



REVIEW

# Evaluating Inflammatory Versus Mechanical Back Pain in Individuals with Psoriatic Arthritis: A Review of the Literature

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## ABSTRACT

Psoriatic arthritis (PsA) is a chronic immune-mediated disease characterized by psoriatic skin and nail changes, peripheral joint inflammation, enthesitis, dactylitis, and/or axial involvement, either alone or in combination with each other. The presence of axial involvement has been shown to be a marker of PsA severity; however, there is no widely accepted definition of axial involvement in PsA (axPsA) or consensus on how or when to screen and treat patients with suspected axPsA. Chronic back pain is a prominent feature of axPsA and is thought to have a relevant role in early identification of disease. Chronic back pain can be caused by inflammatory back pain (IBP) or mechanical back pain (MBP). However, MBP can complicate recognition of IBP and

delay diagnosis of axPsA. While MBP can also be associated with chronic back pain of  $\geq 3$  months in duration that is typical of IBP, IBP is characterized by inflammation of the sacroiliac joint and lower spine that is differentiated from MBP by key characteristic features, including insidious onset at age  $< 40$  years, improvement with exercise but not with rest, and nighttime pain. This review discusses the differences in identification and management of IBP and MBP in patients with PsA with axPsA. The summary of available evidence highlights the importance of appropriate and timely screening, difficulties and limitations of differential diagnoses and treatment, and unmet needs in axPsA.

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## PLAIN LANGUAGE SUMMARY

Psoriatic arthritis (PsA) is a long-term disease that may lead to psoriatic changes in skin and nails; inflammation of some joints, including finger and toe joints (dactylitis); inflammation of sites where tendons and ligaments connect to bone (enthesitis); and/or problems in the spine (axial involvement). Approximately 25–70% of patients with PsA have axial involvement (axPsA); this number varies because there is no widely accepted definition for axPsA. Chronic (long-lasting) back pain is a major feature of axSpA and can help doctors recognize axPsA early. Chronic back pain

can be caused by inflammatory back pain (IBP) or mechanical back pain (MBP). IBP is described by back pain lasting  $\geq 3$  months, gradual onset at age  $< 40$  years, improvement with exercise, no improvement with rest, pain at night (with improvement upon getting up), and changes in some laboratory test results. On the other hand, MBP is caused by a physical injury to the lower back. Both IBP and MBP can occur in patients with PsA, but they are treated in different ways. Being able to tell the difference between IBP and MBP is important to make sure that patients receive the right treatment. This review looks at the differences between IBP and MBP, screening for IBP, the difficulties and limitations of diagnosing and treating axPsA, and the needs of patients with axPsA for better diagnosis and treatment.

**Keywords:** Diagnosis; Inflammatory back pain; Mechanical back pain; Psoriatic arthritis

### Key Summary Points

Axial involvement is present in 25–70% of patients with psoriatic arthritis (PsA) and is an accepted marker of PsA disease severity.

Improved recognition of axial involvement may help to identify patients who are candidates for more aggressive and appropriate therapy that effectively treats the complete spectrum of PsA, including axial disease in PsA (axPsA).

Chronic back pain is also thought to have a relevant role in the early identification of axPsA and is usually accompanied by inflammatory back pain (IBP) symptoms but can be confused with mechanical back pain (MBP).

It is important to differentiate between IBP and MBP to ensure that patients with axPsA receive the most appropriate treatment.

## DIGITAL FEATURES

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## INTRODUCTION

Psoriatic arthritis (PsA) is a chronic immune-mediated disease characterized by psoriatic skin and nail changes, peripheral joint inflammation, enthesitis, dactylitis, and/or axial involvement [1–3]. The prevalence of PsA varies globally, ranging from 0.05 to 0.25% in the general population and increasing in those with psoriasis, with rates of approximately 30%, depending on the epidemiological methods used and populations studied [3, 4]. Early identification and appropriate treatment can significantly improve the quality of life of affected patients [5]. However, PsA is a heterogeneous disease and can have a wide range of effects and symptoms, making it difficult to distinguish from other musculoskeletal conditions [2, 6].

PsA involves genetic, environmental, and epigenetic factors, which contribute to disease risk and pathophysiology [1, 7–9]. For example, the major histocompatibility complex I molecules are involved in the development and proliferation of immune responses, including HLA-B27 [10]. HLA-B27 is a genetic marker of disease expression in PsA [9, 11], and its association with spondyloarthritis (SpA) has been recognized since the 1970s and varies across ethnicities and spondyloarthropathies [12]. HLA-B27 is associated with manifestations related to axial inflammation in SpA (axSpA) [13] and is more common in patients with axial involvement (axPsA) than in those without axial involvement [9]. Thus, HLA-B27 has been proposed as a genetic marker of axPsA [9, 14]. B\*08:01:01–C\*07:01:01 and its component alleles are associated with joint deformities and fusion, asymmetrical sacroiliitis, and dactylitis [15]. HLA-B\*08:01:01–C\*07:01:01 and HLA-B\*37:01:01–C\*06:02:01 have also been linked to the highest propensity score for severe PsA [15].

The association of HLA-B27 with axPsA has led to greater awareness of inflammatory back pain (IBP) as a discrete entity in PsA [16]. Although no laboratory tests specifically diagnose axPsA, testing for HLA-B27 may aid in diagnosis. Because the HLA-B27 gene is expressed in  $\leq 8\%$  of the general population, HLA-B27 positivity alone or the lack of HLA-B27 positivity should not be regarded as diagnostic for SpA. Random HLA-B27 testing is more likely to yield false-positive results than true-positive results [17–19].

Axial involvement is present in 25–70% of patients with PsA [14, 20], with variability that may reflect different criteria used across studies for defining the axial involvement (e.g., clinical and/or imaging criteria), and is an accepted marker of PsA disease severity [21]. Chronic back pain, a prominent feature of axSpA, is thought to have a relevant role in the early identification of axPsA and is usually accompanied by IBP symptoms [22, 23], suggesting potential inflammation of the sacroiliac joint and lower spine [24–26]. Conversely, mechanical back pain (MBP) is an injury or derangement of an anatomical structure in the lower back [27]. Both IBP and MBP can occur in patients with PsA [21, 28]. It is important to differentiate between IBP and MBP to ensure that patients with axPsA receive the most appropriate treatment. Methods for characterizing IBP in patients with axSpA may not perform well in patients with PsA; therefore, improved recognition of axial involvement may help to identify patients who are candidates for more aggressive and appropriate therapy that effectively treats the complete spectrum of PsA, including axial disease [21].

No widely accepted definition of axPsA exists, and guidelines vary on how and when to screen for back pain in PsA [29–39]. In this narrative review, we discuss the differences associated with identification and management of IBP versus MBP in axPsA, highlighting the importance of appropriate and timely screening, the difficulties and limitations of differential diagnosis, and the unmet needs of axPsA patients with IBP.

## SEARCH STRATEGY

We used the following search strings to identify articles of interest published on PubMed between January 1, 2009, and June 1, 2020: the primary search included (“mechanical” OR “inflammatory”) AND “psoriatic arthritis” AND “back pain”; secondary searches included “psoriatic arthritis” AND “back pain,” “psoriatic arthritis” AND “axial disease,” “back pain” AND (“mechanical” OR “inflammatory”) AND (“psoriatic arthritis” OR “axial spondyloarthritis”), “axial psoriatic arthritis,” and “psoriatic arthritis” AND “unmet need.”

The full text and bibliographies of relevant English-language articles were evaluated for specific data relating to IBP and MBP in patients with PsA, thus focusing on those with axPsA. Only those deemed relevant to the objectives of this study were included. This article is a review of previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## IMPORTANCE OF ASSESSING AXPSA

axPsA is accompanied by significant clinical morbidity; it is associated with a higher likelihood of moderate/severe psoriasis, higher PsA disease activity, and greater impact on quality of life [40]. Because PsA (and axPsA) mostly manifest between the ages of 30–50 years [41, 42], back pain from axPsA, as with back pain in the general population, may have a greater impact on work productivity and social and mental aspects of quality of life, including fatigue, than in patients without axial involvement. Work disability is common in PsA, and many with this disease have health-related limitations, including time away or reduced effectiveness at work [38, 40]. In a Work Limitations Questionnaire of 107 patients with PsA, work productivity decreased by 6.7%, and more than half of those surveyed also reported fatigue [43]. In the Corrona Psoriasis Registry, work productivity and activity were significantly affected by axial involvement; patients with axial involvement reported a significantly

higher percentage of work time missed, impairment while working, overall work impairment, and overall activity impairment versus those without axial involvement ( $P < 0.001$ ) [40].

Therefore, patients with PsA should be assessed for axial involvement as soon as possible to ensure that they receive appropriate disease management and treatment [40] because patients with axial involvement may require more aggressive therapy [21]. However, characterization of axPsA remains poorly understood because limited data are available on this specific patient population [40]. Because few adequate studies have been conducted in patients with axPsA, criteria and outcome measures specifically for axSpA have been widely accepted for axPsA; responses to therapy are presumed to be equivalent for axPsA and ankylosing spondylitis (AS) [44]. In addition, no consensus exists on how and when to screen for axial disease in PsA [45]. Patients with PsA with more severe peripheral disease are reported to have a higher risk of underdiagnosed axPsA [29]. Tools currently available to score axSpA, including the modified Stoke Ankylosing Spondylitis Spinal Score, the Radiographic Ankylosing Spondylitis Spinal Score, the Bath Ankylosing Spondylitis Disease Activity Index, and the Ankylosing Spondylitis Disease Activity Score, but not the Bath Ankylosing Spondylitis Radiology Index-spine, are reportedly reliable for axPsA [30, 32, 34, 37]. Spinal mobility measurements and the Bath Ankylosing Spondylitis Metrology Index score may be valuable in differentiating axPsA from peripheral PsA [38]. Imaging can be useful for differential diagnosis and monitoring for inflammatory and structural changes [33]. Radiographic assessment is considered the gold standard for distinguishing axPsA from axSpA and other degenerative or inflammatory conditions [39]; Feld and colleagues recently reported that patients with AS have a higher grade of sacroiliitis than those with axPsA [46]. Ibrahim and colleagues reported the use of an electronic application that specifically documents axPsA manifestations [36]. In this study, radiographs from patients with axPsA were blindly scored by three rheumatologists using the app and yielded

high specificity and moderate sensitivity; these results were independently confirmed by a nonblinded, external expert as true radiographic progression [36]. In addition, the extent of inflammation shown for HLA-B27-related active axPsA on magnetic resonance imaging (MRI) was similar to that associated with axSpA and AS and was superior to that associated with HLA-B27-negative PsA [31].

## APPROPRIATE SCREENING FOR BACK PAIN IN PSA

Back pain is one of the most common reasons for physician visits globally and the most costly in terms of healthcare provider visits [47], leading to significant direct medical costs and indirect societal costs arising from absenteeism, presenteeism, disability, and workers' compensation claims [48]. Because back pain has many different causes that can present with similar symptoms, it can be difficult to identify its fundamental pathological features during musculoskeletal evaluation [27, 48]. Back pain is very common in the general population; approximately 80% of people experience it in some form at least once in their lifetimes [25]. Most (97%) chronic back pain episodes are reported to be mechanical in nature. Nonmechanical causes may include those being of rheumatologic, vascular, gastrointestinal, renal, infectious, or oncologic origin [48].

Back pain can impair productivity, which influences long-term profitability [49]. In a 4-year review of presenteeism data among employees of a large US healthcare system, chronic back pain ranked among the highest for minutes of daily productivity loss (16.7) and annual cost per person (\$1920) [49]. Low back pain with or without lower extremity pain is one of the most common reasons for physician visits, and treatment costs remain a significant burden on healthcare resources [47]. In a recent US study, the total cost of care over 12 months after diagnosis was \$1.8 billion among patients with low back pain with or without lower extremity pain and not undergoing surgery [47].

Therefore, accurate identification of back pain is important in determining the underlying cause and the most appropriate treatment [48]. MBP persisting for > 4 to 6 weeks warrants further investigation for possible nonmechanical causes, such as IBP [48]. It is important that patients with probable axSpA or axPsA, based on the identification criteria for IBP, are referred to a rheumatology specialist [25–27]. This screening approach would ensure the timely identification and management of IBP and result in the best outcome for patients and appropriate utilization of resources [25, 26]. Identification of back pain could be improved by using predictors of axial involvement, including HLA-B27 positivity, nail dystrophy, number of radiographically damaged joints, periostitis, elevated acute phase reactants, and disease duration [9, 16, 50, 51].

## DIFFERENTIAL DIAGNOSIS OF IBP VERSUS MBP

Fibromyalgia, characterized by chronic, widespread pain, reportedly occurs in up to 22% of patients with PsA [52–55]. The presence of comorbid fibromyalgia may mask PsA disease severity, especially when subjective measures and patient-reported outcomes are being considered [56, 57]. Accordingly, distinguishing fibromyalgia from PsA may be addressed using screening instruments such as the Widespread Pain Index and Symptom Severity Score [58, 59].

### IBP Versus MBP Key Features

It is important to distinguish between IBP and MBP as early as possible in the disease course because management and treatment of the two types of back pain are very different. IBP is differentiated from MBP by key characteristic features identified by experts from the Assessment of SpondyloArthritis international Society (ASAS) (Table 1) [27, 48, 60], including chronic back pain of  $\geq 3$  months in duration (which may not always be present in MBP), insidious onset at age < 40 years, improvement with

exercise, no improvement with rest, pain at night (with improvement upon getting up), and elevated acute phase reactants (erythrocyte sedimentation rate and/or C-reactive protein [CRP]). IBP is present in axSpA (nonradiographic and radiographic) and the axial form of PsA, and is typically associated with early pain onset localized to the axial spine, sacroiliac joints, and buttocks [24, 26, 27, 29, 61]. MBP is identified by first ruling out red flags and symptoms, including trauma, unexplained weight loss, neurological signs, age > 50 years, fever, intravenous drug use, long-term steroid use, and history of cancer [62]; however, there is no clear evidence about which are clinically relevant [27, 48]. Onset of MBP can occur at any age and can be acute; pain may worsen with movement and improve with rest [27, 48].

### Identification of IBP

IBP pathophysiology stems from a systemic response to inflammatory mediators localized to the axial skeletal joints that induces proinflammatory intracellular changes [26]. This chronic inflammation leads to a reactive cycle of unbalanced bone remodeling associated with bone loss and possible bone fusion, which may result in ankylosis of the sacroiliac joints and formation of syndesmophytes in the spine [26, 63]. It has been suggested that mechanical strain on the entheses may drive both processes of inflammation and bone remodeling [64].

Numerous criteria exist to identify probable IBP, including the Calin, Berlin, and ASAS criteria [60, 65, 66]. The ASAS criteria are commonly used when patients present with back pain of  $\geq 3$  months in duration; the criteria comprise five parameters (Table 2) [60]. If  $\geq 4$  parameters are present, ASAS criteria have a reported sensitivity and specificity of 77% and 91.7%, respectively, for identifying IBP [60, 67]. Validated classification criteria for IBP in axPsA are not yet available; however, ASAS and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) are making efforts to develop such criteria [68]. Although age of onset < 40 years is one of the parameters used for identifying probable IBP, it should be



**Table 1** Classification criteria of IBP versus MBP from various mechanical and nonmechanical causes

IBP (according to ASAS experts' criteria, axSpA) [60]	MBP (injury to or derangement of spine structures or rheumatologic, vascular, gastrointestinal, renal, infectious, or oncologic causes) [27, 48]
<p>ASAS criteria: when patient presents with back pain of <math>\geq 3</math> months in duration</p> <ul style="list-style-type: none"> <li>• Age at onset &lt; 40 years</li> <li>• Insidious onset</li> <li>• Improvement with exercise</li> <li>• No improvement with rest</li> <li>• Pain at night (with improvement upon getting up)</li> </ul>	<p>Identification of symptoms (no clear evidence about which are clinically relevant)</p> <ul style="list-style-type: none"> <li>• Onset at any age; may be more common in middle-aged, working individuals</li> <li>• Variable onset; may be acute</li> <li>• Pain may worsen with movement</li> <li>• Pain often improves with rest</li> </ul>
<p>Diagnoses are made by combining clinical criteria with radiological findings (MRI, CT, ultrasound) and/or laboratory test results (e.g., testing for HLA-B27)</p>	<p>Physical examination involving patient history, such as an acute injury</p> <ul style="list-style-type: none"> <li>• This process can involve ruling out IBP along with other causes of back pain (e.g., malignancies, infection)</li> </ul>
	<p>Injury or derangement of an anatomical structure in the lower back</p> <ul style="list-style-type: none"> <li>• Soft tissue (lumbar sprain or strain)</li> <li>• Muscle/fascia (myofascial pain)</li> <li>• Disks (herniated disk, discogenic pain)</li> <li>• Joints (zygapophysial joint and sacroiliac joint pain)</li> <li>• Bone (vertebral fractures, spondylolisthesis, kyphosis, scoliosis)</li> </ul>
	<p>MBP persisting for &gt; 4 to 6 weeks may warrant further diagnostic testing and imaging</p>

*ASAS* Assessment of SpondyloArthritis international Society, *axSpA* axial spondyloarthritis, *CT* computed tomography, *IBP* inflammatory back pain, *MBP* mechanical back pain, *MRI* magnetic resonance imaging

noted that axial manifestations develop in patients with PsA at an older age, and that not all patients with radiographic changes may present with symptoms [21, 69–72].

Imaging techniques are also useful in identifying IBP (Fig. 1) [73–75]. MRI can detect the signs of initial inflammatory processes associated with the early stages of axSpA/PsA or structural changes associated with AS/PsA [73]. Ultrasound is being used in PsA to primarily examine peripheral joints and entheses; however, interest in analyzing axPsA and sacroiliitis is increasing [75]. A Bath Ankylosing

Spondylitis Disease Activity Index score of  $\geq 4$ , the cutoff for active disease, can also help identify spinal disease [76]. The ASAS MRI working group recently generated a consensus update on standardized definitions for MRI lesions in the sacroiliac joint of patients with SpA [77]. The reliability of definitions was satisfactory for most inflammatory and mechanical lesions, even among some lesions occurring at a frequency of < 10% [77]. Computed tomography (CT) is useful for detecting bone erosions in joints and entheses, and may be easier to interpret than radiographs due to its

**Table 2** Treatment pathways for managing IBP and MBP in PsA

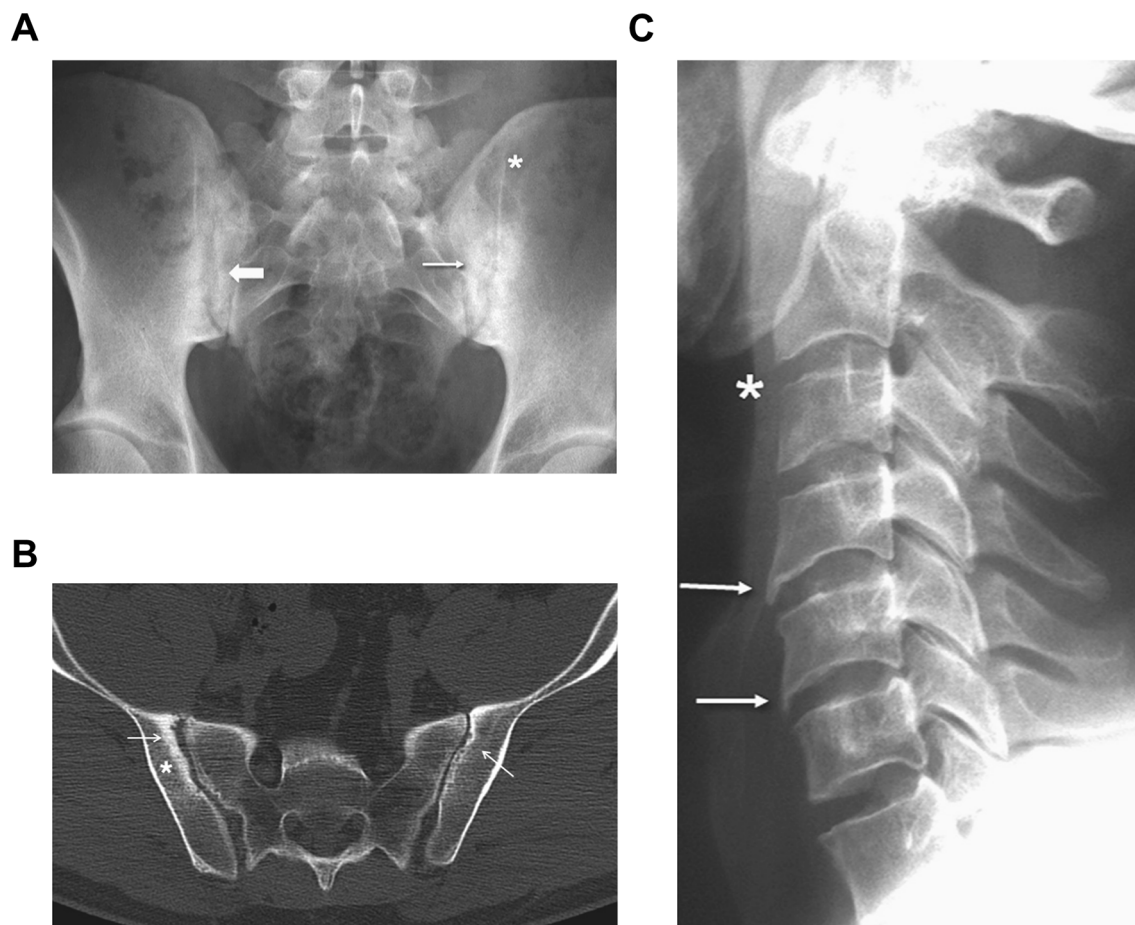
IBP (EULAR recommendations) [51]	IBP (GRAPPA, GRADE recommendations for axPsA) [93]	MBP [27, 48]
NSAIDs may be used to relieve musculoskeletal signs and symptoms ( <b>grade A recommendation</b> )	<i>Biologic naive</i> Strongly recommended: NSAIDs, physiotherapy, simple analgesia, TNFi	Current guidance reinforces the primary emphasis of nonpharmacological measures
Local injections of glucocorticoids should be considered as adjunctive therapy in PsA; systemic glucocorticoids may be used with caution at the lowest effective dose ( <b>grade C recommendation</b> )	Conditionally recommended: IL-17 inhibitor, SI joint CS injections, bisphosphonates, IL-12/23 inhibitor	NSAIDs/analgesics; CS can be used when necessary
In patients with predominantly axial disease that is active and has insufficient response to NSAIDs, therapy with a bDMARD should be considered, which according to current practice is a TNFi; when there is relevant skin involvement, IL-17 inhibitor may be preferred ( <b>grade B recommendation</b> )	<i>Inadequate response to bDMARDs</i> Strongly recommended: physiotherapy, simple analgesia	Physiotherapy (activity over bed rest), but rest (if acute)
In patients who fail to respond adequately to, or are intolerant of a bDMARD, switching to another bDMARD or tsDMARD should be considered, including one switch within a class ( <b>grade B recommendation</b> )	Conditionally recommended: NSAIDs, TNFi, IL-12/23 inhibitor, IL-17 inhibitor	Behavioral approaches (mindfulness)
Optimal management of patients with PsA also requires nonpharmacological strategies, such as patient education and regular physical exercise, and may also require topical medication ( <b>overarching principle</b> )		Patient education (self-management recommendations)

*axPsA* axial psoriatic arthritis, *bDMARD* biologic disease-modifying antirheumatic drug, *CS* corticosteroids, *EULAR* European League Against Rheumatism, *GRADE* Grading of Recommendations, Assessment, Development and Evaluation, *GRAPPA* Group for Research and Assessment of Psoriasis and Psoriatic Arthritis, *IBP* inflammatory back pain, *IL* interleukin, *MBP* mechanical back pain, *NSAID* nonsteroidal anti-inflammatory drug, *PsA* psoriatic arthritis, *SI* sacroiliac, *TNFi* tumor necrosis factor inhibitor

high resolution [33, 78]; however, CT does not show active inflammation and has limited use in diagnosis or in monitoring progression of disease. The role of CT in clinical practice remains unclear and it is largely limited to research settings [78].

### Identification of MBP

Compared with IBP, MBP more often results from acute injury or derangement of an anatomical structure in the lower back and can occur at any age, though it may be more common in middle-aged, working individuals compared with the younger age of onset of IBP [27, 48]. Because of the complexity of



**Fig. 1** **a** Typical findings of sacroiliac joint involvement in a patient with ankylosing spondylitis (AS), showing extensive sclerosis (*thin arrow*), pseudodilation (*thick arrow*), and partial ankylosis (*asterisk*). **b** Computed tomography of the sacroiliac joints of a patient with AS. Note the areas with erosions (*arrows*) and sclerosis (*asterisk*), which represent characteristic signs of the

disease. **c** Typical osteodestructive changes seen as erosion (*asterisk*) and osteoproliferative changes seen as syndesmophytes (*arrows*) in the cervical spine of a patient with AS. Reprinted from Hochberg MC, et al. *Rheumatology*. 7th ed. Copyright © 2019 with permission from Elsevier

identifying MBP, distinguishing IBP from MBP remains difficult. Table 1 describes the criteria used to classify IBP and MBP resulting from various mechanical and nonmechanical causes. Symptoms of MBP often worsen with movement and exercise and appear to correlate with injury and more acute onset [26]. Typically, its insidious onset occurs at an older age than IBP and can be acute or chronic [27, 79].

MBP is usually identified through a physical examination involving patient history, such as an acute injury. This process can involve ruling out IBP based on the above-mentioned criteria,

along with other causes of back pain (e.g., malignancies, infection) [25–27]. Imaging techniques such as X-ray, MRI, and computed tomography can be used if necessary [27, 48].

#### Limitations of Identification Criteria and Measurement of IBP and MBP

The current standard ASAS criteria used to identify IBP are limited by sensitivity and specificity; the reported sensitivity would result in 23% of IBP cases not being identified in patients with chronic back pain [60].



Identification of IBP by MRI is limited by low specificity [80]. Many patients with non-SpA, including healthy individuals, show evidence of sacroiliitis when the sacroiliac joint is examined for lesions [80]. Limitations of MRI include the subjectivity and variability of the radiologist/rheumatologist examining the scan results for signs indicating inflammation, often in terms of confidence levels rather than a simple yes or no [80]. Signs and symptoms of MBP differ across guidelines, and little consensus or evidence exists about which are clinically relevant [27].

### Is There an Inflammatory Component in MBP?

Any inflammation observed in MBP is the result of an initiating event (e.g., injury, wear and tear), which propagates further degeneration [27, 48]. All structures within the spine, including the vertebral bodies, intervertebral discs, zygapophysial joints, sacroiliac joints, spinal ligaments, paraspinal muscles, dura, spinal cord, and nerves are potential pain generators for MBP [48]. For example, intervertebral disc degeneration is a major contributor to MBP and/or lower back pain and can be accompanied by inflammation at the site of the damage/degeneration [81, 82]. It is unclear whether inflammation is the root cause or a consequence of intervertebral disc degeneration [81, 82]. First, an initiating event causes increased production of cytokines and chemokines by nucleus pulposus and annulus fibrosus cells. This is followed by further inflammation, neovascularization, and nerve growth into the structurally deficient discal tissues. Finally, the nerve endings become sensitized and dorsal root ganglion pain channel activity is modulated via inflammatory mediators, which result in pain. Therefore, the inflammatory response to the initiating event perpetuates further degeneration in MBP [81, 82]. In contrast, the inflammatory response of IBP is the cause, with no mechanical initiating event [27, 48].

### IS IBP A SYMPTOM OF DIFFERENT DISEASES?

Once IBP has been determined, it becomes important to identify the root cause of the condition. IBP is associated strongly with, but not diagnostic of, several inflammatory conditions that may have both axial and peripheral pain features [26]. The classic association of IBP symptoms is with axSpA; however, IBP may also be present in conjunction with other seronegative spondyloarthropathies such as PsA, enteropathic arthropathy, juvenile idiopathic arthritis, and reactive arthritis [26]. The accuracy of IBP in differentiating patients with axPsA from patients with other causes of back pain has not been fully clarified [83]. AxSpA consists of several inflammatory conditions—an umbrella state—of which the radiographic version is AS. These disease states are all characterized clinically by IBP [84]. Considerable overlap exists between the symptoms of these diseases, which can make differential diagnosis difficult [26].

Nonradiographic and radiographic axSpA are often considered two stages of the same disease, because the nonradiographic form can progress to the radiographic form; however, not all nonradiographic cases progress to radiographic disease [85]. The only difference between nonradiographic and radiographic axSpA is radiographic changes in the sacroiliac joints [84]. The decision to initiate biologic treatment in the absence of sacroiliitis is predicted mainly by the presence of active inflammation, as identified by MRI findings or elevated CRP levels—the latter of which may be a correlate of radiographic progression [84, 86–88]. Differential diagnosis between nonradiographic and radiographic axSpA can be performed by investigating structural damage with imaging (usually MRI) [85]. Although it is still debatable whether axPsA is radiographic axSpA with concomitant psoriasis or whether they are distinct conditions that share similar characteristics [39, 89], Feld and colleagues concluded from their study that AS—with or without psoriasis—is different from axPsA [46]. The Psoriatic Arthritis Spondylitis Radiology Index is useful for assessing structural

damage in axPsA [30]. Clinicians still struggle to differentiate axPsA from concomitant radiographic axSpA and psoriasis [33, 69, 89, 90]. It may help that spinal involvement in PsA is more frequently unilateral (asymmetric) and is often less severe than radiographic axSpA [69]. Notable differences exist in the morphology of syndesmophytes, the development of which is correlated with elevated CRP levels; those in PsA have a larger volume and appear to progress more randomly along the spine [69, 74, 91]. The finding that inflammation in patients with axPsA responds better to corticosteroids than it does in patients with radiographic axSpA further supports the argument that axPsA and concomitant radiographic axSpA and psoriasis are two distinct diseases [92].

## MANAGEMENT OF IBP AND MBP

Standard management of IBP symptoms includes patient education, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), and structured physiotherapy/exercise programs (Table 2) [25–27]. Patient education is an important aspect of IBP management, allowing patients to make informed shared decisions with their doctors [27]. Conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) can also be prescribed in addition to biologic DMARDs (bDMARDs) in patients with consistently high disease activity [26, 27].

In 2019, the European League Against Rheumatism (EULAR) published updated guidelines for managing PsA with pharmacological therapies (Table 2) [51]. Phase 1 of treatment consists of NSAIDs with or without local glucocorticoid injections, and phase 2 treatment consists of methotrexate; however, patients with predominantly axial disease directly enter phase 3 of treatment after phase 1 failure, which involves initiation of a bDMARD (usually a tumor necrosis factor inhibitor [TNFi]); interleukin (IL)-17A inhibitors would be preferred over TNFis in the presence of relevant skin involvement [51]. Because of the lack of clear efficacy in axSpA, drugs targeting the IL-12/23 pathway are not indicated for patients with predominantly axial disease [51].

GRAPPA guidelines for PsA call for an individualized approach to therapeutic decisions based on specific disease subtypes, including axial arthritis (Table 2) [93]. Treatment recommendations for axial disease are derived from diagnostic criteria, screening, monitoring, and response to therapy in axSpA. NSAIDs, physiotherapy, and TNFis are recommended, while IL-17 and IL-12/23 inhibitors are conditionally recommended [93]; however, GRAPPA guidelines are now a few years old and do not include more recent evidence of biologics targeting IL-17, IL-12/23, and IL-23 for the treatment of axial disease. Moreover, the IL-23 inhibitor risankizumab failed to demonstrate clinically meaningful improvements in patients with AS vs placebo [94].

Biologic treatments that affect the Th17 axis (e.g., ixekizumab and secukinumab) have shown to be beneficial in patients with PsA and in those with axSpA [95–99]. Thus, based on the similar inflammatory mechanisms of disease, these treatments may prove beneficial in patients with axPsA. However, to date, only secukinumab has been shown to have clinical benefits in patients with axPsA [68]. Although targeting the IL-23 pathway has not been effective in treating patients with AS [100] and is not recommended in more recent treatment guidelines for patients with PsA who have axial involvement [51], post hoc analyses have explored the benefit of ustekinumab in biologic-naïve patients with PsA with peripheral arthritis and physician-reported spondylitis [101].

Current guidelines for managing MBP emphasize the use of nonpharmacological measures (Table 2) [27, 48]. However, evidence exists that patients may experience small benefits from anti-inflammatories/painkillers and corticosteroids, rest (if acute), physiotherapy (activity over bed rest), and behavioral approaches [27]. A Cochrane review showed limited, low-quality evidence of reduced pain severity and improved physical function in patients engaging in physical activity and exercise; therefore, patients should be encouraged to remain active if possible [102].

## UNMET NEEDS

Several critical questions still remain, such as how common is IBP as a manifestation of peripheral PsA despite its prominence in axPsA [27], how should axPsA be defined, what role does imaging play in the identification of axPsA among patients with IBP, and how do we evaluate patients with PsA who have inflammation on imaging and yet do not present with inflammatory symptoms or clinical features of IBP or sacroiliitis [21, 51, 103]. A joint effort by ASAS and GRAPPA is underway to better define axial involvement in PsA through a prospective study [103, 104]. It also remains to be seen how data obtained from new therapies will affect refinement of treatment guidelines. The 2019 update to the EULAR recommendations for management of PsA now contains language noting that IL-17 inhibitors may be preferred over TNFis in the presence of relevant skin involvement, and that therapies targeting the IL-12/23 axis are not indicated for patients with axial involvement [51]. GRAPPA bases their recommendations on whether patients are biologic naive (strong recommendations for NSAIDs, physiotherapy, simple analgesia, and TNFis) or have an inadequate response to bDMARDs (strong recommendations for physiotherapy and simple analgesia; conditional recommendations for NSAIDs, TNFis, IL-12/23 inhibitors, and IL-17 inhibitors) [93]. However, phase 3/4 clinical trials for different bDMARDs and targeted synthetic DMARDs are ongoing, including the IL-17A inhibitor secukinumab (NCT02721966 [MAXIMISE]; completed June 2019) and the oral JAK inhibitor tofacitinib (NCT04062695 [PASTOR]; expected to be completed June 2022) [105, 106]. In the phase 3b, double-blind, placebo-controlled, multicenter, 52-week MAXIMISE trial, secukinumab (150 and 300 mg) provided rapid and significant improvement in ASAS20 response through week 12 in patients with axPsA with an inadequate response to NSAIDs [68]. Additionally, at week 52, secukinumab improved clinical and imaging outcomes among patients with axPsA [107]. No interim results have been published for the PASTOR trial [106]. A trial evaluating the impact

of secukinumab on bone health and metabolism is ongoing in patients with AS, which may help provide additional information on bone loss and remodeling among all patients with axial involvement [108]. Improved management and treatment adherence may reduce the unmet need and disease burden of PsA, particularly a patient's mental and physical health, employment, and healthcare utilization [109].

Another unanswered question is whether and to what extent MBP can confound treatment for PsA and what treatment strategies are available for patients with PsA and concurrent MBP. Improved doctor–patient communication is needed to establish realistic goals of care and treatment and to determine whether a patient's back pain has a mechanical or inflammatory origin. Last, a better understanding of the various mechanisms of pain is required, including central sensitization and osteoarthritis, correlation of physical examination with advanced imaging (e.g., ultrasound, MRI), and standardized characterization and measurement of PsA domains [110]. In chronic painful disorders such as PsA, pain stems not only from inflammation and mechanical soreness but from a myriad of mechanisms, including central sensitization—an amplification of neural signaling that leads to pain hypersensitivity [111]. Similarly, osteoarthritis—once thought to be a disease caused by “wear and tear”—is now recognized as low-grade inflammation [112] and possibly shares characteristic features with PsA [113]. Indeed, the mechanisms underlying chronic pain states, such as axPsA, are thought to differ from those underlying acute pain [114].

Multimorbidity, the coexistence of  $\geq 2$  conditions in an individual, is common in axSpA and is associated with more severe disease [115]. However, no published studies on the effects of multimorbidity on axPsA outcomes are currently available.

Finally, clearer education of back pain, communication, and screening approaches (including development of cross-specialty clinics and standardized identification protocols) are needed for rheumatologists, dermatologists, and primary care providers caring for patients with PsA [110].

## EXPERT COMMENTARY

Recognizing and diagnosing axial involvement, either within PsA or independent of it, early in its disease course is challenging, and the diagnosis is often made long after symptoms initially begin. Collaboration and communication between clinicians and their patients may lead to timelier diagnosis with early referral and treatment, which is the goal. This topic is of continual interest to our field because of its very debatable, at times conflated, and unfortunately delayed diagnosis. In the primary care setting, there is a large prevalence of back pain that resolves in a short period of time with conservative management. In the rheumatological setting, demands are much more stringent and require a more specific approach.

There are numerous additional variables to be considered when eliciting a history for potential inflammatory back pain. Is there any family or personal history of AS, psoriasis, uveitis, or inflammatory bowel disease? Is there any secondary history of past or present spontaneous pain or tenderness at the insertion sites of the Achilles tendons or plantar fascia at the calcaneus? Is back pain improved significantly with NSAIDs? Is there any history of spontaneous joint effusions? Is there any history of soft tissue differential such as fibromyalgia? Is there any history of hypermobility in younger patients (e.g., differential Ehlers–Danlos)?

Key takeaways to identify or questions to elicit from patients when assessing for IBP, with or without an established diagnosis, include history or present symptoms of spinal pain in back, dorsal, or cervical regions, with at least four of the following: (a) onset before age 40 years; (b) insidious onset; (c) pain relief with exercise or activity, not improved by rest; (d) associated with morning stiffness or alternating buttock pain; (e) duration of at least 3 months; or (f) pain at night with improvement upon awakening. If  $\geq 4$  of these criteria are fulfilled, and no other diagnosis can be considered in patients displaying PsA symptoms regardless of treatment status, then a referral to a rheumatologist must be made without further delay. In this instance, consider the patient with PsA who develops IBP in later years after he/she

has been diagnosed and treated with not entirely comprehensive therapy. For example, a 56-year-old patient with PsA/psoriasis receiving methotrexate, which does not seem to be effective in axPsA [116] and NSAIDs for years whose symptomatology vastly improves after introduction of effective targeted biologic DMARD treatment addressing IBP based on the above criteria.

## CONCLUSIONS

The presence of axial involvement is a marker of PsA severity. Therefore, recognizing axial involvement may help identify those patients who are candidates for more aggressive and appropriate therapy that effectively treats the complete spectrum of PsA, including axial disease. However, clinicians are still debating the definition of axPsA, how to screen patients, and when to initiate treatment. Few effective first-line treatments specifically for axPsA are available, mainly due to the lack of supporting evidence. EULAR and GRAPPA recommend bDMARDs for active axPsA that insufficiently responds to NSAIDs or TNFis, but most therapies—based on the quality and the range of available data—are only conditionally recommended [51, 93]. Clinical trials studying the efficacy of bDMARDs and targeted synthetic DMARDs for axPsA are ongoing [105, 106], and the results have the potential to change the treatment landscape and influence recommendations for managing axPsA. Chronic IBP is the most prominent feature of axPsA and is thought to play a key role in early identification of disease. It is important to differentiate IBP from MBP based on key characteristic features and to realize that IBP is a key component of other diseases unrelated to PsA.

The summary of available evidence highlights the importance of appropriate and timely screening of IBP, the difficulties and limitations of differential diagnoses and treatment, and unmet needs in axPsA. Additional data regarding the use of therapies targeting the Th17 axis in patients with axPsA, as well as findings from ASAS and GRAPPA on defining classification criteria for axPsA, are eagerly anticipated.



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**Compliance with Ethics Guidelines.** This article is a review of previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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