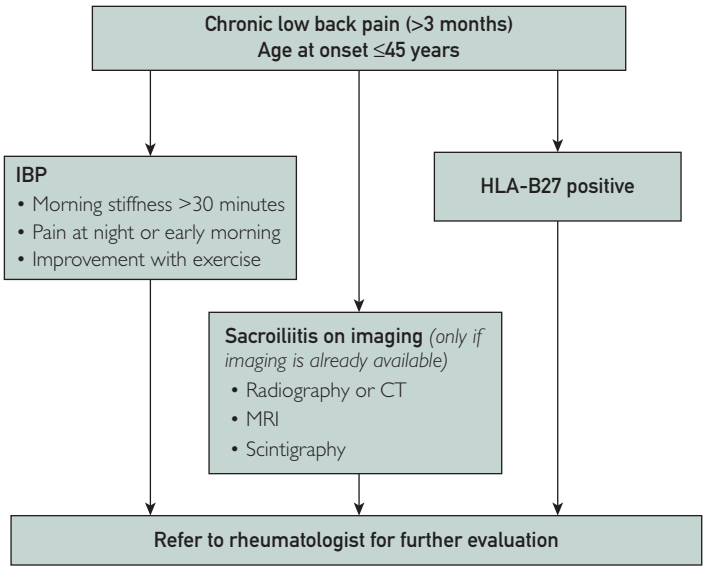

FIGURE 3. Referral strategies for axial spondyloarthritis evaluated in the Prevalence of Axial Spondyloarthritis (PROSpA) and Multicenter Ankylosing Spondylitis Survey Trial to Evaluate and Compare Referral Parameters in Early SpA (MASTER)/Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) studies.[63,65] CT = computed tomography; HLA-B27 = human leukocyte antigen B27; IBP = inflammatory back pain; MRI = magnetic resonance imaging. Adapted from *Nat Rev Rheumatol*,[65] with permission from Springer Nature.

with NSAIDs. Lack of access to a rheumatologist and long waiting times may also contribute to diagnostic and therapeutic delays in some areas.[53]

REFERRAL STRATEGY FOR AXSPA

Axial spondyloarthritis can easily be missed in a primary care setting because no specific physical examination findings or diagnostic tests exist that easily differentiate axSpA from other chronic back pain syndromes.[21] Screening and referral strategies have been developed to help PCPs determine when axSpA should be considered and to guide the initial evaluation for suspected axSpA, including support in making the decision whether to refer patients to a rheumatologist.[55-60] Inflammatory back pain usually develops before age 45 years and is characterized by insidious onset of chronic (≥3 months) back pain. Thus, referral strategies are designed to be applied to patients with back pain for 3 months or longer and onset age younger than 45 years, who we subsequently refer to as "at-risk" patients.[55-60]

Because IBP is the most common symptom in patients with axSpA, IBP has been used as a key component of screening tools for axSpA. In studies in which physicians were asked to refer at-risk patients (back pain ≥3 months with onset age <45 years) with IBP to a rheumatologist, a diagnosis of axSpA was made in 17% to 33% of these patients.[56-58,61] The relatively high sensitivity of IBP for axSpA in at-risk patients (≈77%) makes it useful in screening for axSpA, but nearly one-quarter of patients with axSpA would be missed if screening relied on the presence of IBP alone.[62]

Several studies have therefore evaluated and validated axSpA screening strategies in patients with chronic low back pain using IBP in combination with other SpA features.[57-60,63,64] In the German Multicenter Ankylosing Spondylitis Survey Trial to Evaluate and Compare Referral Parameters in Early SpA (MASTER) study, 2 referral strategies were compared in at-risk patients (those with low back pain of ≥3 months' duration; age at onset ≤45 years).[57] These referral strategies were further tested in an international study—Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR)—that included additional extra-articular manifestations (ie, uveitis, psoriasis, IBD) in strategy 2.[58] Here, axSpA was diagnosed in 35.6% of patients referred per strategy 1 and in 39.8% of patients referred per strategy 2; IBP was the most frequently used referral parameter across both strategies (93% and 96%, respectively). Findings from the RADAR study suggested that a more complicated referral strategy was not more advantageous than the simpler strategy, which required the presence of only one SpA parameter in at-risk patients. In the United States, the Prevalence of Axial Spondyloarthritis (PROSpA) study confirmed that referral of at-risk patients (chronic back pain for >3 months that started before 45 years of age) with IBP, HLA-B27 positivity, or imaging evidence of sacroiliitis was an effective strategy for identifying patients with possible axSpA (Figure 3).[63,65]

Mayo Clin Proc. ■ November 2020;95(11):2499-2508 ■ https://doi.org/10.1016/j.mayocp.2020.02.007
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The ASAS additionally proposed a slightly longer referral algorithm, with the intention of maximizing sensitivity.[60] According to the ASAS strategy, patients with chronic back pain for 3 months or more and onset at age 45 years or younger should be referred to a rheumatologist for further evaluation if they have any of the following parameters: IBP, HLA-B27 positivity, imaging evidence of sacroiliitis (on radiography or MRI), peripheral manifestations (arthritis, enthesitis, and/or dactylitis), extra-articular manifestations (psoriasis, IBD, and/or uveitis), family history of SpA, good response to NSAIDs, or elevated acute-phase reactants.[60] A recent study retrospectively compared 13 referral strategies in the Spondyloarthritis Caught Early (SPACE) cohort.[66] This study showed that the ASAS strategy was indeed most effective at ensuring that no patients with axSpA were missed; however, increased sensitivity came at the expense of lower specificity. Implementing the ASAS strategy may be challenging in locations that are underserved by rheumatologists because those few rheumatologists could be overwhelmed by the volume of referrals. Although the optimum referral strategy may depend on details of the health care environment, axSpA should always be considered in the differential diagnosis of chronic back pain, particularly in younger patients. It is critical that PCPs screen for IBP and other SpA features and refer patients with suspicion for axSpA to a rheumatologist for further evaluation.

TREATMENT APPROACHES

The goals of treatment for axSpA include alleviating symptoms, optimizing function, and preventing structural damage to the spine.[26,67] Although currently available therapies improve symptoms and physical function,[68] the impact of treatment on long-term structural damage remains uncertain, with conflicting data from imaging studies.[69,70]

Recommendations/guidelines for the management of axSpA include pharmacological and nonpharmacological interventions, such as education, physical therapy/exercise, and cessation of smoking.[26,67] The initial medication class for treatment of active axSpA is NSAIDs. A Cochrane review of 39 studies of NSAIDs found high- to moderate-quality evidence suggesting that both traditional and cyclooxygenase 2—selective NSAIDs are efficacious for treating axSpA and moderate- to low-quality evidence that any harms with NSAIDs may not be different from placebo in the short term.[71] Various NSAIDs are equally effective, and longer-acting drugs may be preferable because they are more convenient.[67,72]

Treatment with a biologic drug is indicated for active axSpA if a patient is intolerant of NSAIDs or has an inadequate response to 2 or more NSAIDs at therapeutic doses for 2 weeks each.[26,67] Several tumor necrosis factor and interleukin 17A inhibitors are available for the treatment of axSpA. The selection of biologic therapies may be influenced by comorbidities, availability (eg, insurance formularies), response to prior treatment, patient preference, and other factors. Neither traditional disease-modifying drugs (eg, methotrexate, sulfasalazine) or systemic glucocorticoids are recommended for axial manifestations because there is little evidence of their clinical benefit, although these agents may be appropriate for some patients who have axSpA with peripheral SpA manifestations.[67]

When axSpA is initially diagnosed or suspected, patients should be given a prescription for NSAIDs—up to the maximum dose unless there are contraindications—as an interim first-line treatment while rheumatology consultation is being arranged.[26,73] Early initiation of physical therapy is also recommended. It is usually appropriate to defer the decision to start treatment with a biologic to a rheumatologist to confirm the diagnosis, to assess the risks and benefits of biologic therapy, and to develop a monitoring plan, in conjunction with the patient.

CONCLUSION

Axial spondyloarthritis is a chronic inflammatory disease that causes back pain and stiffness, reduces mobility, and decreases quality of life. It is thought to affect about

1% of the US population, but it is currently underdiagnosed. Patients without a diagnosis are unlikely to receive appropriate treatment and may therefore experience more severe symptoms and unfavorable long-term outcomes. Primary care physicians are the first-line providers of care for patients with back pain and need to be aware of the clinical features that suggest axSpA, particularly in younger patients. Raising awareness of axSpA, including both AS and nr-axSpA, among PCPs should improve recognition of the disease in the primary care setting and facilitate the timely referral of appropriate patients to rheumatologists for early diagnosis and effective management.

ACKNOWLEDGMENTS

Support for third-party writing assistance for the submitted manuscript, furnished by Victoria Kinsley, PhD, of SciMentum and Eric Deutsch, PhD, CMPP, of Health Interactions, Inc, was provided by Novartis Pharmaceuticals Corporation.

Abbreviations and Acronyms: **AS** = ankylosing spondylitis; **ASAS** = Assessment of SpondyloArthritis international Society; **axSpA** = axial spondyloarthritis; **CRP** = C-reactive protein; **HLA-B27** = human leukocyte antigen B27; **IBD** = inflammatory bowel disease; **IBP** = inflammatory back pain; **MRI** = magnetic resonance imaging; **nr-axSpA** = nonradiographic axSpA; **NSAID** = nonsteroidal anti-inflammatory drug; **PCP** = primary care physician; **r-axSpA** = radiographic axSpA; **SPA** = spondyloarthritis

Potential Competing Interests: Dr Magrey has received research funding from AbbVie, Inc for clinical trials, has served as a consultant for Janssen Pharmaceuticals, Inc, and Novartis Pharmaceuticals Corporation, and has been a member of advisory boards for Janssen Pharmaceuticals, Inc, Novartis Pharmaceuticals Corporation, Eli Lilly and Company, and UCB S.A. Dr Danve has consulted or received grants from Janssen Pharmaceuticals, Inc, and Novartis Pharmaceuticals Corportaion. Dr Ermann has received research funding from Boehringer Ingelheim International GmbH and Pfizer (funds paid to his institution) and has served as a consultant for AbbVie Inc, Eli Lilly and Company, Janssen Pharmaceuticals, Inc, Novartis Pharmaceuticals Corporation, Takeda Pharmaceutical Company Limited, and UCB S.A. Dr Walsh has served on advisory boards for Novartis Pharmaceuticals Corporation, UCB S.A., Amgen Inc, Eli Lilly and Company, AbbVie Inc, and Celgene Corporation and has received grants from AbbVie Inc and Pfizer Inc.

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