RHEUMATOLOGY NURSE
PRACTICE

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- How are the SpAs thought to develop and progress in patients?
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- How does juvenile SpA differ from SpA in adults, and what are some of the unique ways it is typically treated?

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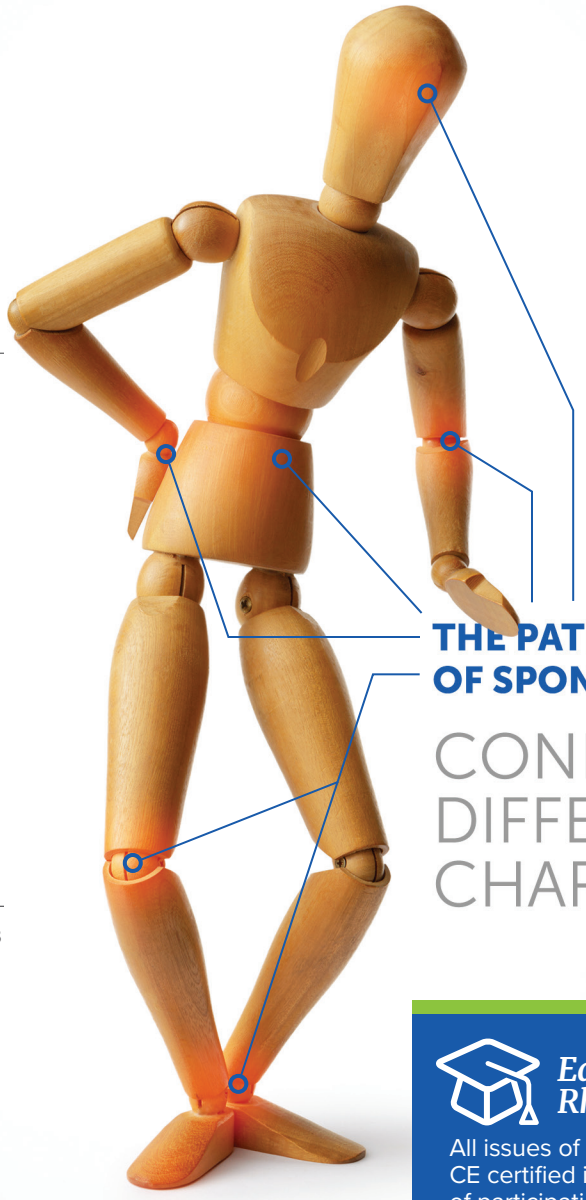

THE PATHOPHYSIOLOGY OF SPONDYLOARTHRITIS:

CONNECTING AND DIFFERENTIATING CHARACTERISTICS

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This activity has been designed to meet the educational needs of nurses and nurse practitioners. Other healthcare providers may also participate.

ACTIVITY DESCRIPTION

In this issue of *Rheumatology Nurse Practice*, we will examine new insights into the pathophysiology of spondyloarthritis (SpA) that have led to changes in disease classification systems. This issue will also explore how the common underlying pathology of SpA subtypes leads to the diverse clinical manifestations.

LEARNING OBJECTIVES

After participating in the activity, learners should be better able to:

- Identify the spectrum of SpA subtypes, along with specific characteristics that differentiate the subtypes most commonly seen in rheumatology practices
- Differentiate axial from peripheral SpA
- Summarize genetic and environmental factors that are thought to play a role in the development of SpA
- Assess the importance of weight loss in altering the clinical course of patients with psoriatic arthritis

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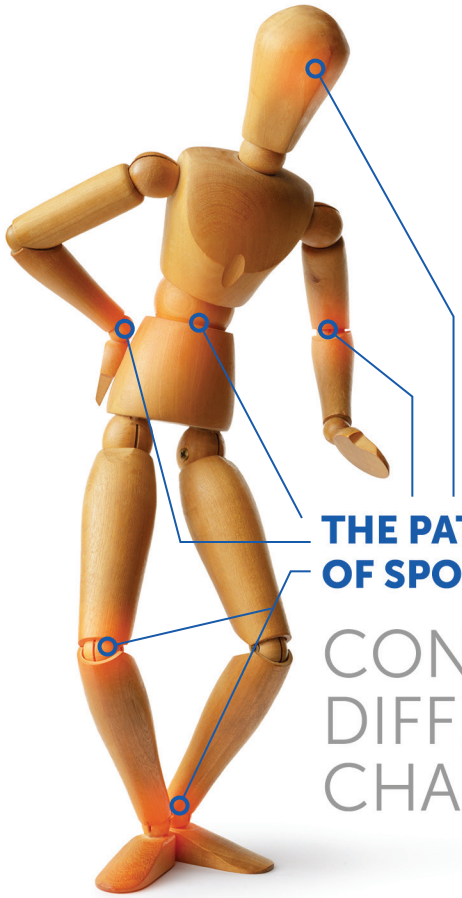


THE PATHOPHYSIOLOGY OF SPONDYLOARTHRITIS: CONNECTING AND DIFFERENTIATING CHARACTERISTICS

Spondyloarthritis (SpA) describes the family of heterogeneous systemic inflammatory disorders that affect the axial and peripheral joints.[1] Confusion over terminology has been a barrier to better understanding these conditions, which over time have been referred to collectively as seronegative arthritis, spondyloarthritides, spondyloarthropathies, and, most recently, have been abbreviated as SpA.[2]

As our understanding of the clinical, genetic, and pathogenic characteristics of these conditions has improved, the naming and classification systems have also evolved. The Assessment of Spondyloarthritis International Society (ASAS), which sets the classification criteria for these conditions, recommends using the term "spondyloarthritis" in current practice. There is also a movement to update the naming convention around ankylosing spondylitis (AS)—the prototypical SpA subtype—to better reflect its place in the spectrum of SpA.

Defining the Spectrum of SpA

The SpA subtypes share many overlapping features, making it challenging to differentiate between individual conditions. The spectrum of SpA subtypes include the following:

- Axial SpA, which is further categorized as either nonradiographic axial SpA (nr-axSpA) or radiographic axial SpA (also called AS)
- Enteropathic arthropathy, a form of arthritis associated with inflammatory bowel diseases (IBDs) such as Crohn's disease and ulcerative colitis

Drug Names Included Within This Supplement

GENERIC	BRAND
Adalimumab	Humira
Infliximab	Remicade
Etanercept	Enbrel
Golimumab	Simponi
Abatacept	Orencia
Certolizumab pegol	Cimzia
Tofacitinib	Xeljanz
Ustekinumab	Stelara
Secukinumab	Cosentyx
Guselkumab	Tremfya
Risankizumab	*TBA*
Brodalumab	Siliq
Ixekizumab	Taltz
Apremilast	Otezla

- Psoriatic arthritis (PsA)
- Reactive arthritis (ReA)
- Undifferentiated SpA, which includes disorders that do not fulfill the diagnostic criteria of the other SpAs

For patients with suspected SpA, the first step in differential diagnosis is to identify whether the clinical features are predominantly **axial** or **peripheral** (see Figure 1).[3] Separate classification criteria for axial and peripheral SpA are discussed in the following sections.[3,4] For additional details on the diagnostic criteria for the SpAs, refer to the *Core Curriculum for Rheumatology Nursing* available on the Rheumatology Nurses Society website.

Axial SpA: One Disease or Two?

Axial SpA is a chronic inflammatory condition characterized by enthesitis, new bone formation, and fusion (ankylosis) of the sacroiliac joints and spine.[1] The modern era of attempting to classify axial SpA started in 1984, when the modified New York criteria outlined the clinical and radiographic features of AS.[5] Within this system, radiographic evidence of sacroiliitis is the defining feature of AS.[5] The main drawback of this definition, however, is that patients can have clinical symptoms for up to 10 years before structural damage is advanced enough to meet the radiographic criteria for AS.[6] Meanwhile, diagnosis and treatment are delayed as the underlying disease continues to progress.

To facilitate the earlier recognition of these patients, the ASAS developed a new classification system in 2009.[4] As part of this new system, the ASAS introduced the term "axial spondyloarthritis" (axial SpA) to describe a wider spectrum of patients, including those with and without radiographic evidence of sacroiliitis.

Under the ASAS system, patients can meet the criteria for axial SpA through 2 routes.[4] The **imaging arm** requires the presence of sacroiliitis on standard radiography or magnetic resonance imaging (MRI) plus at least 1 clinical feature of SpA. These criteria echo the modified New York criteria for AS, with the addition of MRI as an option for imaging. In the ASAS system, axial SpA with radiographic damage is called radiographic axial SpA (also called AS). The **clinical arm** requires the presence of a positive HLA-B27 test plus at least 2 additional clinical features of SpA. These patients are classified as having non-radiographic axial SpA (nr-axSpA).[4]

While the ASAS criteria introduced a mechanism for recognizing patients with nonradiographic disease, the classification system did little to settle the debate about the true nature of axial SpA. Some experts argue that nr-axSpA is a form of "early AS," with nr-axSpA and AS describing different stages of the same underlying disease process. Others regard nr-axSpA as a distinct disease, with its own etiology and prognosis. Understanding how these conditions relate to each other has important implications for monitoring and treatment.

Radiographic Conversion

One approach to this puzzle involves examining rates of conversion from nr-axSpA to AS over time. In one recent long-term epidemiologic study, 83 patients with newly diagnosed nr-axSpA were followed for up to 15 years.[7] During this time, 26% of patients were reclassified as having progressed to AS. The estimated likelihood that patients would keep their original nr-axSpA diagnosis and **not** progress to AS after 5, 10, and 15 years was 93.6%, 82.7%, and 73.6%, respectively. Therefore, the initial diagnosis of nr-axSpA seemed to correctly reflect a long-term stable condition for most patients and did not signal an early form of AS.

In this study, however, the imaging tools used to monitor patients with nr-axSpA influenced the disease classification over time.[7] Compared with patients who were monitored with pelvic radiography only, those who underwent a pelvic MRI at any point during follow-up were significantly more likely to be reclassified as having progressed to AS (17% vs. 28%). This

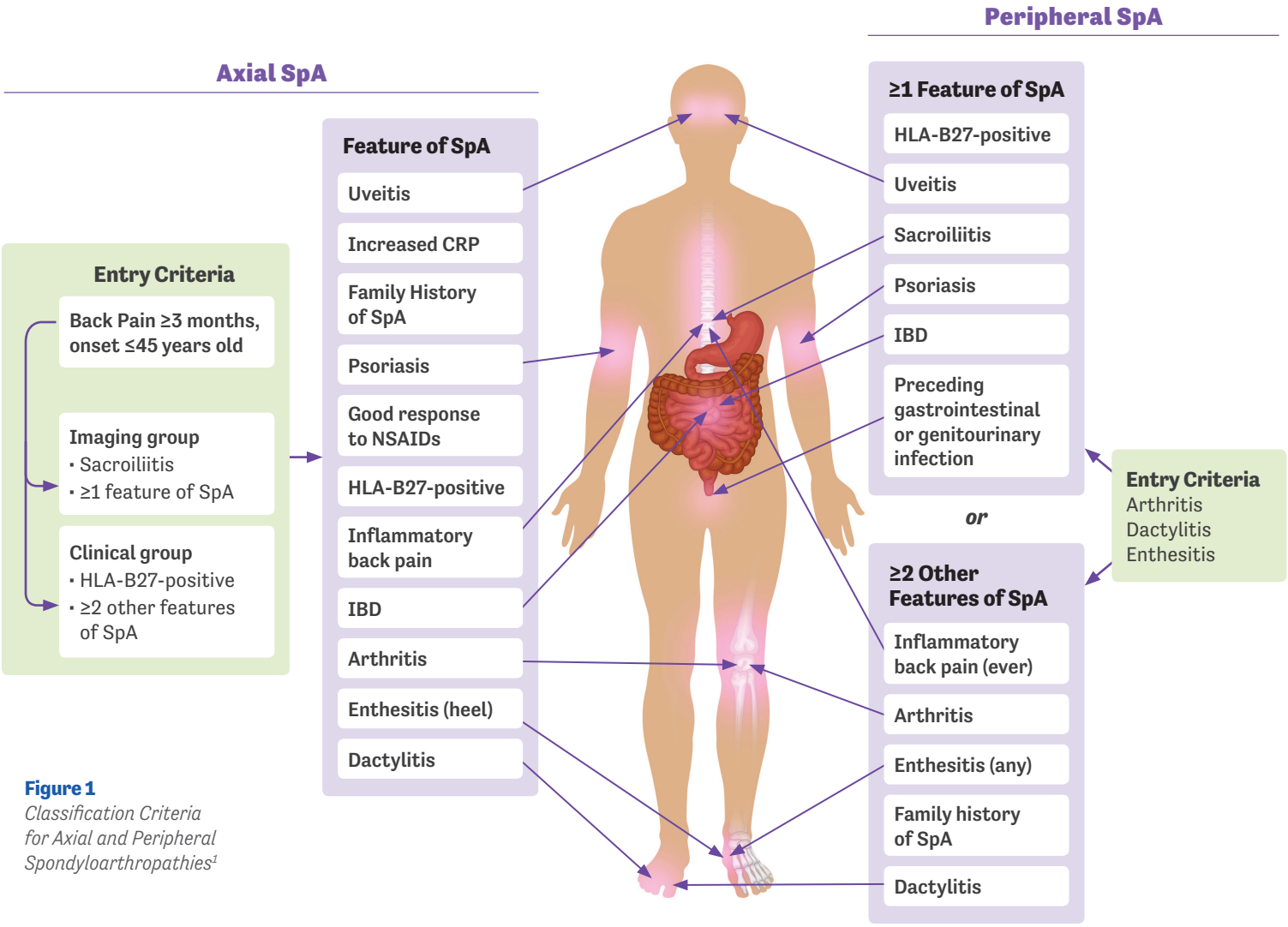


Figure 1
Classification Criteria for Axial and Peripheral Spondyloarthropathies[1]

CRP, C-reactive protein; HLA, human leukocyte antigen; IBD, inflammatory bowel disease; NSAID, nonsteroidal antiinflammatory drug; SpA, spondyloarthropathy.

finding suggests that long-term monitoring with pelvic radiographs alone may underestimate the development of radiographic sacroiliitis, the key criterion for reclassification to AS. In other words, patients with nr-axSpA may be progressing to AS more often and more rapidly than standard imaging tools are able to detect.

Overlap of Clinical Characteristics

One of the dangers of painting nr-axSpA as "early AS" is that clinicians may equate "early AS" with "lesser AS" and lose a sense of urgency around treatment. Patients with nr-axSpA have equal levels of disease activity and pain as patients with AS, and may equally benefit from treatment.[8] The degree to which the clinical characteristics of nr-axSpA and AS overlap may clarify treatment priorities. In a meta-analysis of patients with nr-axSpA (n=1,242) and AS (n=2,236), the main difference between groups involved the gender distribution of patients (see Table 1).[9] The gender split was roughly equal among patients with nr-axSpA (47% male, 53% female), while patients with AS were predominantly male (70% male, 30% female). The prevalence of HLA-B27 was similarly high in both groups, with approximately 78% of all patients testing positive for the allele. This does, however, demonstrate that more than 20% of patients with SpA will not have a positive HLA-B27 test; its absence should not, therefore, rule out a diagnosis of SpA.

Patients in both groups experienced peripheral manifestations at similar rates, with arthritis in approximately 28-30%, enthesitis in 29-35%, and dactylitis in 6% of all patients. Among extraarticular manifestations, patients in both groups also had similar rates of psoriasis (10-11%) and IBD (4-6%). Uveitis was the only feature that

Table 1
Clinical Features of Non-Radiographic Axial Spondyloarthritis and Ankylosing Spondylitis[9]

Characteristic	Non-radiographic axial SpA (n=1242)	Ankylosing Spondylitis (n=2236)
Male patient	46.8%	70.4%
HLA-B27	77.4%	78.0%
Arthritis	27.9%	29.7%
Enthesitis	35.4%	28.8%
Dactylitis	6.0%	6.0%
Psoriasis	10.9%	10.2%
IBD	6.4%	4.1%
Uveitis	15.9%	23.0%

IBD, inflammatory bowel disease; SpA, spondyloarthritis.

differed significantly between groups, occurring more frequently in patients with AS. Overall, 23% of patients with AS had ever had a diagnosis of uveitis, compared with 16% of patients with nr-axSpA.[9]

Peripheral SpA

Conditions under the peripheral SpA umbrella include PsA, ReA, enteropathic arthropathy, and undifferentiated SpA.[3] In 2011, the ASAS introduced new classification criteria for the peripheral SpA subtypes.[3] In this system, patients with predominantly peripheral features (arthritis, dactylitis, and/or enthesitis) should be evaluated for peripheral SpA. The presence of 1 or more of the following features fulfills the criteria for peripheral SpA:

- HLA-B27
- IBD
- Psoriasis
- Uveitis
- Sacroiliitis
- Recent gastrointestinal (GI) or genitourinary (GU) infection

Patients without these features can also meet the criteria for peripheral SpA when any 2 or more of the following are present: history of inflammatory back pain, family history of SpA, and, when not already accounted for by the initial entry criteria, arthritis, dactylitis, and enthesitis.[3]

Axial and Peripheral SpA: Comparison of Features

Given the overlap of symptoms that can be shared by patients with peripheral and axial SpA, it can be challenging to appreciate how these conditions differ in real-world practice. One recent prospective analysis compared disease features and clinical characteristics among 377 patients who were newly diagnosed with axial or peripheral SpA (Table 2).[10] The study included patients who presented with inflammatory back pain, asymmetrical arthritis, and other features suggestive of SpA across a network of rheumatology clinics during a 3-year period. After applying the ASAS classification criteria, 291 patients (77%) were diagnosed with axial SpA and 86 patients (23%) were diagnosed with peripheral SpA. Among those with axial SpA, 109 had AS and 182 had nr-axSpA.

Patients with peripheral SpA were referred to rheumatology more quickly than those with axial SpA. The median duration between symptom onset and specialty referral was 9.3 months for those with peripheral symptoms compared with 13 months for those with axial disease. The distribution of disease features also differed between groups. Patients with peripheral SpA were significantly more likely than those diagnosed with axial SpA to have enthesis, psoriasis, dactylitis, and IBD. Patients with peripheral SpA were also significantly less likely to test positive for HLA-B27 than those with axial SpA (32.6% vs. 75.3%, respectively).[10]

The extent of disease activity, as measured by a range of composite scores, was largely similar in both patient groups. However, patients with peripheral SpA scored lower on the patient's global assessment of disease activity. In regard to quality of life issues, patients with peripheral SpA were more than twice as likely as those with axial SpA to report a temporary work disability (20.9% vs. 8.9%, respectively). In contrast, when measured with tools developed specifically for patients with AS, patients with axial SpA showed a greater degree of functional impairment and significantly worse quality of life than those with peripheral SpA.[10]

The prevalence of cardiovascular risk factors also differs between axial and peripheral SpA. In a study of 3,984 patients with SpA, the overall rate of current or former smoking was approximately 30%,

Table 2
Comparison of Clinical and Disease Features in Axial and Peripheral Spondyloarthritis[10]

Characteristic	Axial SpA (n = 291)	Peripheral SpA (n = 86)	*P* Value
Age	32.0 years	32.8 years	NS
Male patients	65.6%	58.1%	NS
Time from symptom onset to rheumatology referral	13.0 months	9.3 months	<0.001
Disease Features			
Enthesitis	19.6%	50.0%	<0.001
Psoriasis	11.3%	32.6%	<0.001
Dactylitis	5.5%	32.6%	<0.001
IBD	3.1%	11.6%	0.001
Family history	34.7%	36.0%	NS
HLA-B27 positive	75.3%	32.6%	<0.001
IL-17 Pathway Inhibitors			
Swollen-joint count	0.3	1.4	<0.001
CRP	10.8 mg/L	13.7 mg/L	NS
ESR	13.6 mmHg	14.1 mmHg	NS
BASDAI	3.8	3.5	NS
BASFI	2.35	1.68	0.01
VAS (0-100), physician global assessment of disease activity	29	24	NS
VAS (0-100), patient global assessment of disease activity	42	31	<0.01
Temporary work disability	8.9%	20.9%	<0.01
ASQoL	5.89	4.39	0.03

ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; NS; nonsignificant; SpA, spondyloarthritis; VAS, visual analog scale.

regardless of SpA subtype.[11] Compared with patients with peripheral SpA, however, those with axial SpA had a significantly lower prevalence of high blood pressure (34% vs. 19%), dyslipidemia (28% vs. 14%), and diabetes (8.5% vs. 4.3%). Patients with axial SpA were also less likely than those with peripheral SpA to have ischemic heart disease (7.0% vs. 2.4%).[11] These findings demonstrate that the axial and peripheral SpA criteria identify truly distinct patient populations, with significant differences beyond the core clinical features of SpA.

EPIDEMIOLOGY OF SpA

Assessing the epidemiology of SpA is challenging given evolving disease classifications and ever-changing terminology in population-based studies. For instance, nr-axSpA has been recognized as a disease entity only since 2011, and major epidemiologic studies are still catching up.[3]

In the United States, the estimated prevalence of SpA is 0.9%, corresponding with an estimated 1.7 million patients.[12] The pooled prevalence of all SpA subtypes varies about 8-fold around the world, from 0.2% in Southeast Asia to 1.6% in Northern Arctic regions (see Table 3).[13] The prevalence of SpA in different regions, and among descendants from those regions, tends to rise and fall with the background prevalence of HLA-B27. For instance, among patients of European descent, the prevalence of HLA-B27 and AS is approximately 8.0% and 0.5%, respectively.[13] Among African-American patients, the prevalence of both HLA-B27 and AS is slightly lower.[12,14]

Most patients with axial SpA are in their 30s at diagnosis. On average, symptoms manifest 5 years earlier for patients with HLA-B27-positive disease than for those with HLA-B27-negative axial SpA. Patients with AS are predominantly male, with a male-to-female ratio of approximately 2:1-3:1. By comparison, nr-axSpA is equally common in men and women.[9,14,15]

PATHOGENESIS OF SpA

Among the SpA subtypes, the pathogenesis of AS is best understood. The development of AS requires 2 key elements: 1) a genetic background that makes patients susceptible to the disease; and 2) a specific type of environmental (microbial) insult (see Figure 2).[14]

Genetic Predisposition

Approximately 90% of the susceptibility to axial SpA is inherited and can be attributed to a patient's genetic background.[14] Estimates suggest that roughly 20% of the genetic predisposition for axial SpA involves polymorphisms of the major histocompatibility complex (MHC), most often the B27 locus of the HLA-B gene.[16] Non-MHC genes account for another 7% of the genetic risk for SpA. The remaining genetic abnormalities, accounting for more than 70% of the heritable risk for SpA, have yet to be identified.[16]

MHC Genes: HLA-B27

Although HLA-B27 is highly prevalent in some SpA subtypes—more than 90% of patients with AS carry this marker—its presence alone is not sufficient to explain the genetic risk of SpA.[17] Multiple other HLA subtypes are also involved in the genetic predisposition for SpA, including HLA-B40, HLA-B51, HLA-B7, HLA-A2, and HLA-DPB1.[14] Although the exact mechanisms linking HLA-B27 to SpA pathogenesis are not clear, several hypotheses have been gaining support.

Table 3
Global Prevalence of SpA Subtypes[13]

	Prevalence Range
Ankylosing spondylitis	0.02% to 0.35%
Psoriatic arthritis	0.01% to 0.19%
Reactive arthritis	0% to 0.2%
SpA related to IBD	0% to 0.1%
Undifferentiated SpA	0% to 0.7%

IBD, inflammatory bowel disease; SpA, spondyloarthritis.

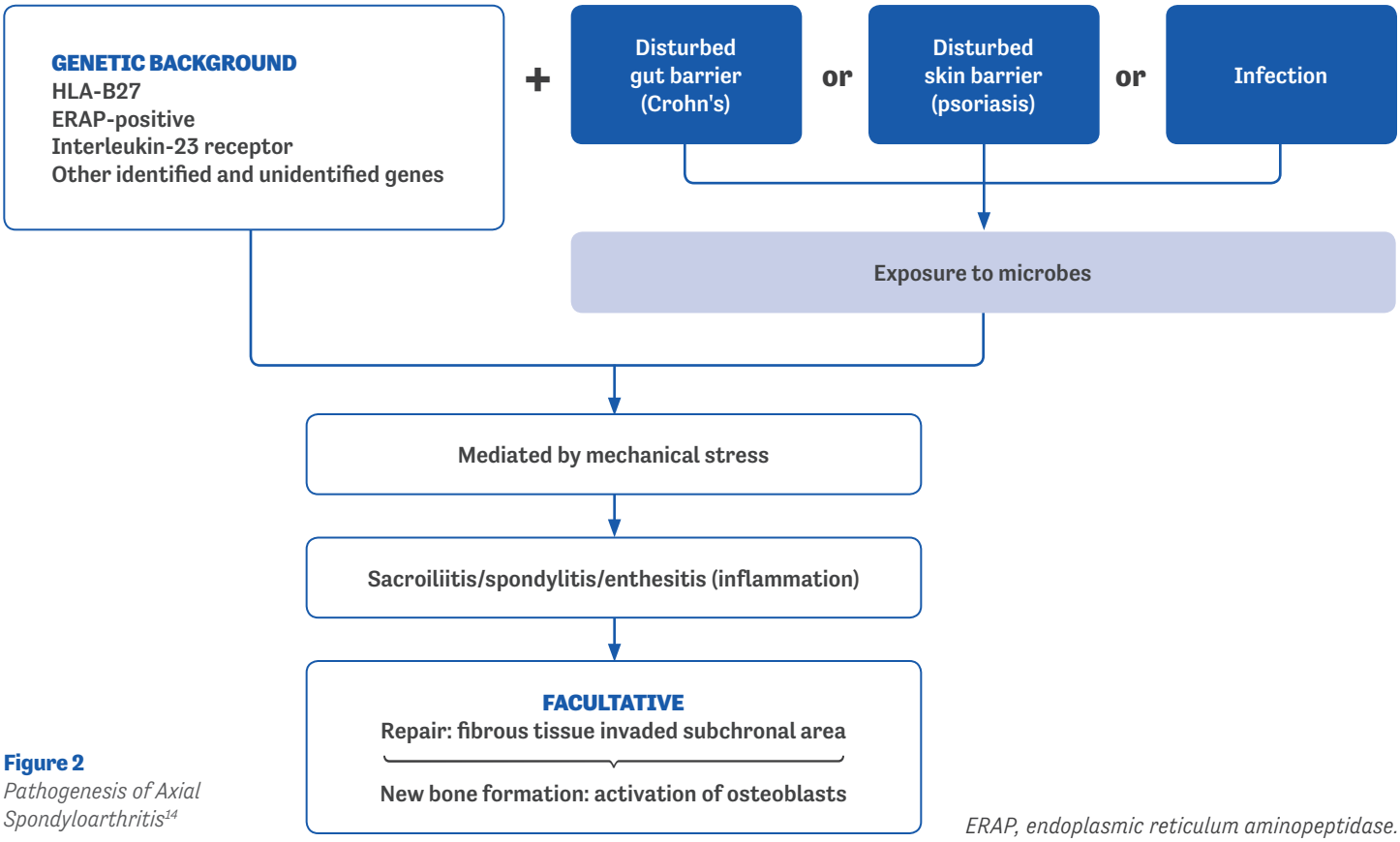


Figure 2
Pathogenesis of Axial Spondyloarthritis[14]

ERAP, endoplasmic reticulum aminopeptidase.

Two of the most popular are the gut microbiome hypothesis and the protein misfolding hypothesis.

The **gut microbiome hypothesis** focuses on HLA-B27 antigens expressed on gut epithelial cells and their interaction with gut bacteria. The gut microbiome describes the unique population of trillions of commensal microbial cells that exist within the gut of each individual. Changes in the gut microbiome can compromise the integrity of gut epithelial cells, leaving patients vulnerable to infection and inflammation. Microscopic gut inflammation is common in SpA, affecting up to 50% of patients with early axial and peripheral disease.[18] In the gut microbiome model of SpA pathogenesis, the presence of HLA-B27 directs the selection of a gut microbiome by shifting the gut immune system in favor of the IL-23/IL-17 pathway.[19]

According to the **protein misfolding hypothesis**, HLA-B27 triggers the inflammatory cascade due to a mishap in intracellular HLA-B27 assembly.[20] The HLA-B27 molecule is assembled within the endoplasmic reticulum, where the HLA-B27 heavy chain proteins have a tendency to misfold. When misfolded HLA-B27 proteins accumulate in the endoplasmic reticulum, the intracellular autophagy response is activated to clean up the mess. In turn, autophagy activates the IL-23/IL-17 pathway. One study found evidence of HLA-B27 protein misfolding in the gut epithelial cells of patients with AS, bringing the two leading hypotheses together.[21] The true mechanistic relationship between HLA-B27 and SpA is likely multifactorial, involving a range of genetic factors, cell types, and immune system pathways.[22]

Non-MHC Genes

As the techniques for genetic analysis become more sophisticated, researchers are able to identify additional low-prevalence polymorphisms with critical roles in the pathogenesis of SpA. Identifying these genes provides further clues into the pathologic mechanism of disease. Beyond genes of the MHC region, the remaining hereditary burden of SpA is from genes involved in intracellular antigen processing and cytokine production.

Genes in the **IL-23/IL-17 pathway** are central to the pathogenesis of SpA.[23] Variants of the IL-23 receptor (IL-23R) gene increase the risk of psoriasis and IBD.[24,25] Additional genes involved in the regulation of IL-23/IL-17 cytokine signaling pathway are also active in AS, psoriasis, and IBD.[23] The consistent association of these genes across axial and peripheral SpA subtypes supports a shared pathologic mechanism of impaired cytokine production.[23]

The **endoplasmic reticulum aminopeptidase (ERAP)** gene encodes a family of enzymes (ERAP1 and ERAP2) that are involved in preparing proteins that will become antigens and trigger an immune response.[14] Certain polymorphisms of ERAP1 are present in patients with AS, but only in those with HLA-B27-positive disease.[26] The link between ERAP1 and HLA-B27 provides additional support for the protein misfolding hypothesis that suggests that HLA-B27 disrupts intracellular antigen processing by getting stuck in the endoplasmic reticulum.[26]

Environmental Triggers

Up to 20% of patients with AS are diagnosed with comorbid psoriasis, IBD, or reactive arthritis. Many other patients with AS may have subclinical forms of these skin, gut, and post-infectious joint conditions. The observation of the frequency of these conditions occurring together led to the current mechanistic model of AS. In this model, the pathogenesis of AS begins with barrier damage that allows an infectious agent to penetrate the skin (psoriasis) or lining of the gut (IBD, Crohn's disease). This microbial exposure triggers an immune system response that, in patients who are genetically predisposed to AS, progresses toward the characteristic inflammation and structural damage of axial SpA.[14]

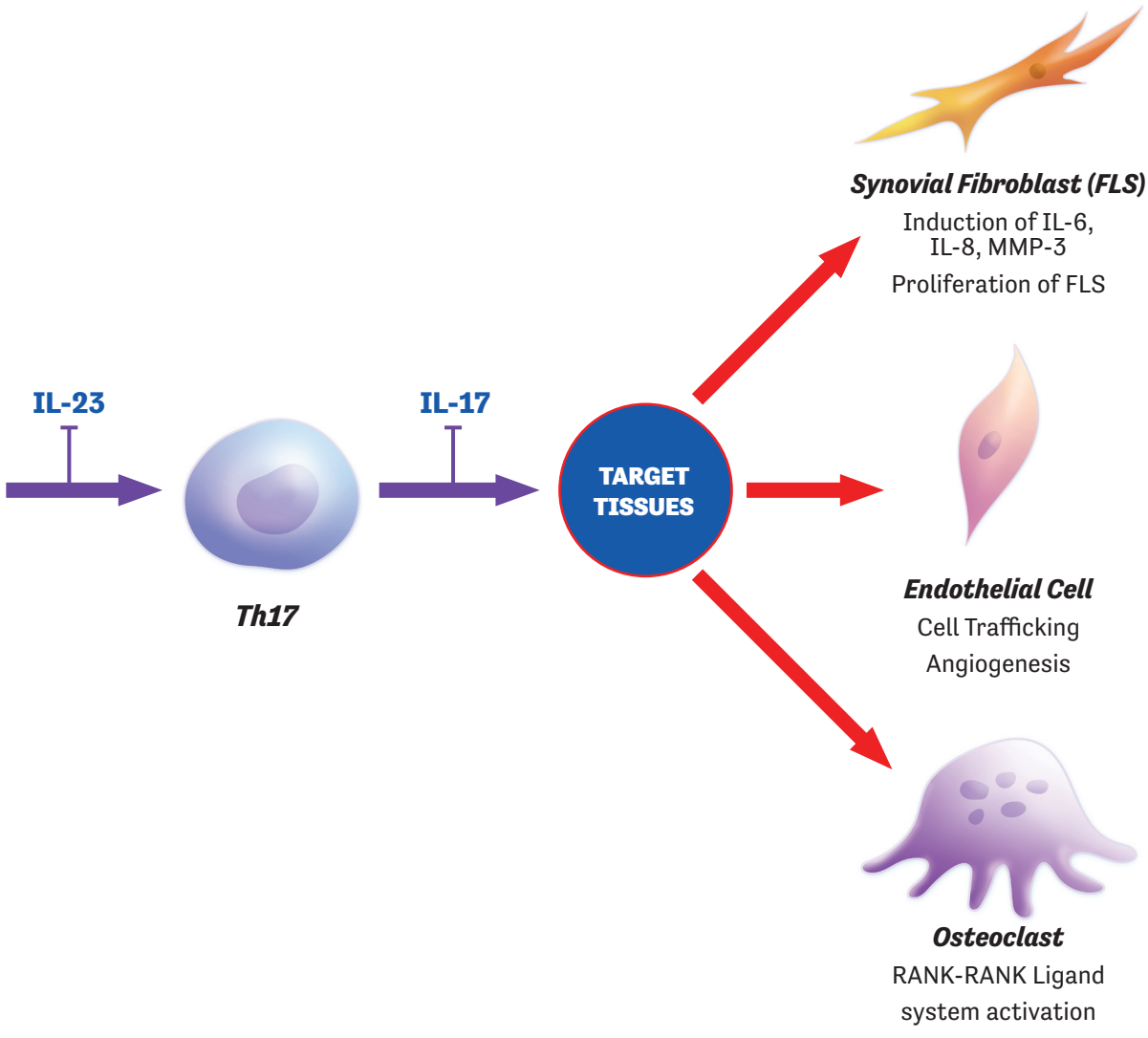
Role of Cytokines

Once the pathogenesis of axial SpA is underway, several cytokines and signaling pathways are responsible for keeping the snowball of proinflammatory events moving forward.

IL-23/IL-17

As discussed in the **Genetic Predisposition** section of this issue, the IL-23/IL-17 axis is the major driver of the pathogenesis of SpA. IL-23 and IL-17 are often described together because their action is closely linked (see Figure 3).[27] First, IL-23 triggers the activation, differentiation, and proliferation of a particularly destructive population of T cells, the Th17 T cells. Next, activated Th17 T cells produce

Figure 3
The IL-23/IL-17 Pathway[27]



IL-17, another potent inflammatory cytokine. IL-17 acts on a range of cell types within joint tissues, including synovial fibroblasts, endothelial cells, and osteoclasts. The cumulative effect of IL-23, IL-17, and Th17 T cells in the joint leads to joint erosion, abnormal pannus tissue development, and new bone formation.[17,27]

Beyond activating Th17 T cells, IL-23 also directly targets other cell types. Cells expressing IL-23R are abundant at the interface between tendons and bone (the entheses), but are rarely found elsewhere along the tendon and bony tissues.[28] In animal models, there is a strong and highly specific correlation between serum IL-23 levels and enthesitis, a characteristic feature of AS.[28]

Given the central importance of the IL-23/IL-17 pathway to SpA, FDA-approved agents targeting IL-23 (ustekinumab) and IL-17 (secukinumab) are important therapeutic tools for controlling disease activity.[29] Several additional agents blocking the action of IL-23 (guselkumab, risankizumab) and IL-17 (brodalumab, ixekizumab) are currently under evaluation across SpA subtypes.

Tumor Necrosis Factor

In some cases, the strongest evidence that certain cytokines are active in the disease process involves the effectiveness of targeted therapies. Therapies targeting tumor necrosis factor (TNF) are a mainstay of biologic disease modifying anti-rheumatic drug (DMARD) therapy across SpA subtypes. All 5 of the currently available TNF-targeted therapies (infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol) are approved for the treatment of both AS and PsA.[1]

Other Pathways and Targets

The Janus kinase (JAK) signaling pathway is also involved in mediating the proinflammatory signals that drive the pathogenesis of axial and peripheral SpA subtypes. In August 2017, a U.S. Food and Drug Administration (FDA) panel recommended the approval of the first JAK inhibitor—tofacitinib—for the treatment of patients with PsA.[30] Tofacitinib is also under evaluation for the treatment of AS.[31]

As the center of the IL-23/IL-17 axis, T cells are an important therapeutic target in SpA.[27] Abatacept, a selective T-cell inhibitor that blocks the inflammatory flow of activated T cells, is an established biologic DMARD used to treat rheumatoid arthritis (RA) and juvenile idiopathic arthritis. In July 2017, abatacept's FDA-approved label was expanded to include the treatment of PsA.[32]

Apremilast, an oral small-molecule inhibitor of phosphodiesterase-4 (PDE4), is effective in patients with PsA, supporting a mechanistic role for PDE4 signaling in PsA pathogenesis.[1] The PDE4 pathway appears to be specific to PsA, however, as apremilast is not effective against the signs and symptoms of axial SpA.[33]

The vascular endothelial growth factor (VEGF) signaling pathway also appears active in SpA pathogenesis and may be a source of future therapeutic targets.[34]

Variable Clinical Course of SpA

The clinical course of SpA is highly heterogeneous across the axial and peripheral subtypes. Some of the signature features of axial SpA, PsA, and reactive arthritis illustrate this variability.

Axial SpA

In patients with axial SpA, inflammation begins at the entheses (ie, the insertion site of ligaments and tendons into bones) in the sacroiliac joints and the spine.[14] Mechanical stress exacerbates this inflammation and fuels its progression, particularly along the weight-bearing areas of the skeleton.[14] The inflammatory back pain associated with axial SpA has a slow and insidious onset, tending to initially present as dull and radiating from the lower back to the gluteal regions. Patients often report that back pain is worse in the morning and improves with activity.[35] Many patients with axial SpA will get out of bed multiple times throughout the night due to back pain; some will report needing to switch from the bed to the couch to the floor every 90 minutes to try to get comfortable. Signs and symptoms of axial SpA include redness, swelling, and warmth that extends above and/or below the affected joints. Patients may also experience inflammation that affects extraarticular structures such as the eye (uveitis), GI system, skin, and aortic valve.[1]

The initial signature feature of axial SpA is the formation of new bone in the sacroiliac joints; this eventually ascends to involve the cervical spine. The resulting spinal deformities limit spinal mobility.[35] Although the process of new bone formation is not well understood, it appears to begin with inflammatory lesions to the bone and cartilage degeneration.[14] The normal tissue-repair mechanisms are altered, and the attempted repair instead results in excess new bone formation.[14] Several biomarkers of structural damage have been identified in patients with axial SpA, including C-reactive protein (CRP), matrix-metalloproteinase-3 (MM3), and VEGF.

Monitoring CRP, MM3, and VEGF levels may identify patients who are at risk for radiographic progression.[14]

Environmental, genetic, and clinical risk factors contribute to radiographic progression in axial SpA.[36] In one study of 449 patients, 4.9% of patients progressed from nr-axSpA to radiographic axial SpA during the 2-year follow-up period. In a multivariate analysis, current smoking, HLA-B27 positivity, and evidence of inflammation of the sacroiliac joints on MRI at baseline was associated with a 3.3-fold, 12.6-fold, and 48.8-fold increase of progressing to radiographic axial SpA after 2 years, respectively.[36]

"Among all patients with AS, only one-third are managed by rheumatology providers..."

Psoriatic Arthritis

Although psoriasis is common among most patients with PsA, patients experience a range of effects on the peripheral joints, axial joints, tendons, fingers and toes, and nails.[1] Key differences between genders suggest differences in the underlying disease process. In one study of men (n=72) and women (n=115) with PsA, women tended to have a longer symptom duration, poorer physical activity, and more severe fatigue than men.[37] Women also had higher tender/swollen joint counts and DAS28 scores, indicating greater levels of joint-related disease activity. Conversely, men with PsA tended to have higher Psoriasis Area and Severity Index (PASI) scores than women, indicating more extensive psoriasis. Despite these differences, male and female patients in the study tended to experience the same risk of extraarticular features (eg, uveitis and iritis), the same articular pattern of affected joints, and the same degree of quality of life impairment related to PsA.[37]

Among risk factors that influence the clinical course of PsA, obesity has been shown to exacerbate the severity of both psoriasis and PsA. Conversely, weight loss can dramatically reduce the risk of psoriasis or PsA, as well as improve long-term prognosis for patients with existing disease.[38] In a recent Danish study, researchers evaluated the incidence of psoriasis and PsA risk among all Danish citizens (N=12,364) who underwent gastric bypass surgery between 1997 and 2012.[38] The mean patient age was 27.8 years at the time of surgery and 41.0 years at the time of the follow-up analysis. Compared with presurgical trends among candidates for weight-loss surgery, the risk of developing psoriasis decreased by 48% after patients underwent weight loss surgery. In addition, the risk of progressing to severe psoriasis fell by 66%, and the risk of developing PsA fell by 71% after weight-loss surgery. These findings highlight the strong link between obesity and poor outcomes related to psoriasis and PsA. For more of the effects of weight loss surgery on the clinical course of PsA, see the **Tackling a Weighty Subject** essay later in this issue.

Reactive Arthritis

ReA is triggered by an infectious agent that occurs outside of the joints (ie, it is not a form or result of joint infection). In most cases, ReA begins 1 to 4 weeks after contracting a GI or GU tract infection. The onset is acute, with 2 to 4 painful and swollen joints appearing over the course of a few days. The distribution of affected joints is typically asymmetric, and enthesitis, dactylitis, and inflammatory back pain are also common. Up to 50% of patients will also develop conjunctivitis, which is often a helpful diagnostic clue.[35]

ReA is self-limiting for most patients, resolving within 3 to 12 months. However, half of patients experience recurrent flares of arthritis, and 15% to 30% will develop chronic arthritis or sacroiliitis.[35]

Challenge of Early Diagnosis

Among all patients with AS, only one-third are managed by rheumatology providers, while the remaining patients are managed in the primary care setting.[39] Patients treated in rheumatology clinics tend to have features indicating more severe disease than those managed in primary care, including an earlier age at diagnosis (32 years vs. 35 years), as well as a higher prevalence of uveitis (34% vs. 22%), IBD (12% vs. 6%), and psoriasis (14% vs. 6%). Among the two-thirds of patients with AS who are managed by primary care providers, many have serious pathology and undertreated disease.[39]

Linking patients with AS to rheumatology providers remains a barrier to better outcomes.[39] In current practice, patients with axial SpA continue to face a delay of 2 to 5 years between symptom onset and diagnosis.[40,41] Some clinicians may still be waiting for radiographic changes, which take years to manifest in AS, and may never appear in those with

nr-axSpA. Another barrier to timely diagnosis involves the overwhelming number of patients with chronic back pain who are managed in the primary care setting and waiting for a rheumatology referral.[14]

To address this barrier, in 2015, the ASAS endorsed an early referral strategy for patients with suspected axial SpA.[42] The criteria apply to all patients who have had chronic back pain for at least 3 months and whose back-pain symptoms started before age 45 years. Patients who meet these initial criteria should be referred to a rheumatologist if at least 1 of the following additional features is present:

- Inflammatory back pain
- HLA-B27 positivity
- Sacroiliitis on imaging (if available)
- Peripheral manifestations (arthritis, enthesitis, dactylitis)
- Extraarticular manifestations (psoriasis, IBD, uveitis)
- Positive family history of SpA
- Good response to NSAIDs
- Elevated acute-phase reactant (erythrocyte sedimentation rate or C-reactive protein)

The ASAS early referral strategy for axial SpA has taken some criticism and may be refined over time. For instance, one recent study found that the "positive family history of SpA" criterion, which applies to first-degree and second-degree relatives, may be too broad.[43] While patients with chronic back pain and a positive family history of AS or acute anterior uveitis had an increased likelihood of axial SpA, those with a positive family history of other SpA subtypes (psoriasis, IBD, or reactive arthritis) did not.[43] Referring patients with a low likelihood of SpA defeats the purpose of streamlined referral criteria and contributes to the bottleneck that delays the diagnosis of patients with active but untreated disease.

Summary

Despite their diverse clinical presentations, the SpA subtypes share common triggers that ignite the disease process. Advances in the understanding of underlying genetic and pathogenic causes of SpAs have real consequences for clinical practice, beginning with how to classify the different subtypes of disease. The primary distinction between nr-axSpA and AS involves the presence of structural damage advanced enough to meet the definition of radiographic sacroiliitis—a goalpost that continues to move as imaging techniques improve. Ultimately, the goal of revising the SpA classification criteria is to improve the ability to diagnose patients who have historically been underrecognized and undertreated. New and emerging treatments are now available to target the specific inflammatory pathways most active in SpA—notably the IL23/IL17 signaling pathway—and change the prognosis for these patients. For additional details on the treatment of SpA, refer to our review earlier this year in *Rheumatology Nurse Practice* Volume 3, Issue 3.

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Tackling a Weighty Subject

by Jacqueline Fritz, RN, MSN, CNS, RN-BC

One of the most interesting parts of our jobs as rheumatology nurses—and one of the biggest challenges—is that our patients come in all shapes and sizes, each with a unique combination of symptoms and complaints for us to manage.

A recent patient of mine—JP—posed a novel challenge that required our team to think creatively and do some targeted research to come up with the best approach to his care.

JP came to our office 5 years after his dermatologist diagnosed him with psoriasis. He had been stable for several years on a regimen of weekly methotrexate (MTX) 15 mg, although he recently began having joint pain and stiffness, which brought him to our office. Approximately 30% of patients with psoriasis develop joint involvement within 5 years of their diagnosis,[1] so JP's appearance in our office wasn't what makes him notable.

What made JP a challenging patient was his sheer size. With a BMI >40 and weighing 315 pounds, JP was one of the larger (but certainly not the largest) patients who came into our office that month.

Overweight patients are at increased risk of both the development and progression of psoriatic arthritis (PsA). Excess adipose tissue can increase the presence of inflammatory markers such as tumor necrosis factor, interleukin-6, and leptin *(adipokines too)*. Obesity can also exacerbate cardiometabolic risk factors in patients with PsA and serve as a negative predictor of response to biologic agents.[2]

Fortunately, other than joint pain, JP had no other significant symptoms upon initial exam (no effusions or erosions). Adalimumab 40 mg biweekly was added to MTX, which controlled most of JP's joint pain as well as his psoriasis.

JP understood that being overweight carried several health risks. Soon after he came to our office, he began a liquid diet and lost 90 pounds over the course of several months. Unfortunately, like many yo-yo dieters, he put back on most of the weight when he returned to "normal eating" patterns. At that point, JP opted for a more permanent solution—a Roux-en-Y gastric bypass.

A Roux-en-Y gastric bypass is both a restrictive and malabsorptive procedure. It reduces the stomach to a restrictive gastric pouch that accepts only 20-30 cc of food. Alteration of the jejunal limb also promotes malabsorption by preventing the mixing of food and digestive enzymes.[3]

The surgery was a success, as JP lost nearly 130 pounds within 9 months. However, while beneficial for JP's life from many perspectives, the surgery presented a number of challenges related to the management of his PsA. By altering his body's absorption processes,

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JP was now at increased risk of anemia of chronic disease, vitamins B12, C, and D deficiency, and folate deficiency.[3] To reduce some of these risks, we started JP on a folic acid supplement and reinforced the need for him to exercise regularly.

Things were going extremely well for the first few months following JP's surgery. His weight loss was an obvious benefit, but we were also able to successfully manage his pain with limited alterations to his treatment regimen. His Psoriasis Area Severity Index (PASI) score was down to 0.3 (see Figure 1), indicating low disease activity.

Just as we began to feel that we had things under control, a complication arose: JP's insurance provider changed, and his co-pay for adalimumab was set to jump from $5 to $700 a month. Fortunately, we were able to switch JP to infliximab, another TNF inhibitor, that had a much lower co-pay. However, JP's disease started to flare more frequently, so we had him visit our infusion center every 6 weeks instead of the usual 8 weeks. We kept his dosage low at 200 mg, or 2.3 mg/kg, which is far below the recommended infliximab dose of 5.0 mg/kg in patients with PsA. After some initial hiccups, we were able to get JP's PASI score back down to 0.3.

A few months later, another challenge crept up when JP was diagnosed with squamous cell carcinoma of the lower lip. Skin cancer is a known risk of treatment with infliximab,[4] and so we stopped both the biologic and MTX until the lesion had been resected and completely healed, restarting only MTX at that time. Unfortunately, this was unable to control JP's arthralgia, although X-rays still showed the absence of effusions or joint damage.

The recent introduction of new injectable biologics to treat PsA with novel mechanisms of action has helped give us more options in patients like JP. Naturally, JP was fearful of the financial repercussions of a new addition to his treatment regimen after his earlier experience, but after some pointed discussions weighing the risks and benefits of various options, we started him on a low dose of apremilast, with the hope to titrate to the therapeutic dose of 30 mg BID.

Because apremilast is absorbed through the gastrointestinal (GI) tract, there may be initial related issues such as diarrhea and nausea, though these symptoms can subside with repeated exposure to the medication.[5] Unfortunately, JP's diarrhea became severe, and he lost an additional 10 pounds within 6 weeks of starting apremilast. His PsA flared as well, with a PASI score of 4.3 (see Figure 2) and C-reactive protein level of 29.5 mg/L (his acute phase reactants had previously always been within normal levels). Our best guess is that JP's bariatric surgery had altered the normal absorption pathway of apremilast—which we knew from the start was a possibility—and was causing his GI issues.

Figure 1
PASI Score Calculation

	Head	Arms	Trunk	Legs
Area *Scale of 0-100%*	<10%	<10%	<10%	<10%
Erythema (redness) *Scale of 0-4*	1	1	0	0
Induration (thickness) *Scale of 0-4*	0	0	0	0
Desquamation (scaling) *Scale of 0-4*	0	0	0	0
PASI = 0.3 (complete)				

This brought us back to infliximab, despite JP's recent skin cancer episode. We started him on the same low dose as before—200 mg—and monitored him carefully for any skin lesions. Since he had only been off of infliximab for approximately 3 months, we felt the likelihood of JP having developed any anti-drug antibodies was slight.

It has now been approximately 3 months since we restarted JP on infliximab. He's back up to his previous dose of 200 mg every 6 weeks, along with MTX 15 mg, daily folate, and desonide ointment 0.05%. JP's PsA is again stable, with his most recent PASI score back down to 0.3. Acute phase reactant levels are back to normal as well, and JP reports feeling fine.

We have gone through a variety of ups and downs with JP, and have been forced to nimbly adjust as his life situations have changed. What is best for our patients' rheumatic disease is not always what is best for their overall quality of life, and it's our responsibility to help patients evaluate the potential tradeoffs of specific medical interventions and adjust treatment plans to help meet their goals. JP is now in a much better place overall than he was when we first saw him, and is happier and healthier as an individual, which at the end of the day, is all that we can ask for.

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Figure 2
PASI Score Calculation

	Head	Arms	Trunk	Legs
Area *Scale of 0-100%*	10-29%	10-29%	<10%	<10%
Erythema (redness) *Scale of 0-4*	2	2	1	1
Induration (thickness) *Scale of 0-4*	1	1	1	1
Desquamation (scaling) *Scale of 0-4*	0	1	1	1
PASI = 4.3 (complete)				

LIVING WITH ANKYLOSING SPONDYLITIS:

One Patient's Journey

by Linda Grinnell-Merrick, MS, NP-BC

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I met JK a few years ago. She had come in for her regularly-scheduled infliximab treatment and was stunned to find out that her out-of-pocket costs for the biologic had gone up significantly since her husband had changed insurance. She started crying, telling our infusion nurse that there was no way that she could afford the co-pay. Our infusion nurse rushed into my office to ask if I could help her to manage this crisis. So began my role in a story of a truly amazingly and inspiring woman.

JK's road to diagnosis is quite familiar. She experienced lower back pain for many years before finally being referred to rheumatology at the age of 39. At her initial evaluation, she reported lower back pain that radiated down her buttocks. Pain improved with exercise. Daily morning stiffness lasted up to 1 hour with some peripheral joint stiffness, primarily involving the ankles. She had taken indomethacin for pain relief—it was initially effective but had not done much recently to blunt the pain. Adopted as a child, JK did not know about any potentially relevant family history.

On her initial physical exam, JK demonstrated limited lumber mobility on a Schober's test. Her occiput-to-wall distance was normal, chest expansion was slightly diminished, and she tested positive for sacroiliac (SI) joint dysfunction on a Patrick's test. She had tenderness through the lower spine, SI joints, and right elbow. Lab testing revealed that JK was HLA-B27 positive. An MRI demonstrated right sacroiliitis. We also had JK complete a baseline Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scoresheet (Figure 1); her score came back as a 6.0, indicating active disease.

Prior to coming to our office, JK was extremely active in the autism community (she has a son who is autistic), leading camps for children with autism and art nights for mothers caring for children with autism. JK also enjoyed a variety of outdoor activities, including yoga, gardening, and caring for her family. One of her biggest frustrations when we she first came to us was that her constant pain was forcing her from many of the activities she so enjoyed. During the span between referral and diagnosis, JK developed a mild-to-moderate case of depression and was started on an antidepressant.

To treat her overall pain, JK was initially started on etanercept, with about a 50% improvement in symptoms after 4 months. However, she continued to struggle with significant SI joint pain, and so our office made a referral to orthopedics for SI corticosteroid injections, which eventually helped relieve some of JK's symptoms in the short term.

Two years after JK started etanercept, it stopped having any beneficial effect on her symptoms. In addition to worsening lower back and SI joint pain, JK developed plantar fasciitis and Achilles tendonitis. We changed her to a regimen of infliximab and methotrexate, which provided significant benefit for many years and brings us back to the beginning of this story when JK and I met.

Due to the change in her husband's insurance, we were forced to change JK from infliximab to adalimumab, which fortunately also provided consistent and extended relief of JK's pain for several years. Her BASDAI score remained stable (Figure 2).

A few years ago, JK received a concomitant diagnosis of ulcerative colitis, which is uncommon but not unheard of in patients diagnosed with AS.[1] The worst, however, was yet to come. As I noted earlier, JK loves spending time outside in her garden. About a year ago, she developed sudden muscle pain and soreness a few hours after an afternoon outside, which she initially chalked up to a pulled muscle. Within 24 hours, however, JK could not get out of bed. Her husband took her to the emergency room and, within an hour, JK was in surgery, diagnosed with necrotizing fasciitis.

JK was hospitalized for 75 days; it was a life-and-death battle. JK underwent 30 surgeries during her hospitalization, including skin grafts over her right breast, shoulder, forearm, and flank (by the time

BASDAI Score Calculation	Figure 1	Figure 2
Medication	Indomethacin	Infliximab
Effectiveness of medicine on a ten point scale *(1 is not effective, 10 is very effective)*	4	8
Age	39	44
Gender	Female	Female
Pain on a ten point scale *(1 is none, 10 is the worst)* *Indicate level of ability with each of the following activities during the past week*		
Overall level of fatigue/tiredness	6	3
Overall level of AS neck, back, or hip pain	7	2
Overall level of pain/swelling in joints other than neck, back, or hips	5	3
Overall level of discomfort from areas tender to touch or pressure	6	2
Overall level of discomfort from time you woke up	6	2
How long does morning stiffness last from the time you woke up?	1.2 hrs	0.2 hrs
BASDAI Score	**6.0**	**2.3**

she was discharged, it looked like a shark had taken a bite off her right side). Additionally, JK had to have her right hand amputated at the wrist as well as her left index finger and the tips of several toes. JK coded twice during her hospitalization, but she survived. Two years later, no one is quite sure how JK developed necrotizing fasciitis—our best guess is that she was bit by some sort of exotic bug while gardening.

JK recently celebrated her 50th birthday and is again active in the community, sharing her story with neighbors and strangers alike and caring for her family and home. Of course, she continues to live with AS, which fortunately is relatively quiescent without biologic therapy, as we are hesitant to reintroduce any specific biologic (she is back on indomethacin and has received several corticosteroid injections). Our team feels that our best future option, if needed, is a biologic with a different mechanism of action, such as an IL-12/23 or IL-17 inhibitor.

JK's story is truly an inspiring example of faith, strength, and perseverance. I am honored to be part of her care team and amazed by this woman who, despite all the pain, suffering, and loss she has endured, keeps on living life to its fullest. It is a valuable lesson to remember and share.

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Staying Attuned to Changing Patient Presentations

by Iris Zink, MSN, NP, RN-BC

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GV is a 28-year-old female social worker who presented to my clinic in January as a new patient. During our initial conversation, she said she suffered from regular joint pain since her late teens, with her hips often bothering her so much at night that she slept with a pillow between her knees to alleviate the pain. She also complained of inflammatory back pain that woke her nearly hourly every night and was not alleviated by increasing doses of NSAIDs.

Three months before her initial visit, GV began having changes in her bowel habits and was regularly constipated despite increasing her fiber and water intake. One more important note – GV and her husband were hoping to soon get pregnant.

GV was particularly concerned about her emerging symptoms as her father battled ankylosing spondylitis (AS) for years. She asked me for a thorough evaluation and workup.

Upon examination, GV had extensive nail pitting. Lab results were normal with exception of the positive presence of the HLA-B27 gene. As her clinical picture began coming together, it looked like we'd be making a diagnosis of AS based on GV's symptoms and family history.

GV's desire to become pregnant in the immediate future limited our treatment options. Both methotrexate and leflunomide are considered category X drugs in pregnancy, so neither of those was an option. GV said she was allergic to sulfasalazine, so we nixed that as well. I wanted to try to start GV on a biologic right away, so I had her complete a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) questionnaire that would hopefully satisfy her insurance company (see Figure 1). Her initial score was 6.7, indicating poorly controlled disease.

Once her insurance company signed off on biologic therapy, GV expressed interest in trying golimumab since that is the drug that seemed to help her father's AS the most. She began monthly 50 mg injections.

Three months later, GV came back for her initial follow-up. Her constipation had resolved, her hip pain was now reduced to just an occasional twinge, and her BASDAI score was down to 1.75 (see Figure 2). Certainly, it seemed like the golimumab was doing the job.

On her next follow-up visit, however, GV had a new symptom that worried me—itchy and crusting psoriasis on her scalp. There have been numerous case reports in the medical literature regarding the induction and exacerbation of psoriasis in patients beginning anti-TNF therapy.[1-3] In a recent lecture at the Congress of Clinical Rheumatology, Dr. Jack Cush recommended two possible pathways when this occurs:[4]

1. Wait it out, and see if the psoriasis resolves on its own after longer exposure to the anti-TNF
2. Switch to a different medication in the same class (ie, another anti-TNF) to see if that resolves the issue

I presented GV with these options. She told me that, before switching to golimumab, her father had been on adalimumab, which had done little to improve his symptoms. Consequently, she opted to remain on golimumab to see if her psoriasis would resolve.

BASDAI Score Calculation	Figure 1	Figure 2
Medication	NSAIDs	Golimumab
Effectiveness of medicine on a ten point scale *(1 is not effective, 10 is very effective)*	3	8
Age	27	28
Gender	Female	Female
Pain on a ten point scale *(1 is none, 10 is the worst)* *Indicate level of ability with each of the following activities during the past week*		
Overall level of fatigue/tiredness	5	2
Overall level of AS neck, back, or hip pain	6	3
Overall level of pain/swelling in joints other than neck, back, or hips	6	1
Overall level of discomfort from areas tender to touch or pressure	10	1
Overall level of discomfort from time you woke up	8	1
How long does morning stiffness last from the time you woke up?	1 hr	0.4 hrs
BASDAI Score	**6.7**	**1.7**

Personally, however, my mind continues to churn. Is GV's psoriasis truly the result of golimumab, or was she misdiagnosed with AS instead of PsA (or another spondyloarthopathy)? Had I let her father's history of AS cloud my judgment? Patients with spondyloarthritis often have overlapping symptoms, and it's not always easy or straightforward to come to the correct diagnosis. It can often take years to come to the correct conclusion.

It is important as rheumatology nurses to keep our radars carefully attuned to our patient's changing symptoms and to be ready to modify a diagnosis or treatment plan no matter how sure the team is of the initial path. There is no shame in admitting, "We were wrong" to a patient if it leads to better decisions.

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Talk about Rough Teenage Years…

by Cathy Patty-Resk, MSN, RN, CPNP-PC

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One of our office's most interesting and complicated juvenile spondyloarthritis (SpA) cases involved AZ, who presented to us as a 13-year-old male with a 3-year history of bilateral hip pain and approximately 6 months after bilateral hip pinning for slipped capital femoral epiphysis (SCFE), a hip condition that occurs in growing teens and pre-teens. The bilateral nature of AZ's SCFE was somewhat unusual, as it is a condition that is usually limited to one side.[1]

AZ's initial radiographic history was consistently normal, and he never complained of any other joint pain besides in his hips.

Following the hip pinning, AZ had initially progressed well and he was able to walk approximately 100 feet with mild pain, but after 3 months, his mobility began to decrease and his pain increased. He came to us bound to a wheelchair.

Prior to his appointment in our office, an MRI with/without contrast was ordered that showed left sacroiliitis and degenerative disc disease at L5-S1.

By this time, AZ had been homeschooled for most of 7th and all of 8th grade, and he said that he was feeling socially isolated. His parents strongly disagreed about the source of AZ's issues—his father thought he was "faking" his symptoms to get attention while his mother was convinced that there was a true source of the pain that needed to be discovered.

Upon physical examination, AZ was found to have excruciating pain with any movement of his legs or back. He needed significant assistance just to get up onto the exam table and was consistently anxious throughout the exam. AZ had a swollen and mildly warm left knee, though he said that it did not bother him. He complained of consistent pain that did not necessarily worsen at any particular time of day. AZ slept on the first floor of his house as getting up the stairs to his bedroom was too difficult. In general, he appeared defeated and depressed, which was not surprising based upon his symptoms and quality of life.

AZ's lab results showed highly elevated acute phase reactants (APRs) with a C-reactive protein of 180 mg/L, erythrocyte sedimentation rate of 65 mm/hr, white blood cell count of 15,000 cells/mL, hemoglobin of 10.5 g/dl, and platelet count of 459,000 cells/µl. X-rays of his pelvis and hips showed dysmorphic appearance of femoral heads with spurring and joint space narrowing. We obtained another bilateral hip MRI with/without contrast that was negative for bone marrow edema in the spine, pelvis, and proximal femurs, and showed no synovitis or joint effusion. However, the radiologist remarked that it was difficult to get a good view of the femoral heads due to artifact caused by the hip pins. AZ's sacroiliac joints were unremarkable.

After our full workup, the diagnosis remained murky, so we began AZ on a conservative regimen of naproxen 500 mg (10 mg/kg) BID. The differentials included juvenile SpA, an infection, or an underlying inflammatory disorder of the gastrointestinal tract. After a consultation with orthopedics, AZ's hip pins were removed, and we collected fluid cultures near the affected area. We again ordered an MRI with/without contrast to get a better look at the femoral heads and epiphysis.

The repeat MRI showed synovial enhancement, acetabular cartilage loss, labral tears, and joint space narrowing with findings that strongly correlated with

juvenile idiopathic arthritis. Fluid cultures were positive for gram positive bacteria.

We now felt confident beginning more aggressive treatment for a SpA, but we first knew we had to treat AZ's possible infection before a possible progression to biologic therapy. AZ therefore received 30 days of antibiotics via a PICC line at his home. He also continued with physical therapy.

After seven months, we added sulfasalazine and methotrexate to AZ's treatment regimen, but he remained unable to attend school and was only able to walk approximately 100 feet using a cane or walker. As with his prior treatment following the hip pinning surgery, AZ's improvements had plateaued, and his pain began to increase.

We referred AZ back to orthopedics for re-evaluation, and they recommended a bilateral hip replacement. Our team felt that a trial of infliximab would be more appropriate before such a drastic surgery. AZ's mother was torn between these recommendations. All she knew for certain was that her once active and popular son could not attend school or have friends over because of his current physical limitations. She requested a second opinion from another pediatric rheumatologist, who concluded that AZ did not have a SpA and agreed with the orthopedist that a bilateral hip replacement was warranted. It was explained to AZ's mother, however, that this was a serious surgery and that, once performed, there was no going back. She was told that AZ would still likely be limited in some of his activities. Both the adult and pediatric orthopedist were reticent to perform such a procedure on a young, growing boy, even with the potential benefits.

During these months of multiple evaluations from multiple specialists, AZ's APR's fluctuated wildly, making it difficult to determine if his pain was being caused by inflammation or infection. Prior to scheduling the hip replacement, AZ's orthopedist agreed to try bilateral steroid injections, and AZ was walking with less pain within three days. His left knee swelling also finally resolved.

For the next several weeks, AZ's improvement—consistent with his prior history—waxed and waned, and we finally convinced his mother to allow us to try monthly infliximab in addition to the naproxen, sulfasalazine, and MTX. Within a month, AZ's APRs normalized and, most importantly, they stayed normal for 6 months. AZ began walking up and down stairs and had a steadier gait with a more upright posture. Everything was not, however, perfect. Three months after starting infliximab, AZ started complaining of gastritis, which we learned was due to his complacency in taking his oral medications, a common issue in teenaged patients who are responsible for managing their own medication regimens.

As he neared the start of ninth grade, we encouraged AZ's mom (his father had mostly disappeared as a medical decision maker in recent months) to send her son back to school. As many of his friends would be starting a new school—high school—we all felt it was an opportune time to re-engage AZ with his peers. It took many months of difficult conversations to convince them, and that first year was extremely bumpy, but AZ did indeed go back to school, where he stayed for 4 years. Adherence to a complex medication regimen remained an issue throughout AZ's high school years, although it got better as he matured.

We're now more than 4 years out from AZ's initiation of infliximab, and he's seeing less and less benefit from biologic therapy. His bilateral hip pain is again increasing, and the most recent MRI is negative for inflammation. Our team is now in agreement that a bilateral hip replacement is needed at this time. We did our best to delay AZ's bilateral hip replacement as long as possible since his bones and muscles were still growing rapidly, and a bilateral hip replacement could ultimately cause a severe arthritis flare down the line.

There is currently a suspicion that AZ may have had a reaction to the metal used in the SCFE pinning; he will be making a trip to an allergist before his orthopedist decides which type of hip hardware to use during his upcoming surgery. AZ should have an excellent outcome after bilateral hip replacement now that he is almost 19 years old and won't be growing much more. He is also in a much better place emotionally and feels ready to handle the next steps in his care.

A wise rheumatologist frequently reminds our multidisciplinary team that it is possible for our patients to have concomitant conditions that need to be managed carefully, along with the importance of systematically progressing through differential diagnoses. Cases like AZ are very tough. While we weren't certain that, for example, the addition of infliximab would help, we saw that AZ was physically and emotionally deteriorating and felt this was our best option. It was either going to help him or it wasn't, plain and simple. We never ordered any narcotics for AZ, and his mother never asked for them. We were all in agreement that the risk of potential opioid addiction was too great and would add an unnecessary layer of complexity to his care.

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