Spondyloarthritides

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KEYWORDS

• Spondyloarthritides • Axial spondylitis • Ankylosing spondylitis • Psoriatic arthritis
• Inflammatory bowel disease–associated spondyloarthritis • Reactive arthritis

KEY POINTS

- Evaluation of a patient with a spondyloarthropathy should include consideration of possible complications of the disease as well as its treatments.
- The expanded diagnostic criteria of axial spondylitis allow MRI to diagnose patients with sacroiliitis that may not be apparent on radiograph.
- A trial of nonsteroidal anti-inflammatory drugs can safely be given to patients with suspected spondyloarthritis in the absence of known contraindications and active bowel disease.
- Subsequent treatment should evaluate the axial and peripheral features of spondyloarthritis with attention given to adverse effects.

INTRODUCTION

The term spondyloarthropathy links ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, and inflammatory bowel disease (IBD) -associated arthritis as interrelated disease processes owing to overlapping clinical features and shared genetic predisposition. From early adulthood, these disorders present with musculoskeletal manifestations like inflammatory back pain, enthesitis (inflammation at tendon attachment sites to bone), oligoarthritis (usually of the lower extremities), and dactylitis (sausage digits) as well as extraskeletal manifestations, such as uveitis, psoriasis, and IBD. A patient diagnosed with 1 disease may experience symptoms prominent in another disease process. Genetically, the spondyloarthritides have been associated with the presence of HLA-B27. Despite similar genetics, some disease states are thought to be precipitated by environmental triggers, such as gastrointestinal and genitourinary (GI/GU) infections, whereas others do not appear to have an inciting event.[1,2]

The wide range of signs and symptoms of the spondyloarthritides can make a diagnosis challenging. It has been noted to take 6 to 8 years for most patients to have a

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Emerg Med Clin N Am 40 (2022) 159–178
https://doi.org/10.1016/j.emc.2021.08.005 **emed.theclinics.com**

definite diagnosis established.[3] This delay can lead to unchecked inflammation, structural damage, and later restriction in physical mobility. Once a diagnosis is made and treatment is started, there are complications the physician should be aware of because of the natural progression of the disease process, and its treatments.

First-line treatment of the spondyloarthritides aims to reduce inflammation with nonsteroidal anti-inflammatory drugs (NSAIDs). Although there is variation in how treatment is escalated, tumor necrosis factor (TNF) inhibitors can generally achieve suppression of symptoms if NSAIDs fail. Conventional disease-modifying antirheumatic drugs (DMARDs) can be used to target specific symptoms, whereas interleukin inhibitors can be used as additional treatment tools.

CLASSIFICATION OF SPONDYLOARTHROPATHIES AND DEFINITIONS

The spondyloarthritides, which are sometimes also referred to as the seronegative spondyloarthropathies owing to the lack of association with a positive rheumatoid factor, are divided into 2 groups: axial spondyloarthritis (SpA) and peripheral SpA. Axial SpA, which refers to patients with predominantly axial spine involvement, is further divided into patients who present with radiographic findings of SpA and patients who lack radiographic Axial SpA findings. Radiographic SpA (also referred to as ankylosing spondylitis) refers to "patients who have already developed structural damage in the sacroiliac joints or spine visible on radiographs while patients without structural damage [are] labelled as non-radiographic SpA."[4] Peripheral SpA consists of PsA, IBD-associated arthritis, and reactive arthritis.

Axial SpA is currently classified by the Assessment in Spondylo-Arthritis International Society (ASAS) criteria developed in 2009 (**Fig. 1**). The ASAS criteria expanded the current (modified New York) definition of sacroiliitis (radiographic finding of grade >2 bilaterally or grade 3–4 unilaterally) to include MRI as a diagnostic modality. An MRI finding of active/acute inflammation highly suggestive of sacroiliitis meets the diagnostic criteria for axial SpA. This addition allows more patients to meet the diagnostic criteria of axial SpA and denotes those without standard radiographic findings of sacroiliitis as nonradiographic SpA.[5–7] Of note, although these 2 processes likely progress along the same spectrum, nonradiographic SpA does not always result in radiographic SpA.[4]

In 2011, the ASAS criteria for peripheral SpA were developed to standardize the diagnoses of patients with peripheral manifestations of SpA (see **Fig. 1**).[8] The presence of arthritis, enthesitis, or dactylitis serves as the basis for making the diagnosis of a peripheral SpA. For the purposes of these disease processes, the ASAS defined the components of these criteria as seen in **Table 1**.

In contrast, reactive arthritis can occur as an oligoarthritis with 5 or fewer joints being inflamed while progressing in either an additive (progressive inflammation without the earlier joint inflammation resolving) or a migratory (joint inflammation in 1 joint resolves as another joint becomes inflamed) pattern, after an inciting GI/GU infection between 1 and 6 weeks prior.[9] Reiter syndrome exists as a subset of reactive arthritis and refers classically to inflammatory arthritis of a large joint, urethritis (men) or cervicitis (women), and either conjunctivitis or uveitis.

There are no classification criteria for reactive arthritis. The diagnostic criteria for the diagnosis of "definite" versus "probable" reactive arthritis are based on major and minor criteria. Definite reactive arthritis is defined as the presence of both major and relevant minor criteria, whereas a probable diagnosis is made by the presence of both major criteria but no relevant minor criteria (or 1 major and 1 or more minor criteria) (**Box 1**). Of note, there must be identification of an infectious source in order to

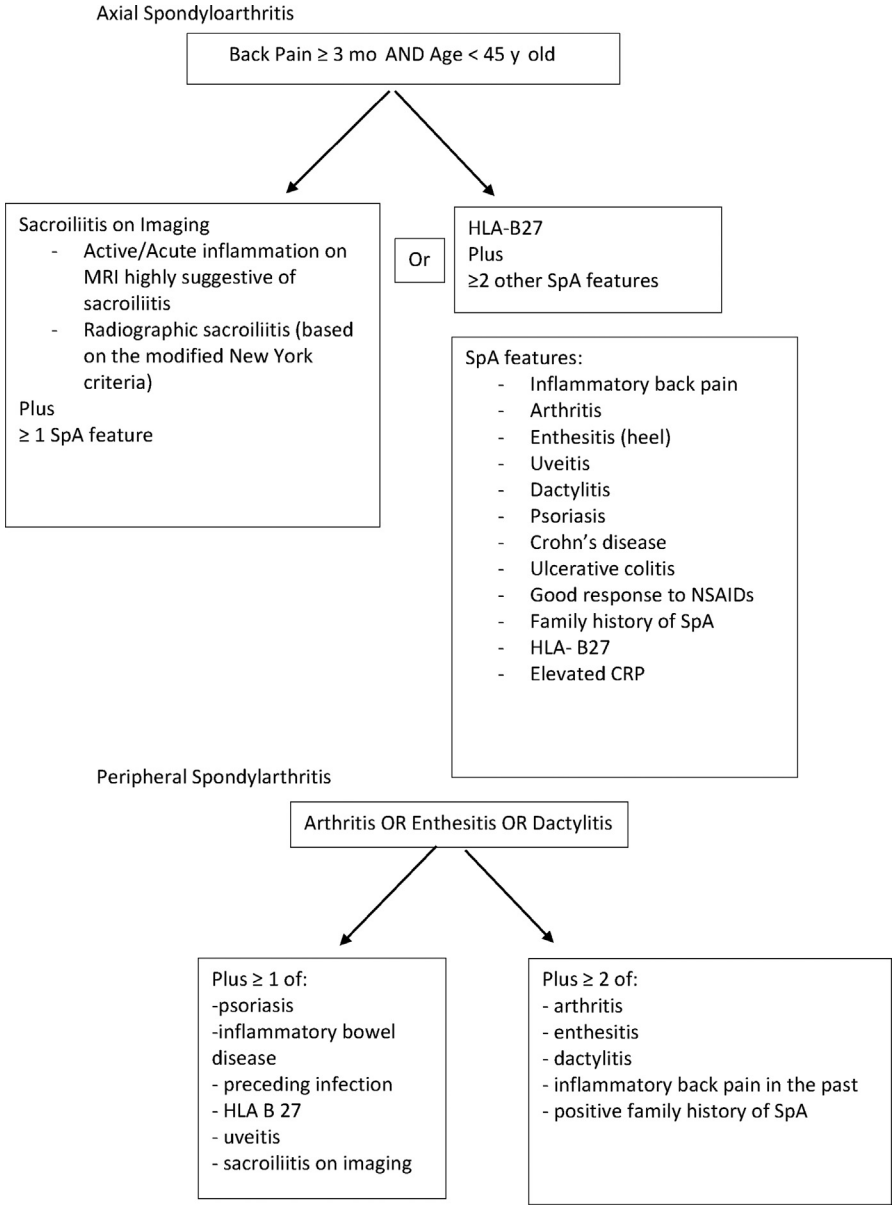

Fig. 1. ASAS criteria for axial and peripheral SpA. (*Adapted from* Hayward RJ, Machado PM. Classification Criteria in Axial Spondyloarthritis: What Have We Learned; Where Are We Going?. Rheum Dis Clin North Am. 2020;46(2):259-274 and the Assessment of Spondyloarthritis International Society)

make any of the above diagnoses. Commonly identified pathogens causing urogenital tract infections include *Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma genitalium,* and *Ureaplasma urealyticum*. GI illnesses can be caused by *Yersinia*, *Shigella*, *Salmonella,* and *Campylobacter jejuni*. Less frequently, *Clostridium difficile*, *Chlamydia pneumoniae,* and *Chlamydia psittaci* are found as causative agents.[9,10]

Table 1
Definitions of axial spondyloarthritis features for use in Assessment in Spondylo-Arthritis International Society classification of peripheral axial spondyloarthritis

Peripheral Arthritis Symptoms	
Arthritis	Current peripheral arthritis (asymmetric, lower limb predominant)
Enthesitis	Current enthesitis
Dactylitis	Current dactylitis
Additional Spondyloarthritis Symptoms	
Inflammatory back pain	Past history of inflammatory back pain diagnosed by a rheumatologist
Arthritis	Past or present arthritis
Enthesitis	Past or present spontaneous pain or tenderness on examination of an enthesitis
Uveitis	Past or present anterior uveitis, confirmed by an ophthalmologist
Dactylitis	Past or present dactylitis
Psoriasis	Past or present psoriasis
Inflammatory bowel disease	Past or present Crohn disease or ulcerative colitis
Preceding infection	Gastrointestinal (diarrhea) or genitourinary (urethritis, cervicitis) illness 1 mo before onset of the above peripheral arthritis symptoms
Family history of SpA	Presence of axial SpA, psoriasis, acute uveitis, reactive arthritis, or IBD in a first- or second-degree relative
HLA-B27	Positive blood test
Sacroiliitis	Identified on imaging • Modified New York criteria: grade 2–4 bilateral or grade 3–4 unilateral sacroiliitis on radiographs • MRI indicative of acute/active inflammation of the sacroiliac joints

Adapted from the Assessment of Spondyloarthritis International Society.

PsA was defined by Moll and Wright[11] in 1973. Previously, PsA had been regarded as 2 distinct entities of psoriasis and arthritis with a possible association with rheumatoid arthritis. Moll and Wright adapted the existing definitions of psoriasis and arthritis to reflect that PsA is psoriasis associated with inflammatory arthritis and usually with a negative serologic test for rheumatoid factor. With this expanded definition, they generated 5 subtypes of PsA. They are as follows:

1. Distal interphalangeal arthritis
2. Arthritis mutilans (a severe, deforming arthritis)
3. Symmetric arthritis (may appear similar to rheumatoid arthritis but has negative serology)
4. Asymmetrical arthritis with only a single or few joints involved (may also include dactylitis as inflammation of the soft tissues between 2 affected joints)
5. Predominant spondylitis with or without peripheral joint involvement[11]

In 2006, the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria (**Fig. 2**) were developed based on the evaluation of 1124 patient with PsA, rheumatoid

Box 1
Diagnostic criteria for reactive arthritis

Definite Diagnosis requires both major criteria and 1 minor criteria.

Probable Diagnosis requires both major criteria and no minor criteria OR 1 major criterion and 1 or more minor criteria.

Major criteria:

1. Arthritis with 2 or 3 of the following:
   a. Asymmetric
   b. Monoarthritis or oligoarthritis
   c. Lower-limb involvement
2. Preceding symptomatic infection with 1 or 2 of the following:
   a. Enteritis (diarrhea for 1 day minimum; 3 days to 6 weeks before arthritis onset)
   b. Urethritis (dysuria, discharge for 1 day minimum; 3 days to 6 weeks before arthritis onset)

Minor criteria: Laboratory evidence of infection

1. Triggering infection
   a. *Chlamydia trachomatis*
      i. Positive urine ligase reaction
      ii. Positive urethral/cervical swab
2. Persistent synovial infection
   a. Positive immunohistology or polymerase chain reaction for chlamydia

Adapted from Selmi C, Gershwin ME. Diagnosis and classification of reactive arthritis. Autoimmun Rev. 2014;13(4-5):546-549., 2014

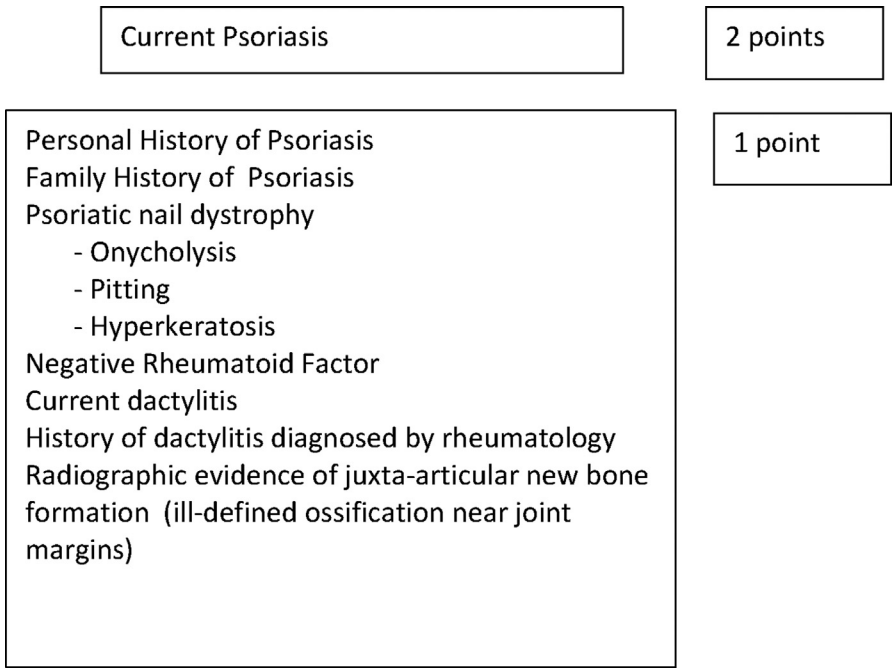

Fig. 2. The ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria. (*Adapted from* Rudwaleit M, Taylor WJ. Classification criteria for psoriatic arthritis and ankylosing spondylitis/axial spondyloarthritis. Best Pract Res Clin Rheumatol. 2010;24(5):589-604)

arthritis, AS, undifferentiated arthritis, connective tissue disorders, and other diseases. The goal was to compare the performance of several criteria that had developed since 1973 and to create unified criteria moving forward. For patients with an established inflammatory articular disease (joint, spinal, or entheseal), a score of ≥3 using the CASPAR criteria had a sensitivity of 98.7% and specificity of 91.4% for diagnosis of PsA. (Of note, current psoriasis is assigned a value of 2 points, whereas all other criteria receive 1 point.)[12–15]

IBD-associated SpA, also referred to as enteropathic arthritis, is defined by the presence of peripheral involvement, axial involvement, or both. The diagnosis of IBD-associated peripheral arthritis, which is common in both ulcerative colitis and Crohn disease, is mostly clinical, as peripheral arthritis is nonerosive. There are 2 subtypes of peripheral arthritis associated with IBD. Type 1 is pauciarticular, acute, and usually self-limited. It tends to follow the course of IBD flares. Type 2 peripheral arthritis is polyarticular and chronic in nature. It does not follow the course of IBD. It is known to be strongly associated with uveitis. The axial type of IBD-associated SpA requires the identification of spondylitis or sacroiliitis.[16,17]

EPIDEMIOLOGY

Categorization of the prevalence and incidence of the spondyloarthropathies has been complicated by their considerable overlap, their evolving definitions, and the methodological differences between studies. However, the National Arthritis Data Workgroup estimated in 2008 that the overall SpA prevalence within the United States ranged between 0.34% and 1.3% for adults ≥25 years old.[18] A strong association with the HLA-B27 gene was shown by an analysis of the COMOSPA registry (comprising 3984 patients from 22 countries in Asia, Africa, Europe, and North America with SpA) demonstrating 78.4% of the patients who met ASAS criteria for axial SpA were also HLA-B27 positive.

Ankylosing Spondylitis

A 2013 review of 29 population-based cross-sectional studies estimated the global prevalence of AS as ranging between 74 (South Africa) and 319 (North America) per 100,000 patients.[19] A review of the NHANES data from 2009 to 2010 using the ESSG criteria estimated the prevalence of AS at 550 per 100,000 patients, and the prevalence of axial spondyloarthritides (which includes AS and nonradiographic SpA) at 1400 per 100,000 patients (ranging from 900 for non-Hispanic blacks to 1500 for Mexican Americans and non-Hispanic whites).[20]

Peripheral Spondyloarthritides

Manifestations of spondyloarthritides are seldom confined to the peripheral skeleton, as demonstrated by an analysis of the COMOSPA registry, which found that, of patients with peripheral manifestations of SpA, 91% also demonstrated concurrent axial or psoriatic symptoms.[21]

Psoriatic

Estimates of the prevalence of PsA range between 20 (China and Mexico) and 420 per 100,000 patients (Italy).[22] Within the United States, an analysis of patients from Olmsted County, Minnesota who met CASPAR criteria demonstrated a prevalence of 158 per 100,000 patients.[23]

Reactive

Data on incidence of reactive arthritis are generally derived from outbreak studies and questionnaires. Among these, a population study from Oregon and Minnesota of patients with positive cultures for *Escherichia coli* 0157, *Salmonella, Campylobacter, Shigella,* and *Yersinia* estimated an incidence of 0.6 to 3.1 cases of reactive arthritis per 100,000 patients. Risk for rheumatologic sequelae was correlated with GI symptom severity, but not with HLA-B27 prevalence.[24] The overall prevalence of acute reactive arthritis is estimated as ranging between 0.09% and 1%.[22]

Inflammatory Bowel Disease

SpA is a frequently cited extraintestinal manifestation of IBDs, such as Crohn's disease and ulcerative colitis, with a systematic review of available epidemiologic studies finding a prevalence of 13% for peripheral arthritis, 10% for sacroiliitis, and 3% for AS.[25]

CLINICAL MANIFESTATIONS

Musculoskeletal

Low back pain is an extremely common complaint with approximately 25% of US adults reporting 1 day of low back pain in the past 3 months.[26] Its cause is usually intrinsic to the spine ranging from lumbosacral strain and disk herniation to compression fractures, although several factors can suggest a more severe cause to the emergency physician. They include presence of fever, age less than 18 years, age greater than 50 years, GU complications (urinary retention, fecal incontinence), use of steroids or anticoagulants, intravenous drug abuse, recent spinal surgery or epidural injection, and history of malignancy.[27,28] In contrast, the presence of low back pain, before the age of 45, affecting patients for 3 or more months without a mechanical cause should raise suspicion of an SpA prompting imaging and further evaluation.

Inflammatory back pain, as described above, is one of the distinguishing features of SpA. It can be associated also with enthesitis, oligoarthritis (usually of the lower extremities), and dactylitis. Patients may experience nonmusculoskeletal symptoms, such as psoriasis, anterior uveitis, Crohn disease/ulcerative colitis and may report a history of GI/GU illness, a family history of SpA, or presence of the HLA-B27 gene.

IMAGING FINDINGS

The 2 main imaging modalities for the spondyloarthritides are radiographs and MRI of the sacroiliac joint. MRI is more useful for early diagnosis, as it may detect manifestations of the spondyloarthritides before they become visible on plain radiographs.[29]

The common radiographic findings associated with the spondyloarthritides are sacroiliitis and enthesitis. Sacroiliitis involves erosions, sclerosis, and bony bridging. Erosions may be visualized with obscuration of joint outlines that progress to irregular contours in the caudal joint, and finally, to a string-of-pearls appearance with joint space widening.[30] Sclerosis may involve the entire sacroiliac joint, and bony bridging is manifested by blurring of joint outlines on radiograph.

MRI findings associated with sacroiliitis include osteitis (periarticular and subchondral bone marrow edema) and synovitis.

Other radiographic manifestations of AS may include vertebral bone spurs, discitis, and square- or bamboo-shaped vertebrae on plain films. MRI manifestations include

capsulitis, enthesitis (inflammation of transitions points between soft tissue and bone), intra-articular enhancement, erosions, and sclerosis.[30]

Radiographic manifestations of PsA are characterized by osteodestructive and osteoproliferative manifestations.[31] Ultrasonography may be used to evaluate for enthesitis at tendon insertion points, which manifests as thickening, loss of uniform linear pattern, blurring of tendon margins, and microcalcifications.[32]

LABORATORY FINDINGS

Although there is no laboratory test or combination of laboratory tests that is diagnostic for the spondyloarthritides, 75% to 95% will carry the HLA-B27 gene, and many will have elevated inflammatory markers, such as C-reactive protein (CRP) (40% of the axial SpA) or erythrocyte sedimentation rate (ESR).[33] However, although the HLA-B27 gene is associated with the spondyloarthritides, it is neither sensitive nor specific for them.

Laboratory findings can be helpful to assess for associated extraskeletal complications, such as IBD. The presence of iron deficiency anemia, leukocytosis, hypokalemia, hypoalbuminemia, or inflammatory markers, such as thrombocytosis, elevated ESR, and elevated CRP, can alert the provider to the presence of concomitant IBD and may prompt a gastroenterology referral.[34]

OUTPATIENT THERAPIES

The treatment options for the spondyloarthritides vary but often overlap because of the similar pathogenesis of these distinct disease states. SpA can be subdivided based on clinical features into axial (back pain and stiffness) and peripheral manifestations (arthritis, dactylitis, and enthesitis). Treatment strategies are summarized in **Fig. 3**.

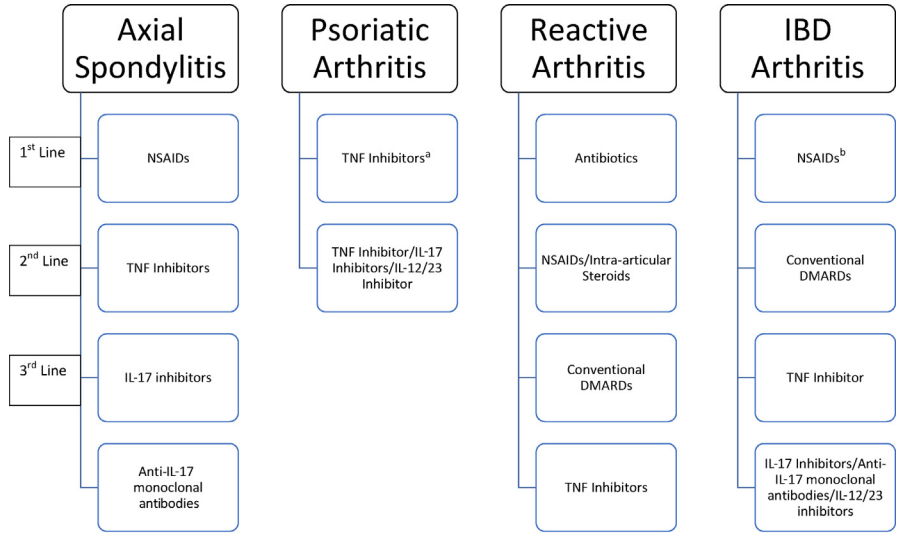

Fig. 3. Treatment pathways for the spondyloarthritides. [a]NSAIDs or conventional DMARDs can be used as first line treatment if PsA is not severe. [b]First line if IBD is stable.

The first-line therapy for all symptoms of axial SpA is NSAIDs, which have demonstrated efficacy when compared with placebo with pain improvement of patients with inflammatory back pain.[35] A 2015 Cochrane review of 39 randomized control trials (RCTs)/quasi-RCTs and cohort studies found that for traditional NSAIDs versus placebo and COX-2 inhibitors versus placebo, NSAIDs and COX-2 inhibitors were more efficacious than placebo in the reduction of pain and improvement in disease activity and functioning. Traditional NSAIDs and COX-2 inhibitors were comparable in efficacy. The most frequently studied NSAID was indomethacin with diclofenac and naproxen as the second and third most evaluated NSAIDs, respectively.[36] The American College of Rheumatology (ACR) does not currently recommend 1 NSAID over another in the treatment of stable or active SpA; they do however recommend continuous NSAID use for active SpA and on-demand NSAID use for stable SpA.[37,38] Dosages for common NSAIDs include naproxen 500 mg twice daily, ibuprofen 800 mg 3 times per day, and celecoxib 200 mg twice per day. Patients often need the maximum dose and benefit from trials of various NSAIDs if the initially selected NSAID is not effective. Each NSAID should be trialed for 2 to 4 weeks before declaring treatment failure. The use of NSAIDs should be paired with nonpharmacologic treatment, such as education, exercise, and physical therapy.

The second-line treatment for axial SpA is biologic DMARDs. Although traditional DMARDs (sulfasalazine, methotrexate) are ineffective for treatment of axial SpA, they have been useful for patients with peripheral manifestations of axial SpA. As TNF and interleukin-17 (IL-17) have been implicated in the pathogenesis of axial SpA, biologic DMARDs (TNF inhibitors and IL-17 antagonists) have been closely examined. There are currently 5 TNF inhibitors approved for use of AS. They are infliximab, etanercept, adalimumab, golimumab, and certolizumab. In patients who have failed NSAID therapy, treatment with these medications has been shown to improve "articular manifestations, CRP levels and MRI-detectable inflammation in the sacroiliac joints or spine in active patients with ankylosing spondylitis."[4] The selection of which TNF inhibitor is used is based on the patient's disease profile, coexisting conditions, and patient/physician preference.

In the event of primary failure to a TNF inhibitor, the ACR recommends trial of an anti-IL-17 monoclonal antibody, such as secukinumab or ixekizumab. If secondary failure occurs, the next drug option should be another TNF inhibitor.[37,38] Of note, the ACR *does not* recommend the routine use of systemic glucocorticoids for the treatment of axial SpA, although they may be considered for peripheral arthritis flares, axial SpA therapy during pregnancy, or an IBD flare.

Tailored treatment for PsA is selected after evaluation of the spectrum of disease manifestation and severity. There are mild discrepancies between the recommendations of the ACR, the European League Against Rheumatism (EULAR), and the Group for Research and Assessment in Psoriasis and Psoriatic Arthritis (GRAPPA) for treatment of PsA, specifically in the order of therapy selection. These discrepancies are also likely due to differences in the approach to treatment targets; the ACR refers to active PsA with the presence of or absence of associated symptoms, whereas GRAPPA and EULAR approach disease processes based on disease domains. The 2018 ACR PsA management guidelines recommend that for treatment-naive patients with active PsA, a TNF inhibitor be tried first over a conventional DMARD, such as methotrexate, leflunomide, sulfasalazine, cyclosporine, or apremilast; if the patient does not have severe PsA or severe psoriasis, NSAIDs or methotrexate (as a conventional DMARD) can be tried first. If TNF inhibitor monotherapy fails to suppress active disease, the ACR recommends trial of either a different TNF inhibitor, IL-17 biologic, or IL-12/23 biologic. It does not delineate order of therapy selection as do the other guidelines.[39–44]

EULAR and GRAPPA both recommend treatment strategies based on clinical manifestations of PsA. For active peripheral arthritis, TNF inhibitors can be used as first-choice agents after conventional DMARDs. GRAPPA recommends IL-12/23 inhibitors and IL-17 inhibitors in addition to TNF inhibitors as first choice after conventional DMARDs.[44] NSAIDs can also be used as treatment. If poor prognostic factors are present, it is preferred that treatment begins with a conventional DMARD. Axial disease involvement can be treated with NSAID therapy first.

Treatment of reactive arthritis should address arthritis symptoms and the precipitant infection. For acute reactive arthritis, NSAIDs are used for symptomatic improvement of peripheral arthritis symptoms. Patients may require a trial of 1 or 2 NSAIDs at maximum dosages to relieve their symptoms. A trial of corticosteroids (intra-articular) can also be considered for the treatment of peripheral arthritis. Systemic steroids can be used at a low/moderate dose if there is incomplete response to NSAIDs or intra-articular steroid injections, although there is little evidence to support their use.

Acute arthritis symptoms that are not completely relieved by NSAIDs can be treated with conventional DMARDs. DMARDs can also be used for chronic (>6 months) reactive arthritis. Sulfasalazine is the DMARD of choice; other DMARDs, such as methotrexate, can be used, but there are limited studies using these medications. Conventional DMARDs can be especially effective if extra-articular manifestations are present. After a 3- to 4-month trial of 1 or 2 conventional DMARDs, treatment-resistant patients can be started on a TNF inhibitor.

The preceding infection of reactive arthritis can be treated with antibiotics provided it is not a self-limited disease. Multiple studies have shown no benefit over placebo in treating self-limited illnesses.[45] Enteric diseases are typically self-limited and do not require antibiotics. Antibiotic treatment can be considered in patients who are of advanced age, patients who are immunocompromised, or if the infection is severe. There are limited data indicating the benefit of treating urogenital disease especially because of the risk of infertility.[45] Patients with GU infections should receive antibiotic treatment. For example, *C trachomatis* should be treated with azithromycin or doxycycline with empiric treatment for *N gonorrhea* as indicated. Treatment should be offered to sexual partners. Repeat symptoms should prompt repeat testing. Treatment failure should prompt consideration of alternative causative pathogens of reactive arthritis (ie, *Mycoplasma, Ureaplasma*) for which antibiotic resistance to first-line agents can occur.[46]

The treatment for IBD-associated arthropathy begins with assessment of the bowel disease. If the IBD is stable and not in flare, NSAIDs can be tried for peripheral and axial disease. NSAIDs, as a first-line therapy, should be given for 2 weeks at inflammatory doses. If there is no improvement and if there are no new GI complaints, a second NSAID can be trialed for 2 weeks. If new or worsening symptoms of bowel disease occur, NSAIDs should be discontinued. If there continues to be peripheral arthritis symptoms in the absence of axial involvement, patients should be given a 3-month trial of a conventional DMARD such as sulfasalazine. If there is no improvement, or if axial disease is present, a TNF inhibitor should be started for at least 3 months. Treatment failure of 1 TNF inhibitor does not reflect the success of this drug class as a whole; a second TNF inhibitor can be trialed before moving on to therapies, such as IL-12/23 inhibitors.

Patients should be treated in collaboration with their gastroenterologist to monitor for active bowel disease that may require treatment. If active bowel disease exists on presentation, NSAID therapy should not be prescribed. Active IBD with axial disease should be started on TNF inhibitors, whereas active IBD with peripheral disease should begin treatment with conventional DMARDs.[34,47]

COMPLICATIONS

Drug-Related

Nonsteroidal anti-inflammatory drugs

Complications owing to NSAID use can be divided into 3 major categories: GI, renal, and cardiovascular. NSAIDs reduce prostaglandin synthesis in the gastric mucosa and can lead to dyspepsia, peptic ulcer disease, and, more seriously, bleeding, perforation, and gastric outlet obstruction (**Table 2**). A review evaluating serious adverse GI events in long-term use of NSAIDs found that there was no significant difference in serious adverse GI events (symptomatic ulcers and ulcer complications) between patients who used COX-2 inhibitors and patients who used nonselective NSAIDs. Several factors increase the risk of NSAID-associated serious GI events: high doses of NSAIDs, age greater than 60 years, history of ulcers and ulcer complications, use of glucocorticoids, anticoagulants, or antiplatelet medications, smoking, and alcohol consumption.[35]

Renal complications of NSAID use include acute renal failure, worsening hypertension, and fluid and electrolyte abnormalities. Acute renal failure, although rare, can occur from lack of prostaglandin-induced vasodilation at the level of the kidneys, resulting in acute renal failure. Hypertension occurs via a similar mechanism; the lack of prostaglandins can ultimately result in sodium and water retention causing hypertension. Hyperkalemia and hyponatremia occur owing to alterations of the RAAS pathway. Of note, acute interstitial nephritis can occur from NSAID use via a different mechanism.

The cardiovascular complications of NSAID use include myocardial infarction and stroke. Several large trials and reviews (PRECISION trial, CNT Collaboration analysis) have indicated that nonselective NSAIDs and COX-2 inhibitors have similar cardiovascular risks over many years.

Table 2
Summary of treatment complications

Treatment	Complications
NSAIDs	Gastrointestinal: • Dyspepsia • Peptic ulcer disease • Bleeding • Perforation • Gastric outlet obstruction Renal: • Acute kidney injury • Acute renal failure • Hypertension • Electrolyte abnormalities (hyperkalemia, hyponatremia) • Acute interstitial nephritis Cardiovascular: • Myocardial infarction • Cerebrovascular accident
DMARDs (select)	Methotrexate: • Gastrointestinal (nausea, vomiting, abdominal pain, decreased oral intake)

(*continued on next page*)

Table 2
(*continued*)

Treatment	Complications
	• Hepatotoxicity (elevated liver enzymes) • Nephrotoxicity (elevated creatinine and renal failure) • Interstitial lung disease • Bone marrow toxicity • Infection Sulfasalazine • Dose-dependent reactions (headache, nausea, vomiting, abdominal pain) • Immune-related reactions (hemolytic anemia, agranulocytosis, aplastic anemia, pneumonitis, cutaneous reactions [toxic epidermal necrolysis and Steven-Johnson Syndrome], and hepatotoxicity)
TNF inhibitors	Infection: • Opportunistic infections: Mycobacterium, Pneumocystis pneumonia • Bacterial: *S aureus, Listeria, Pseudomonas* • Fungal • Viral infections (hepatitis B, hepatitis C, herpes simplex virus) Neutropenia Acute infusion reactions (infliximab) Delayed infusion reactions (infliximab) Injection site reactions Demyelinating disease Congestive heart failure Malignancy Antibody formation (antidrug antibodies and autoimmune)
IL-17 inhibitors (select)	Secukinumab: • Diarrhea • Headache • Nasopharyngitis/upper respiratory tract infections • Inflammatory bowel disease Ixekizumab (include above side effects) • Candida infections
IL-12/23 inhibitors (ustekinumab)	• Headache • Cough • Upper respiratory tract infections • Arthralgias • Injection site erythema • Infection • Malignancy • Cardiovascular events
Steroids	• HPA axis suppression (adrenal insufficiency) • Infection (fungal, bacterial, viral) • Cushingoid features • Catabolic skin changes (high dose) • Weight gain (high dose) • Hyperglycemia (high dose) • Hypertension (high dose) • Cataracts (long-term use) • Osteoporosis

Conventional disease-modifying antirheumatic drugs

Conventional DMARDs include medications such as methotrexate and sulfasalazine. Reported adverse effects are primarily taken from studies in patients with rheumatoid arthritis. Well-known adverse effects of methotrexate include hepatotoxicity, interstitial lung disease, and bone marrow suppression. However, other side effects may occur in patients receiving this treatment. A systematic review by Wang and colleagues[48] found that for methotrexate use in rheumatoid arthritis patients, 20% to 70% of patients experienced adverse GI symptoms, including nausea, vomiting, abdominal pain, and poor appetite. Methotrexate is renally cleared and at low doses can cause a decrease in creatinine clearance; high doses have been shown to cause nephrotoxicity.[49] The risk of infection to patients using methotrexate is not abundantly clear, as it is not an immunosuppressive agent, although concomitant use of steroids or other immunosuppressive agents could lead to higher rates of infection.

Adverse effects owing to sulfasalazine use are generally categorized as either a dose-dependent reaction or an immune-related reaction. Dose-dependent reactions are typically benign and result in headache, nausea, vomiting, and abdominal pain. More serious reactions have been reported as immune-related reactions, such as hemolytic anemia, agranulocytosis, aplastic anemia, pneumonitis, cutaneous reactions (toxic epidermal necrolysis and Steven-Johnson syndrome), and hepatotoxicity.[50,51]

Tumor necrosis factor inhibitors

TNF inhibitors have a wide range of adverse effects that necessitate careful consideration before use. Major adverse effects are infections, mild neutropenia, effects of administration (infusion reactions and local site reactions), and cutaneous reactions.

Infections. A notable risk of TNF inhibitor therapy is immunosuppression and risk for opportunistic infections. TNF inhibitors disrupt the body's natural ability to make granulomas and maintain them. Patients should be screened for latent tuberculosis (TB) infection before initiation of TNF inhibitors, as they are at risk of mycobacterium infections (tuberculous and nontuberculous); latent TB is usually treated if detected before the start of TNF inhibitors.[52]

Patients should also be screened for hepatitis B and C before initiation of a TNF inhibitor and treated for chronic infection before initiation, as hepatitis B can reactivate during TNF inhibitor treatment. Patients with acute hepatitis C should not receive TNF inhibitor therapy.

Opportunistic infections associated with use of TNF inhibitors include fungal (histoplasmosis, coccidioidomycosis, cryptococcosis) infections, common bacterial infections (*Staphylococcus aureus, Listeria, Pseudomonas*), *Pneumocystis jirovecii* pneumonia, and viral infections, such as herpes simplex virus and herpes zoster activation.

Effects of administration. Complications with administration of TNF inhibitors include acute and delayed infusion reactions as well as local site reactions. True anaphylaxis does occur, but many reactions are nonallergic and are not mediated by immunoglobulin E.[53] Delayed infusion reactions occur 1 to 14 days after infusion and mimic serum sickness with the development of fever, rash, myalgias, and arthralgias; they can be treated with supportive care. Local injection site reactions include pain, redness, swelling, and bruising and can be treated with supportive care. Other notable reactions are psoriasis, eczema, and lichen planus.

Other complications. Complications, such as demyelinating disease, heart failure, malignancy, the development of autoantibodies, and other autoimmune illnesses,

have been linked temporally to TNF inhibitor use. Briefly, drug-induced demyelinating disease can mimic multiple sclerosis in the wide breadth of presenting symptoms; a potential causal relationship has been identified with use of etanercept and infliximab.[54] The same medications also have been linked to worsening of established heart failure. Many autoimmune conditions can increase one's risk of malignancy, and the use of TNF inhibitors is postulated to further increase that risk, although this requires further investigation. Finally, patients using TNF inhibitors are at an increased risk of developing antidrug antibodies (eg, anti-adalimumab antibody) and autoantibodies (eg, anti-dsDNA), with some going on to develop clinically significant autoimmune illnesses, such as systemic lupus erythematosus.

Monoclonal antibodies

Monoclonal antibodies used against rheumatic diseases include IL-17 inhibitors and IL-12/23 inhibitors. Secukinumab (a fully human monoclonal antibody) and ixekizumab (a humanized monoclonal antibody) target IL-17 and are approved for use for radiographic and nonradiographic SpA as well as PsA and plaque psoriasis. Mild adverse effects of secukinumab include diarrhea, headache, nasopharyngitis, and other upper respiratory tract infections (URIs). A more significant adverse effect is IBD in patients without prior history of GI disease.[55] Ixekizumab has a similar adverse effect profile with additional increased risk for candidal infections.[56]

The IL-12/23 inhibitor ustekinumab has been frequently referenced as a treatment option in the spondyloarthritides. Mild adverse effects include headache, cough, URIs, arthralgias, and injection site erythema. Serious adverse effects, such as infection, malignancy, and cardiovascular events, have been reported at low frequency in long-term trials.[57,58]

Glucocorticoids

The side effects of steroids use are well known, with risk for adverse effects increasing with dosage and duration of use. These side effects include the following:

- Suppression of the hypothalamic-pituitary-adrenal axis leading to loss of cortisol secretion and secondary adrenal insufficiency
- Increased risk of fungal, bacterial, and viral infections owing to immunosuppression
- Development of Cushingoid features and other catabolic skin effects (skin thinning, atrophy, and ecchymosis)
- Weight gain, hyperglycemia, and hypertension at higher doses of glucocorticoids
- Development of cataracts with prolonged usage[59]
- Osteoporosis
- Neuropsychiatric and neurocognitive symptoms

Disease related

Complications owing to each individual spondyloarthropathy are numerous, and a brief overview of extra-articular manifestations and complications is provided in **Box 2**. As the disease processes are interrelated, complications that are listed under 1 disease process can occur in another disease process.

EMERGENCY DEPARTMENT EVALUATION

Suspected New Diagnosis

The emergency department (ED) evaluation of a patient with suspected spondyloarthropathy should begin with assessment of hemodynamic stability. Airway patency, respiratory status, and circulation should be the first 3 items evaluated on presentation in

Box 2
Complications and extra-articular manifestations of the spondyloarthritides

- Ankylosing spondylitis
  - Cardiovascular disease
    - Aortic regurgitation
    - Aortic and mitral valve thickening
    - Conduction disturbances
    - Acute coronary syndrome
    - Stroke
    - Venous thromboembolism
    - Conduction abnormalities
  - Pulmonary disease
    - Restrictive lung disease due to decreased chest wall and spinal mobility
    - Pulmonary fibrosis
  - Musculoskeletal
    - Osteopenia
    - Fractures
    - Atlantoaxial subluxation
  - Neurologic
    - Cord compression
    - Spinal nerve compression
  - Renal disease
    - Immunoglobulin A nephropathy
    - Nonspecific glomerulopathy
    - Renal amyloidosis
- Reactive arthritis
  - Ophthalmologic Involvement
    - Uveitis
  - Cutaneous involvement
    - Skin or oral ulcers
    - Keratoderma blennorrhagica
- Psoriatic arthritis
  - Metabolic disease
  - Hypertension
  - Diabetes
  - Atherosclerosis
  - Cardiovascular disease (myocardial infarction, stroke, death)
- Inflammatory bowel disease–associated arthritis
  - Constitutional
    - Weight loss
  - Gastrointestinal
    - Fistulas/abscess
    - Colitis complications: GI bleed, toxic megacolon, perforation
  - Cutaneous
    - Erythema nodosum
    - Pyoderma gangrenosum
    - Aphthous ulcers
  - Ophthalmologic
    - Uveitis
    - Episcleritis
    - Corneal ulcers
  - Hepatobiliary
    - Fatty liver disease
    - Primary sclerosing cholangitis
    - Autoimmune liver disease
  - Musculoskeletal
    - Osteoporosis/osteopenia

that order. Once stability is determined, a careful history and physical examination should be performed. This should include family history and a thorough review of systems to assess for extra-articular manifestations if present. First-line treatment for arthritis symptoms, NSAIDs, can generally be started in the ED unless there is concern for a possible complication of NSAID use. A concern for a new diagnosis should prompt referral to a rheumatologist and additional subspecialist if there is concern for an extra-articular manifestation such as IBD or pulmonary fibrosis.[60]

Suspected Complications

The ED evaluation of a patient with known spondyloarthropathy should include consideration of potential complications of the disorder itself, as well as complications of the medical therapy. The wide range of potentially serious complications associated with individual spondyloarthritides and the used therapeutic modalities necessitates an elevated index of suspicion from the ED physician. Examples would include increased potential for atlantoaxial subluxation in a trauma patient, or opportunistic infection in a febrile patient. Other complications are cataloged in **Table 2** and **Box 2**.

SUMMARY

The spondyloarthritides are a group of chronic rheumatological disorders that include musculoskeletal and extraskeletal manifestations, often share a genetic predisposition, and have overlapping clinical features. Musculoskeletal features can include inflammatory back pain, oligoarthritis, enthesitis, and dactylitis; extraskeletal features can include uveitis, IBD, and skin disorders, such as psoriasis. Patients suffering from the spondyloarthritides can experience complications involving multiple body systems, either as a result of their inherent disease process or as a result of therapeutic modalities. Appropriate ED care for these patients requires maintaining an index of suspicion for the presence of these multisystemic complications.

CLINICS CARE POINTS

- Unless there is a contraindication, nonsteroidal anti-inflammatory drugs should be the first-line treatment for the spondyloarthropathies in the emergency department.
- Clinical suspicion for a spondyloarthropathy should trigger a prompt referral to a rheumatologist.
- The spondyloarthropathies include musculoskeletal and extraskeletal manifestations and have overlapping clinical features.
- Emergency department visits may be prompted by complications of the underlying spondyloarthropathy or of the medical therapies.

DISCLOSURE

None.

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