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374 Spondyloarthritis

Dry eyes and/or dry mouth1 And/or Major salivary gland enlargement, fatigue, Raynaud’s phenomenon, arthralgias/arthritis (particularly small hand joints), palpable purpura/urticarial lesions, renal tubular acidosis/membranoproliferative glomerulonephritis, ILD/small airways disease, autoimmune cholangitis, peripheral neuropathy, MS-like lesions Ocular staining score ≥5 (or van Bijsterveld’s score ≥4) on at least one eye2 Unstimulated whole saliva flow rate ≤0.1 mL/min Schirmer’s test ≤5 mm/5 min on at least one eye If any of those present If any of those present + Sjögren’s disease FIGURE 373-3 Diagnostic algorithm for Sjögren’s disease. 1Defined as a positive response to at least one of the following questions: (a) Have you had daily, persistent, troublesome dry eyes for more than 3 months? (b) Do you have a recurrent sensation of sand or gravel in the eyes? (c) Do you use tear substitutes more than three times a day? (d) Have you had a daily feeling of dry mouth for more than 3 months? (e) Do you frequently drink liquids to aid in swallowing dry food? 2Ocular staining score described in Whitcher et al. van Bijsterveld score described in van Bijsterveld et al. 3Focus score count ≥1 (based on the number of foci per 4 mm2 of salivary gland tissue) following a protocol described in Daniels et al. ILD, interstitial lung disease; MS, multiple sclerosis. thrice daily) appears to improve sicca manifestations, and both are well tolerated. Hydroxychloroquine (200 to 400 mg daily) and/or methotrexate (0.2–0.3 mg/kg body weight/weekly) are helpful for arthralgias and mild arthritis. Patients with renal tubular acidosis should receive sodium bicar bonate by mouth (0.5–2 mmol/kg in four divided doses). Gluco corticoids and monoclonal antibody to CD20 (rituximab) appear to be effective in patients with systemic disease, particularly in those with purpura and persistent arthritis. Novel monoclonal antibodies targeting the CD40L/CD40 costimulatory pathway or the BAFF receptor or sequential treatment of belimumab and rituximab seem to be promising therapeutic strategies. Data for a beneficial role of other conventional immunosuppressants are limited. Treatment of lymphoma in the setting of Sjögren’s disease follows the general guidelines for lymphoma management in the general population. Detailed recommendations on Sjögren’s disease management have been issued by EULAR and British Society of Rheumatology. ■ ■FURTHER READING Daniels TE et al: Associations between salivary gland histopathologic diagnoses and phenotypic features of Sjögren’s syndrome among 1,726 registry participants. Arthritis Rheum 63:2021, 2011. Fragkioudaki S et al: Predicting the risk for lymphoma develop ment in Sjogren syndrome: An easy tool for clinical use. Medicine (Baltimore) 95:e3766, 2016. Mavragani CP, Moutsopoulos HM: Sjögren’s syndrome. CMAJ 186:579, 2014. Mavragani CP, Moutsopoulos HM: Sjogren’s syndrome: Old and new therapeutic targets. J Autoimmun 110:102364, 2020. Moutsopoulos HM: Sjögren’s syndrome: A forty-year scientific jour ney. J Autoimmun 51:1, 2014. Nocturne G, Mariette X: Expert perspective: Challenges in Sjögren’s disease. Arthritis Rheumatol 75:2078, 2023. Price EJ et al: British Society for Rheumatology guideline on man agement of adult and juvenile onset Sjögren disease. Rheumatology (Oxford)16:keae152, 2024. Shiboski CH et al: 2016 American College of

Rheumatology/European League Against Rheumatism Classification Criteria for Primary

CHAPTER 374 Exclude History of head and neck radiation treatment Active hepatitis C infection Acquired immunodeficiency syndrome Sarcoidosis Amyloidosis Graft-versus-host disease IgG4-related disease Spondyloarthritis

- Serum antibodies against Ro antigen
- Minor salivary gland biopsy3 Sjögren's Syndrome: A consensus and data-driven methodology involving three international patient cohorts. Arthritis Rheumatol 69:35, 2017. van Bijsterveld OP: Diagnostic tests in the Sicca syndrome. Arch Ophthalmol 82:10, 1969. Whitcher JP et al: A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry. Am J Ophthalmol 149:405, 2010. Atul Deodhar, Dirk Elewaut

Spondyloarthritis Spondyloarthritis (SpA) refers to a family of immune-mediated inflammatory arthritis disorders that share many clinical, genetic, and pathologic characteristics. Moll and Wright are credited in recogniz ing these diseases in 1974 as distinct from rheumatoid arthritis (RA), a well-recognized inflammatory arthritis at that time. While axial skeletal involvement is hinted at in the word "spondyloarthritis," it is not mandatory. The musculoskeletal manifestations of SpA include sacroiliitis, inflammatory spinal lesions, peripheral inflammatory arthritis, enthesitis (inflammation at the attachment of tendons and ligaments to the bones), tendonitis, tenosynovitis, and dactylitis ("sau sage digits"). Other clinical manifestations include uveitis, skin pso riasis, inflammatory bowel disease (IBD, Crohn's, or ulcerative colitis), absence of rheumatoid factor (RF) and nodules (to differentiate from RA), familial correlation, and association with the gene human leuko cyte antigen (HLA)-B27. The 2009 Assessment of Spondyloarthritis International Society (ASAS) classification criteria divided SpA under "axial" (axSpA) and "peripheral" (pSpA). "Peripheral" SpA may seem a misnomer, but it simply indicates that peripheral musculoskeletal

TABLE 374-1 Spectrum of Spondyloarthritis SPONDYLOARTHRITIS (SPA) AXIAL SPONDYLOARTHRITIS (axSpA) PERIPHERAL SPONDYLOARTHRITIS (pSpA) CONDITION CLINICAL FEATURES CONDITION CLINICAL FEATURES Conditions commonly included under pSpA PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders Radiographic axSpA (r-axSpA, also called ankylosing spondylitis [AS]) Sacroiliitis grade 2 (bilateral), grade 3 or 4 (unilateral or bilateral) Psoriatic arthritis Skin psoriasis and nail involvement usually preceding arthritis, enthesitis, dactylitis Nonradiographic axSpA (nr-axSpA) Sacroiliitis grade 1 (unilateral or bilateral) or grade 2 (unilateral) Inflammatory bowel disease–associated arthritis Reactive arthritis Urethritis, history of preceding infection with Salmonella, Shigella, Yersinia, Campylobacter, and Chlamydia, mucosal ulcers, conjunctivitis, keratoderma blennorrhagica Undifferentiated peripheral SpA Enthesitis, dactylitis, family history of SpA, HLA-B27, acute anterior uveitis, and not fitting in any of the other conditions mentioned above Conditions sometimes included under pSpA SAPHO syndrome Synovitis, acne, pustulosis, hyperostosis, and osteitis; typical involvement of anterior chest wall joints Acne-associated arthritis Acne conglobata, peripheral arthritis Hidradenitis suppurativa–associated arthritis manifestations are predominant and more troublesome to the patient than the spinal involvement. AxSpA is further divided into radiographic (r-axSpA, also known as ankylosing spondylitis [AS]), and nonradiographic (nr-axSpA). The conditions included under pSpA are psoriatic arthritis (PsA), reactive arthritis (ReA), arthritis associated with IBD, and

undifferentiated SpA, where patients cannot be classified under any known categories. Patients with axSpA can have peripheral musculoskeletal manifes tations, and patients with pSpA may have additional axial skeletal involvement at presentation or may develop it later in the course of their disease. Other conditions sometimes included under pSpA are SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syn drome, acne-associated arthritis, and arthritis associated with hidrad enitis suppurativa. Table 374-1 shows the full spectrum of conditions included under "spondyloarthritis." Pattern recognition is important for the diagnosis of SpA. Typical patterns include asymmetric, mono- or oligoarticular (four or less joints) inflammatory arthritis of large joints in the lower limb (usu ally knee), with enthesitis, tendonitis, and dactylitis. This contrasts with RA, where polyarticular symmetric involvement of metacarpo phalangeal (MCP)/proximal interphalangeal (PIP) joints predomi nates. The cumulative prevalence of all conditions under SpA is 2–3% of the population, much more common than RA. PATHOLOGY OF SPONDYLOARTHRITIS SpA is a prototypic chronic immune-mediated inflammatory disease that couples inflammation to structural damage. A unique feature of SpA is that inflammation-induced bone loss coexists with pathologic new bone formation, which occurs at specific sites in the skeleton. These sites include not only the sacroiliac joint but also the anterior spinal ligaments or at entheses in the peripheral skeleton. If uncon trolled, axSpA may ultimately lead to a complete ankylosis of the sacroiliac joints and the spine, termed "bamboo spine." With increas ing awareness of SpA resulting from early diagnosis and treatment, there has been a steady decrease in the amount of structural damage observed over the past decades with a gradual shift of higher preva lence from r-AxSpA to nr-AxSpA. While histopathologic studies have led to an increased under standing of local inflammatory and structural changes, the acces sibility to target tissue particularly in the axial skeleton and tendons/ entheses has been hampered by technical issues. Most of the informa tion to date comes from surgically derived specimens from patients with longstanding disease. Accordingly, many of the described

Crohn's disease or ulcerative colitis with inflammatory arthritis Hidradenitis suppurativa, peripheral arthritis, rarely asymmetric sacroiliitis features represent disease under treatment, which inevitably impacts histopathology. Obtaining synovial tissue from an array of joints such as knees, wrists, and small joints in fingers has become much more readily accessible through ultrasound-guided synovial tissue biopsy, which permits study of synovial tissue alterations in an early treatment-naïve stage. PATHOGENESIS OF SPONDYLOARTHRITIS Although the exact mechanisms that initiate the disease are not fully delineated, genetic and environmental risk factors and molecular and cellular alterations at key disease sites have been implicated in the pathophysiology of SpA (Fig. 374-1). At these sites, which include the axial and peripheral joints, entheses, skin, and gut, variation is seen in the disease mechanisms and perturbations of the key cytokine path ways. These tissue-based variations are most likely associated with the dissimilar clinical responses observed between the spine, peripheral joints, and gut during treatment with cytokine inhibitors. ■ ■GENETIC ASSOCIATIONS IN AXIAL SPONDYLOARTHRITIS AND OTHER SPONDYLOARTHRITIS: HLA-B27 AND BEYOND HLA-B27 is a major histocompatibility complex (MHC) class I allele that forms the strongest genetic risk factor for SpA and specifically axSpA. MHC class I molecules are expressed on the surface of nucle ate cells and can present peptides to CD8+ T cells. HLA-B27 is present in 85–90% of the patients with r-axSpA and 50–90% in nr-axSpA, in contrast to about 5% of the healthy Caucasian population. Besides HLA-B27, other MHC class I genes and non-MHC coding genes have been identified in large genome-wide association stud ies (GWAS) in axSpA. Within the group of non-MHC coding genes, genes linked to innate immune processes, interleukin (IL)-23/IL-17

immunity, joint and bone remodeling, epithelial function, and antigen presentation are seen, which are processes relevant in the immuno pathogenesis of axSpA. Whether all of these represent independent risk factors is still not clear, although some appear to be interconnected. For example, genetic epistatic interaction has been suggested between ERAP1, a peptide-trimming enzyme, of which single nucleotide poly morphisms (SNPs) are associated with AS and HLA-B27. How HLAB27 fosters development of SpA remains unclear despite the discovery of this strong genetic association 50 years ago. At present, several theories exist with limitations to each of them. The “arthritogenic peptide” theory proposes that HLA-B27 pres ents pathological microbial peptides to CD8+ cytotoxic T cells that

Genetic predisposition e.g., HLA-B27 Gut Gut iNKT MAIT Urogenital system Tc17 Th17 γδT ILC3 Joint Skin IL-17 Axial SpA IBD PsA PsO Fibroblast Fibroblast Fibroblast Fibroblast MAIT ILC3 T17 T17 T17 T17 ILC3 γδT γδT Mø Mø Mø Neutrophil Neutrophil Neutrophil Neutrophil DC AntiIL-17 AntiIL-17 Anti-IL-17 JAKi JAKi JAKi JAKi AntiIL-23 AntiIL-23 Anti-IL-23 Anti-TNF Anti-TNF Anti-TNF AntiTNF FIGURE 374-1 Pathogenesis and signature cytokines across different disease domains in spondyloarthritis (SpA). In genetically predisposed individuals, SpA may arise from mechanical stress, a well-known disease precipitator in psoriatic arthritis and axial SpA, or by altered host-microbial interplay at inner (gut, urogenital tract) or outer (skin) surfaces culminating in a cytokine crosstalk characterized by both tumor necrosis factor (TNF)- and interleukin (IL)-17-driven immune responses. Drivers of disease include cells of both innate and adaptive immune system, along with tissue-resident stromal cells. Different disease domains (gut, spin, peripheral joints, and skin) harbor overlapping (e.g., TNF-α) but also distinct (e.g., IL-17, IL-23) signature cytokines, which has major therapeutic implications. Janus kinase (JAK) inhibitors, which interfere with signaling of several cytokines, are effective across all domains. then target cross-reactive human peptides leading to inflammation and resulting in molecular mimicry. Presumably, this first antigenic exposure could take place in the gut or at the urogenital tract. Several allotypes of HLA-B27 exist, but not all of them represent risk factors for axSpA. For example, HLA-B*2704 and HLA-B*2705 subtypes confer a genetic risk, whereas the HLA-B*2706 and HLA-B*2709 allotypes are not associated with axSpA even though they only differ in one peptide

Mechanical strain Barrier integrity loss CHAPTER 374 Urogenital system Spondyloarthritis Skin Neutrophil Mø T cell Joint TNF-α Disease domains ILC3 γδT Mø γδT residue or amino acid. This would suggest that there could be spe cific peptides that can only be presented by the pathogenic HLA-B27 subtypes to induce the “arthritogenic” response. In the arthritogenic peptide hypothesis, inflammation is driven by antigen presentation to CD8+ T cells. Existence of HLA-B27-restricted CD8+ T cells in the synovial fluid of AS patients was shown three decades ago, whereas more recent next-generation sequencing T-cell receptor (TCR) studies

showed expansion of both CD4+ and CD8+ TCR clonotypes in blood and synovium of HLA-B27-positive SpA. Expansion of CD8+ TCR clonotypes with the CAS **STDTQYF CDR3 motif were found in AS patients versus HLA-B27-positive controls in blood and synovium, which was recently suggested as a target for therapeutic intervention.

The second theory relates to the ability of HLA-B27 to homodimer ize. These HLA-B27 homodimers can be expressed at the cell surface and interact with innate immune receptors, such as the KIR3DL2 receptor, on T and natural killer (NK) cells resulting in IL-17 produc tion, one of the key

pathogenic cytokines in axSpA. However, there is still some controversy regarding whether various allotypes of HLA-B27 differ in their ability to form homodimers. PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders A third theory links HLA-B27 to unfolded protein responses (UPR) and autophagy, which may promote type 17 immune responses through release of IL-23. Support comes from the HLA-B27 transgenic rat model, while no evidence for an increase in UPR in synovial tissue or blood of HLA-B27-positive AS patients was found in steady state, which questions its role in humans. Although HLA-B27 has the strongest genetic link, other MHC class I associations have also been found, for example (HLA-Cw6) in PsA. IL-23R gene polymorphisms are shared across most forms of SpA. This suggests overlapping yet distinct features across different disease domains. ■ ■FACTORS INSTIGATING THE ONSET OF SPONDYLOARTHRITIS IN GENETICALLY PREDISPOSED INDIVIDUALS Despite the strong genetic association between HLA-B27 and AS, only a minority of HLA-B27-positive subjects develop disease. In addition, the risk of developing AS in HLA-B27-positive first-degree relatives of AS patients is only 20%. This indicates that additional factors are needed to induce disease. Because SpA affects seemingly distinct tis sues (spine, peripheral joints, enthesis, anterior eye chamber, intestine, skin), it has been a challenge to seek a common denominator between these different organs. Two main mechanisms are currently under con sideration: the role of intestinal microbiota following a loss of barrier integrity and an aberrant response to mechanical stress. Barrier Integrity Loss and the Intestinal Microbiota in SpA In view of the link between gut inflammation and SpA, much attention has been focused on barrier integrity loss in the intestine and the role of the intestinal microbiota. Evidence supporting this mecha nism has been the development of ReA following an infectious gas troenteritis with Salmonella typhimurium, Shigella enteritidis, Yersinia enterocolitica, or Campylobacter enteritidis. Studies have highlighted the loss of barrier integrity, which may facilitate translocation of bac teria and microbial peptides that can elicit an immune response. The human microbiome is shaped by genetic and environmental factors. Changes in diversity and composition of the gut microbiome have been identified in SpA, pinpointing an intestinal dysbiosis that is similar to patients with IBD. While most information on host-microbial interplay in SpA relates to the intestine, other mucosal surfaces and particularly the urogenital tract (e.g., Chlamydia) may serve as an entry route for pathogens to instigate the onset of SpA. Germ-free HLA-B27 transgenic rats fail to develop SpA, suggest ing a crucial pathogenic role for intestinal microbiota. In humans, microbiome profiling in stool and biopsy samples of HLA-B27–positive individuals found that HLA-B27 affects the gut microbiome even in the absence of disease. This supports the concept that in HLA-B27– positive individuals, intestinal dysbiosis occurs prior to the onset of clinical manifestations and may contribute to the risk of disease. Earlier research suggested that HLA-B27 may promote intracellular survival and persistence of pathogens such as Chlamydia trachomatis in monocytes, which could travel to joints and promote synovial inflam mation. More recent studies indicate that not all preclinical models of combined gut and joint disease mimicking SpA impact these sites similarly: in a tumor necrosis factor (TNF) cytokine-dependent model with Crohn’s-like ileitis and peripheral arthritis, gut inflammation was found to be microbiota dependent but not joint inflammation. This

suggests that intestinal microbiota may play a role in some, but not all, SpA patients or disease features. The skin, as the outer barrier of the body, is also vulnerable to the development of immune-mediated inflammatory disease. Like the inner barriers of the intestines and joints, the skin plays a key role in preserving tissue homeostasis at a site exposed to microbial, chemical, and mechani cal challenges. Alterations in the cutaneous microbiome of patients with psoriasis and PsA

have been described with striking similarities between nonlesional and lesional skin. However, the functional impact of skin microbiota on the disease trajectory is still ill defined. Mechanical Stress as Gateway to Joint Disease in SpA The entheses in SpA and PsA are key inflammatory target tissues, and patients can present with both axial and peripheral entheseal inflam mation. In both SpA patients and in individuals without inflammatory conditions, mechanical stress in entheses may lead to microdamage that leads to immune activation and tissue repair. The importance of mechanical strain in the pathophysiology of enthesitis in SpA is supported by observations in patients and animal models. Enthesitis occurs more often in the lower limbs, which are subject to higher mechanical strain. In patients with AS, exposure to physical labor was related to more structural damage. In mouse models, mechanical strain was shown to be causally related to development of enthesitis and SpA-related new bone formation through mechanisms that support chronicity of inflammation. Responses to mechanical stress are physiologic and self-limited, but they appear to be enhanced and prolonged in SpA. The reason for this is unclear, but this may be influenced by genetic factors and/or impaired intestinal barrier function. Chronic entheseal inflammation in axSpA also leads to excessive local bone responses. This is associated with osteoblast differentia tion initiated by prostaglandin E2, IL-17-A and -F, and IL-22 followed by activation of downstream bone morphogenic proteins and Wnt proteins, which are thought to play a role in pathological new bone formation. This culminates in the generation of bony spurs at vertebral bodies and sacroiliac joints, eventually leading to ankylosis. Common Versus Private Cytokine Hubs in Disease Domains in SpA Regardless of the route of disease initiation, several common effector pathways have emerged, with TNF and IL-17 representing sig nature cytokines in the immunologic basis of axSpA. The impact of TNF-α as a common effector pathway that acts down stream in the inflammatory process has been long recognized given its broad therapeutic efficacy across all disease domains (gut, enthesis, skin, eye, spine, and joints). TNF-α is an important activator and prod uct of macrophages that stimulates cytokine production in immune cells and activates fibroblasts. TNF-α can also be made by neutrophils and activated T cells in the inflamed synovium, enthesis, and intestine. By activating osteoclasts, it promotes inflammation-induced bone loss and bone erosions in SpA. Even though axSpA and IBD share a similar genetic predisposi tion in IL-23R polymorphisms, the two disorders differ substantially in their cytokine dependency. IL-17A blockade is effective in axSpA, whereas IL-23 inhibition does not provide benefit. Conversely, IL-23 blockers are approved in IBD, but agents targeting IL-17A are contra indicated in active IBD, due to the barrier protective roles of IL-17. In PsA, IL-23 and IL-17 inhibitors both appear to be effective. These observations instigated a search into cellular sources of IL-17 in SpA and their dependency on IL-23. Several IL-17A–producing cell types, including T17 cells (consisting of both CD4+ TH17 and CD8+ cytotoxic T17 [Tc17] cells), γ/δ T cells, and ILC3, are present at enthe seal sites in steady-state conditions. In synovial fluid of SpA patients, innate-like T cells such as γδ T cells were found to be the major T-cell source of IL-17 in the presence or absence of IL-23. This is of particu lar interest as these γδ T cells also survey epithelial sites such as skin or intestine. Thus, entheses, synovium, and mucosal sites appear to harbor cells that may boost IL-17A responses in the absence of IL-23. Janus kinase (JAK) inhibitors, which block signaling of several cytokines, are effective in a wide range of SpA including all clinical domains (Fig. 374-1).

AXIAL SPONDYLOARTHRITIS AxSpA is a chronic, immune-mediated inflammatory disorder pre dominantly involving the axial skeleton (sacroiliac joints and the spine) and also the peripheral skeleton. The axial skeleton is always involved, and involvement of the peripheral joints occurs in ~30–40% of patients. The hips, historically considered “root joints,” are the most common

nonspinal joints affected. Enthesitis in the axial and peripheral skel eton is a common feature, but dactylitis is relatively rare. Extraarticular manifestations include psoriasis, acute anterior uveitis, and IBD. Some patients with axSpA experience gradual spinal bony fusion over several years, which leads to reduced spine and neck flexibility. Despite these osteoproliferative changes in the skeleton, osteoporosis is a common morbidity. AxSpA significantly affects patients' well-being, function, productivity, and health-related quality of life. ■ ■DEFINITIONS AND NOMENCLATURE AxSpA is divided into r-axSpA (also called AS) and nr-axSpA, the dif ference based on the presence or absence of definitive sacroiliitis on plain radiographs. "Definitive sacroiliitis" is defined by the modified New York criteria (Table 374-2) as grade 2 bilateral or grade 3 or 4 unilateral or bilateral (Table 374-3). Patients with sacroiliitis of lower grade are classified as nr-axSpA. Since the differentiation between r-axSpA and nr-axSpA is based on the degree of sacroiliitis, it is open to disagreements even between trained musculoskeletal radiologists. The interreader reliability as measured by the kappa statistic is between 0.35 and 0.45. nr-axSpA and r-axSpA have the same clinical features and share similar disease burden, though in late-stage r-axSpA, fusion of spine and hip involvement can add to functional loss. ■ ■EPIDEMIOLOGY The male-to-female ratio is 2:1 for r-axSpA and 1:1 for nr-axSpA. The population prevalence of axSpA depends on the prevalence of HLAB27 in that geographic region. In Europe, HLA-B27 frequency in the population increases from south to north, and so does the prevalence of axSpA. For example, the prevalence of HLA-B27 in Spain and Nor way is 7 and 9%, respectively, and the prevalence of AS and axSpA in these two countries is 0.1 and 0.56%. The 2009–2010 National Health and Nutritional Examination Survey (NHANES) estimated that in the United States, the population prevalence of HLA-B27 is 6% and that of axSpA is between 0.9 and 1.4%, of which 0.5% were reported to have AS. The population prevalence of axSpA in the rest of the world is not well studied and is believed to be between 0.02 and 1.5%. Diagnostic prevalence of axSpA in the United States, which includes only the diag nosed cases in a population, is one-tenth that of population prevalence, suggesting a large undiagnosed population. Based on insurance claims databases in the United States, the diagnostic prevalence of axSpA increased between 2006 to 2019, which could be attributed to increased disease awareness. The incidence rates of AS are 0.005–0.01 per 100 patient-years globally and are not available for nr-axSpA. The risk of axSpA is 5% in HLA-B27-positive people but increases to 20% in HLA-B27-positive first-degree relatives of affected individuals with axSpA. TABLE 374-2 Modified New York Classification Criteria for Ankylosing Spondylitis (AS) Clinical Criteria

1. Low back pain >3 months Improved with exercise Not relieved by rest
2. Limited lumbar motion in fontal and lateral planes
3. Reduced chest expansion Radiographic Criteria
4. Bilateral grade >2 sacroiliitis on x-ray
5. Unilateral or bilateral grade 3 or 4 on x-ray Definite AS requires ≥1 clinical criterion plus 1 radiographic criterion Source: Adapted from S van der Linden et al: Arthritis Rheum 27:361, 1984.

TABLE 374-3 Grading of Sacroiliitis GRADE DESCRIPTION Grade 0 Normal Grade 1 Suspicious change CHAPTER 374 Grade 2 Minimum abnormality (small, localized areas with erosions or sclerosis, without alterations in the joint width) Grade 3 Unequivocal abnormality (moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis) Grade 4 Severe abnormality (total ankylosis) Spondyloarthritis Source: Reproduced with permission from S van der Linden et al: Evaluation of diagnostic criteria for ankylosing spondylitis. Arthritis

Rheum 27:361, 1984. ■ ■CLINICAL MANIFESTATIONS The most common first manifestation of axSpA is low back, hip, or buttock pain, which starts before the age of 40–45 years, usually in the 20s to 30s. The typical characteristics of this back pain include any combination of the following: insidious onset, chronicity (>3 months' duration), age of onset <45 years, improvement with exercise or activ ity and no improvement with rest, worse back pain in the second half of the night with improvement after getting out of bed and walking around, and prolonged (>30 min) morning stiffness. Back pain with these characteristics is termed "inflammatory back pain" (IBP) to dif ferentiate it from the common "mechanical back pain" (Table 374-4), but the term is a misnomer because only 15% of patients with IBP have demonstrable inflammation in their axial skeleton. Rarely, thoracic or neck pain can be a presenting feature, and when present, it is more commonly seen in women. Fatigue and stiffness are the two most both ersome symptoms after back pain in axSpA. Fatigue is multifactorial, secondary to sleep disturbance, active inflammation, and anemia, and may also indicate underlying depression and anxiety of chronic disease. Peripheral arthritis is seen in 30–40% of patients with axSpA. Typi cally, this is an asymmetric, oligoarticular inflammatory arthritis involv ing the large joints of the lower extremities and rarely the small joints of hands and feet. Hip involvement, presenting as pain in the groin with radiation to medial thigh or the knee, is common and is associated with significant functional impairment. Enthesitis is a common manifesta tion of axSpA. Enthesitis may present as heel pain (plantar fasciitis, Achilles tendon insertion pain), chest wall pain, intercostal muscle insertions, medial or lateral epicondylitis, quadriceps or patellar tendon insertion pain around knees, or pelvic rim pain. Dactylitis is an uncom mon manifestation of axSpA. Persistent axial inflammation may lead to bony fusion of sacroiliac joints, apophyseal joints, and development of syndesmophytes by osteoproliferation in the outer fibers of the annulus fibrosus of the intervertebral disks. These bony changes lead to limitation of spinal, including neck, mobility in all directions and are a major cause of significant functional impairment in late stages of the disease. Extramusculoskeletal manifestations of axSpA, such as psoriasis, IBD, and acute anterior uveitis, can also be the presenting symptom of axSpA in some patients, and such patients may first present to a der matologist, gastroenterologist, or an ophthalmologist. Uveitis, the most TABLE 374-4 Clinical Features of Inflammatory Versus Mechanical Back Pain MECHANICAL

BACK PAIN FEATURE INFLAMMATORY BACK PAIN Age at onset Before 40–45 years 20–65 years Onset Insidious Acute or insidious Morning stiffness Prolonged (more than 30 min) Less than 30 min Pain at night Yes, usually after midnight No, usually late in the day Exercise/activity Improves pain and stiffness Worsens pain Rest/inactivity Worsens pain and stiffness Improves pain Duration Chronic Acute or chronic Response to fulldose NSAIDs More than 50% relief in 48 hours Limited relief Note: Not all features are required for diagnosis of inflammatory back pain, nor are they present in every patient. Abbreviation: NSAIDs: nonsteroidal anti-inflammatory drugs.

common extramusculoskeletal manifestation, is seen in 40% of patients with axSpA and presents as eye discomfort followed by redness, pain, photophobia, and miosis. The typical phenotype of uveitis associated with axSpA is acute, anterior, unilateral, and episodic. While frank IBD is seen in 10%, histologic evidence of subclinical gut inflammation is seen in up to 50% of patients. Psoriasis is seen in 10%, and osteoporosis can be present in 40%.

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders AxSpA can affect multiple organ systems. The two renal manifesta tions of axSpA are IgA nephropathy, which can present at

any time in the disease course as microscopic hematuria, and nephrotic syndrome secondary to renal (AA) amyloidosis, which is a late complication only seen after prolonged uncontrolled inflammation. Conduction abnor malities (heart blocks) can be seen at any stage of the disease, whereas aortic valve insufficiency and cauda equina syndrome presenting as urinary hesitancy and/or saddle anesthesia are late complications. Pulmonary manifestations of axSpA include apical fibrosis, cavitary lung lesion, or fibrotic parenchymal lesions. Sleep apnea syndrome and restrictive lung disease seen in late-stage axSpA are mostly related to osteoproliferative structural changes of the cervical spine and rib cage. The course of axSpA can be variable, with close to 50% of patients progressing from nonradiographic to radiographic stage over 20 years and <10% progressing to significant spinal involvement with bamboo spine. Risk factors for osteoproliferation include male sex, persistent inflammation (seen on magnetic resonance imaging [MRI] of sacro iliac joints and spine, high C-reactive protein [CRP]), syndesmophytes, presence of HLA-B27, and smoking. ■ ■DIAGNOSIS A diagnostic delay of 5–14 years from symptom onset of axSpA reported in various parts of the world is mostly related to the common ality of mechanical back pain in the general population. Traditionally, Chronic back pain >3 months, Insidious onset <45 years, common causes such as mechanical back pain, fibromyalgia ruled out SI joint x-ray positive for definite sacroiliitis Yes No Presence of SpA features: IBP, inflammatory arthritis, uveitis, dactylitis, enthesitis, psoriasis, IBD, family history, good response to NSAIDs, high CRP AS (R-axSpA) ≥ 4 SpA Features Compelling clinical picture Yes Nr-axial SpA Nr-axSpA FIGURE 374-2 Schema for the diagnosis of axial spondyloarthritis in a patient complaining of chronic back pain (back pain lasting >3 months).

AS is thought to be a disease of males, and back pain and enthesitis in women are commonly mistaken for fibromyalgia. This delays the diagnosis in females even further. Lower prevalence of HLA-B27 in nonwhite populations also adds to the delay in diagnosis. The diagnosis of axSpA is based on pattern recognition, ruling out common causes for the symptoms, and clinical reasoning. Figure 374-2 shows a schema for the diagnosis of axSpA in a patient complaining of chronic (>3 months) back pain. While elevated inflammatory mark ers, erythrocyte sedimentation rate (ESR), and CRP help in making the diagnosis of axSpA, these tests are neither sensitive (seen in only 30–40% of patients with active axSpA) nor specific for axSpA. Imaging plays a very important role in the diagnosis of axSpA. A single anteroposterior (AP) view or a Ferguson view x-ray of the pelvis is sufficient to image sacroiliac joints. Multiple views (e.g., oblique) of the sacroiliac joints add little in making the diagnosis; in addition, they increase radiation risk to gonads. Radiographic features of sacroiliitis include marginal sclerosis, erosions, narrowing and widening of the joints, and in late stages, fusion (Fig. 374-3A and Table 374-3). As a gen eral rule, plain radiographs of the spine should be avoided in patients with chronic back pain. However, there are some characteristic changes of axSpA seen in the lateral radiograph of the spine, and they include Romanus lesions or the shiny corner sign and squaring of the vertebral body seen as a result of erosions at the attachments of the spinal liga ments at the vertebral corners. Andersson lesion is an uncommon find ing and is characterized by vertebral body erosion and sclerosis at the intervertebral disk level. In the late stages, ossification of the outer layer of annulus fibrosus leads to syndesmophyte formation (Fig. 374-3B). Typical syndesmophyte orientation is vertical, differentiating it from the horizontal orientation of osteophytes, which is commonly seen with osteoarthritis (OA) of the spine. Bamboo spine, or ankylosis of the entire spine, is seen in a very small percentage of late-stage AS patients. <4 SpA Features MRI SI Joints positive for sacroiliitis Yes No Compelling clinical picture plus HLA-B27 positive Clinical picture not compelling and/or HLA-B27 negative Nr-axSpA Not axSpA

A B FIGURE 374-3 Radiographic axial spondyloarthritis. A. Bilateral sacroiliitis (modified New York grade 3) with sclerosis and erosions. B. Lateral view cervical spine in advanced radiographic axial spondyloarthritis showing anterior syndesmophytes and fused facet joints. Low-dose computed tomography (CT) of the sacroiliac joints and spine in the diagnosis of axSpA is emerging as an alternative to plain radiog raphy for diagnosis and assessing progression (Fig. 374-4). Magnetic resonance imaging (MRI) of the sacroiliac joints and spine has evolved as an important tool in making the diagnosis of axSpA. During the early stage of disease, MRI of the sacroiliac joints may show evidence of active inflammation, or “osteitis,” and that may be the only abnormality. As time passes, the active inflammatory changes transition to fatty metaplasia, and this may further transform to new bone forma tion. The structural changes of sclerosis, fat metaplasia, erosions, fat metaplasia in an erosion cavity (backfill), and new bone formation, in addition to the inflammatory changes seen on MRI, aid in making the diagnosis of axSpA (Fig. 374-5). Sole presence of inflammatory lesions in early stages or sole presence of ankylosis in very late stage may be enough for the diagnosis of axSpA, but as a general rule, multiple types of inflammatory and structural lesions increase the suspicion of axSpA. In the spine, multiple corner inflammatory lesions and/or multiple cor ner fatty lesions increase the confidence of axSpA diagnosis. MRI is a very sensitive imaging technique, and mechanical stress on the sacroiliac joints in professional athletes, postpartum women, and even in normal individuals, especially above the age of 40, may show changes of osteitis. Fat metaplasia-type changes in the sacroiliac joints are also seen in degenerative arthritis as well as in normal individuals. Inappropriate utilization of MRI can lead to overdiagnosis.

CHAPTER 374 Spondyloarthritis FIGURE 374-4 Computed tomography of the thoracic spine sagittal view in radiographic axial spondyloarthritis showing anterior and posterior syndesmophytes. ■ ■DIFFERENTIAL DIAGNOSIS Chronic nonspecific “mechanical” back pain is common in the general population, and axSpA is the etiology in only 4–5% of such patients. Mechanical causes of back pain therefore should be considered first in a patient presenting with chronic back pain. The so-called “red flag” A B FIGURE 374-5 Magnetic resonance images of spondyloarthritis. A. T1-weighted image of sacroiliac joints with bilateral erosions (left-sided erosions marked by **), left fatty metaplasia (single *), and right bone marrow edema (marked with white arrows). B. Short tau inversion recovery (STIR) image with bilateral bone marrow edema suggestive of joint space inflammation (shown by *) and anterior capsulitis (shown by a white arrow).

signs of fever, weight loss, advanced age, and past history of malig nancy should alert the examiner to look for osteomyelitis, osteoporotic fracture, or metastatic disease. In young patients with generalized body pain, fibromyalgia, central sensitization, hypermobility, hypothyroid ism, and hypovitaminosis D may be considered.

Abnormalities on incidental imaging in a patient with or even without chronic back pain lead to other differential diagnoses such as diffuse idiopathic skeletal hyperostosis (DISH) or osteitis conden sans ilii (OCI). DISH is a noninflammatory, degenerative condition affecting the spine, with exuberant new bone formation in the form of anterior and posterior longitudinal ligament ossification of at least four contiguous vertebral bodies and bulky “flowing” osteophytes typically on the right side of the thoracic spine, but normal sacroiliac joints. It is generally seen in obese, diabetic males, often older than 50 years of age. DISH is sometimes mistaken for bamboo spine of AS. OCI is usually an asymptomatic condition of multiparous women character ized by radiographic

findings of a triangular area of dense sclerosis on the lower and inferior part of the iliac side of the sacroiliac joints. This can be mistaken for sacroiliitis, and in early stages, MRI of the sacroiliac joints may be indistinguishable from that of axSpA. Lack of erosions should help distinguish OCI from axSpA. OCI can be seen in nulliparous women and even men. While DISH and OCI are generally asymptomatic, some patients with either condition may present with chronic back pain. PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders Inflammatory back pain with sclerotic changes on sacroiliac joint radiographs can also be seen in conditions such as postpartum insuf ficiency fracture of the sacrum; septic sacroiliitis from tuberculosis, brucellosis, fungi, and other infectious agents; and rarely, malignancies such as acute lymphoblastic leukemia. ■ ■MONITORING AxSpA patients should be monitored at every visit for disease activ ity, function, and medication safety. The frequency of monitoring is individualized. Assessment of disease activity can be performed by using the Bath Ankylosing Spondylitis Disease Activity Index (BAS DAI) or the Ankylosing Spondylitis Disease Activity Score (ASDAS). Functional impairment can be measured by the Bath Ankylosing Spondylitis Functional Index (BASFI). This is a patient-administered questionnaire that includes 10 activities of daily living. The Bath Ankylosing Spondylitis Metrology Index is an index of spinal and hip mobility in patients with AS. The ESR and CRP may be useful in monitoring disease activity. MRI of the sacroiliac joints or spine is expensive and is not indicated to monitor disease activity of AxSpA. Spine radiographs and MRI are not used for monitoring purposes in daily practice, although they may be used if back pain persists or relapses to rule out active inflammation despite therapy or complications such as spinal fractures. TREATMENT Axial Spondyloarthritis Principles of treatment of nr-axSpA and r-axSpA are identical and are described as one disease. Some agents are approved to treat only AS (r-axSpA) and are mentioned below. The targets for treatment include low disease activity or remis sion. Traditionally, the treatment of axSpA was limited to exer cise, physical therapy, and nonsteroidal anti-inflammatory drugs (NSAIDs), but with the advent of biologics and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), great strides have been made in in the last two decades. Shared decision-making regarding all modes of therapy is the key to success. Treatment of axSpA can be divided into nonpharmacologic, pharmacologic, and surgical. NONPHARMACOLOGIC INTERVENTIONS Physical exercise in the form of active physical therapy (on land or aquatic) and self-directed physical exercise are strongly recom mended by all international guidelines and should be promoted.

Physical therapy improves fatigue, mobility, and posture. Smoking cessation is encouraged in all patients. PHARMACOLOGIC INTERVENTIONS The American College of Rheumatology (ACR), Spondylitis Associ ation of America (SAA), Spondyloarthritis Research and Treatment Network (SPARTAN) treatment guidelines, and ASAS-EULAR (European Alliance of Associations for Rheumatology) treatment recommendations have many commonalities regarding the order of treatments, choices of agents, and precautions. Table 374-5 outlines pharmacologic interventions for the treatment of axSpA. The use of immunosuppressive biologics and tsDMARDs has been associated with an increased risk of serious infections. While bacterial infections are seen in both classes, herpes zoster is mostly seen with JAK inhibitors (JAKis), and reactivation of latent tubercu losis is mostly seen with TNF inhibitors (TNFis). Mucosal and skin Candida infections are associated with IL-17 inhibitor (IL-17i) use. Other side effects of biologic therapy include injection-site reac tions with subcutaneous injections or infusion reactions with intra venous (IV) medication. TNFi adverse effects include development of demyelinating disease, worsening of congestive heart failure, and paradoxical development of psoriasis-like skin lesions. Adverse events associated with

IL-17i therapy include leukopenia and devel opment or worsening of IBD. JAKis have a higher risk of major cardiovascular adverse events and cancers (lymphoma and lung cancers), especially in patients aged 65 years or older and in those with current or past history of smoking, with history of cardiovas cular disease, or with malignancy. As a result, the U.S. Food and Drug Administration (FDA) suggests reserving these medicines for patients who have had an inadequate response or intolerance to one or more TNFi. SURGICAL INTERVENTIONS Hip involvement in axSpA leads to significant functional impair ment, and total hip arthroplasty should be considered in patients with refractory hip pain or functional decline in the presence of radiographic evidence of structural damage. Spinal osteoto mies should be reserved for severe fixed kyphotic deformities in advanced AS that affect horizontal vision and should be performed in centers of expertise. ■ ■COMPLICATIONS The prevalence of osteoporosis is ~25% after 10 years of axSpA. Verte bral fractures are seen in ~10% of patients with AS. The lower cervical spine is the most commonly involved area, where there is often also neurologic compromise. One should consider vertebral fractures in patients with neck and back pain that has changed in intensity or character from baseline. Another rare complication is the cauda equina syndrome from long-standing AS resulting from inflammation of the lumbosacral nerve roots caused by arachnoiditis. Cardiac manifesta tions include aortic valve insufficiency and conduction abnormali ties. Pulmonary manifestations are rare and include chest expansion restriction from ossification of costovertebral joints and upper lobe–predominant interstitial lung disease. Patients with AS can have IgA nephropathy or, in late stages, renal amyloidosis if the disease is left untreated. Cardiovascular disease is being recognized as a common comorbidity in patients with AS and is linked to chronic inflammation. All patients with AS should be counseled about the traditional risk factors for cardiovascular disease, and appropriate treatment should be instituted if necessary. PSORIATIC ARTHRITIS PsA is a relatively common immune-mediated inflammatory condition that may lead to progressive joint damage. If left untreated, it is associ ated with poor quality of life, loss of function, and increased morbid ity and mortality. PsA, associated with cutaneous and nail psoriasis, involves peripheral joints, axial skeleton (sacroiliac joints and spine), entheses, and tendon sheaths. In addition, uveitis and inflammatory bowel disease may coexist with PsA. Common comorbidities of PsA

TABLE 374-5 Pharmacologic Management of Axial Spondyloarthritis (axSpA) • Nonsteroidal anti-inflammatory drugs (NSAIDs) should be used in highest tolerable doses continuously in active disease and on an as-needed basis if the disease is stable. No particular NSAID is preferred over any other. Side effects to monitor are gastric ulcer disease, hypertension, renal insufficiency, and cardiovascular disease. • Conventional synthetic DMARDs like sulfasalazine, up to 3 g/d, and methotrexate, up to 25 mg/wk, are useful for the treatment of peripheral joint and entheses involvement, but not for axial disease in axSpA. • If the disease remains active despite a 4-week trial of full-dose NSAIDs, treatment should be escalated to start a biologic from either the TNFi or IL-17i class. • Before initiating therapy with biologics or JAKi, screening for latent tuberculosis, hepatitis B, and hepatitis C should be performed. • All five TNFi agents are approved for the treatment of AS, while selective TNFis are approved for nr-axSpA in various countries. • Soluble receptor of TNF–etanercept 50 mg subcutaneous (SC) injection once weekly. • TNFi monoclonal antibodies: • Adalimumab 40 mg SC every 2 weeks. • Certolizumab pegol 200 mg SC twice a month or 400 mg SC once a month. • Golimumab 50 mg SC once a month or golimumab 2 mg/kg intravenous (IV) at weeks 0, 4, and then every 8 weeks thereafter. • Infliximab 5 mg/kg IV infusion at weeks 0, 2, 6, and then every 6 weeks. • No TNFi is preferred, except in patients with concomitant uveitis or IBD in whom TNF monoclonal antibodies are preferred over soluble receptor

TNFi therapy. • In the case of primary failure of TNFi, treatment can be switched to IL-17i or JAKi. In the case of secondary failure of TNFi therapy (failing after initial benefit), an alternative TNFi can be used. • Two IL-17Ais are approved for the treatment of nr-axSpA and AS. • Secukinumab 150 mg SC at weeks 0, 1, 2, 3, and 4, followed by 150 or 300 mg every 4 weeks. • Ixekizumab 160 mg SC once, followed by 80 mg every 4 weeks. • In case of primary failure of IL-17Ai, treatment can be switched to TNFi or JAKi. In the case of secondary failure of IL-17Ai therapy, an alternative IL-17i can be used. • Two JAKis are approved for the treatment of AS, while only one is approved for nr-axSpA. JAKi should be used in patients who have failed TNFi. • Tofacitinib 5 mg orally two times a day is approved for the treatment of AS only. • Upadacitinib 15 mg once a day is approved for the treatment of AS and nr-axSpA. • One IL-17A and IL-17F inhibitor is approved in certain parts of the world to treat both nr-axSpA and radiographic axSpA. • Bimekizumab 160 mg SC every 4 weeks. • Local glucocorticoid injections for upper extremity enthesitis or intraarticular injections for peripheral arthritis are indicated. Injections around lower limb weightbearing entheses are not recommended because of the risk of rupture. • Systemic glucocorticoids do not have any efficacy in axSpA and should be avoided. Abbreviations: AS, ankylosing spondylitis; DMARDs, disease-modifying antirheumatic drugs; IBD, inflammatory bowel disease; IL-17i, interleukin 17 inhibitor; JAKi, Janus kinase inhibitor; nr-axSpA, nonradiographic axial spondyloarthritis; TNFi, tumor necrosis factor inhibitor. include depression, metabolic syndrome, diabetes mellitus, and car diovascular disease. Sometimes the term “psoriatic disease” is used to emphasize these varied manifestations. In 1973 Moll and Wright defined PsA as an inflammatory arthritis (peripheral arthritis and/or sacroiliitis or spondylitis), with presence of cutaneous psoriasis and absence of RF. They demonstrated the association between PsA and the gene HLA-B*27 and described five phenotypes of PsA, namely asymmetric oligoarticular inflammatory arthritis, symmetric polyarticular arthritis, distal interphalangeal joint arthritis, spondylitis, and arthritis mutilans. Over the years, enthesitis and dactylitis have been added to these musculoskeletal manifesta tions. It is important to remember that these clinical phenotypes are not exclusive and frequently coexist. ■ ■EPIDEMIOLOGY With a prevalence of 2–3%, skin psoriasis is one of the most common immune-mediated diseases. The prevalence of PsA in patients with psoriasis is 30% (range, 6–42%). The incidence of PsA in patients with psoriasis is 3 per 100 patient-years (range 2–10) and depends on the severity of skin psoriasis. The likelihood of developing PsA in psoriasis patients does not change over time. ■ ■CLINICAL FEATURES Clinical features of PsA include peripheral arthritis, axial arthritis (spondylitis), enthesitis, dactylitis, and tenosynovitis. Inflammatory arthritis presents with joint pain, swelling, prolonged stiffness, and reduced mobility. Typically, early PsA is oligoarticular (<4 joints) and often asymmetric, and as the number of affected joints increases, the disease becomes polyarticular and the distribution becomes more sym metric. Distal interphalangeal joint involvement is typical of PsA and is associated with psoriatic nail changes since the nail bed is closely linked to the distal interphalangeal (DIP) joints. Inflammatory arthritis of the axial skeleton occurs in 5% of PsA patients in early stage and can be seen in 50% of patients after 20 years

CHAPTER 374 Spondyloarthritis of disease. Axial inflammatory arthritis presents with inflammatory back and/or neck pain and stiffness, which is typically worse after peri ods of prolonged inactivity and improves with activity. However, axial arthritis can be asymptomatic or overshadowed by patients’ peripheral arthritis symptoms. Most patients with axial involvement have sacroi liitis, although axial involvement without sacroiliitis may distinguish axial PsA from axial SpA. While many of the radiographic features may resemble AS, presence of asymmetric sacroiliitis, nonmarginal and asymmetric bulky syndesmophytes, and frequent involvement of cervical spine

have been more often assigned to axial PsA then AS. These phenotypic differences have led to the suggestion that this may reflect potential pathogenic distinctions. Whether axial PsA pathogen esis differs substantially from axSpA and especially whether this has therapeutic consequences are the subjects of investigations by several international consortia. Other important musculoskeletal manifestations of PsA include dactylitis, enthesitis, and tenosynovitis. Dactylitis is defined as inflam matory swelling of an entire finger or toe. Dactylitis is due to inflam mation of the joints, tendons, bones, and soft tissues within the digit. Dactylitis is a marker of severity of PsA, and persistent dactylitis leads to structural damage to the joints within that digit. Arthritis mutilans is an end manifestation of a severe arthritis process. Enthesitis is another important manifestation of PsA. The most common sites affected by enthesitis are the plantar fascia and Achil les tendon insertion on the calcaneum (plantar fasciitis and Achilles enthesitis). Other common sites for enthesitis include quadriceps tendon insertion on the patella, patellar tendon insertion on tibia, medial and lateral epicondyle, pelvic rim, spinous processes, and intercostal muscle insertion on ribs. Tenosynovitis, or inflammation of the tendon sheath, may affect tendons in the hands, wrists, and around the ankles. Most patients with PsA have psoriasis vulgaris. In ~80% of people with PsA, psoriasis develops first, and the musculoskeletal mani festations develop after a variable duration. In ~10%, both arthritis

and psoriasis develop simultaneously. While patients with PsA have psoriasis by definition, in 10% of patients, the arthritis develops first and cutaneous psoriasis manifests a few years later. Diagnosis of PsA is challenging in such patients, and family history of psoriasis, with typical musculoskeletal involvement, can help make the diagnosis. Although 40% of patients with psoriasis without PsA have nail lesions, nail involvement is much more frequent in patients with PsA, affect ing close to 90% of patients. Psoriatic nail manifestations may be classified into nail matrix disease and nail bed disease. Nail pitting, leukonychia, crumbling, and red spots in the lunula are manifestations of nail matrix disease, whereas onycholysis, subungual hyperkeratosis, oil drop change, and splinter hemorrhages are manifestations of nail bed disease.

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders Patients with PsA may also have involvement of the eye and gastro intestinal tract. Uveitis may occur in 5% of patients, and conjunctivitis is rarely seen. While unilateral acute anterior uveitis is the commonest form, posterior uveitis and bilateral eye involvement are also reported. IBD (Crohn’s disease or rarely ulcerative colitis) may coexist in patients with PsA. Mucous membrane inflammation presents with painful mouth ulcers and rarely urethritis. The disease course of PsA is variable. Whereas some patients do well with few joints involved and no significant damage, others progress very quickly to develop marked joint damage within a few months. Patients with PsA have a worse quality of life and function compared with the general population as well as to patients with psoriasis without PsA. Patients with psoriasis and PsA have an increased risk of cardiovas cular disease, as high as the risk in people with diabetes mellitus. The increased risk is independent of cardiovascular risk factors and cor relates with more severe skin disease, disease duration, and increased inflammatory markers. Patients with PsA have more severe subclinical atherosclerosis compared with psoriasis patients without PsA. The prevalence of hypertension, type 2 diabetes, obesity, metabolic syn drome, fatty liver disease, angina, and myocardial infarction is higher among patients with PsA compared with the general population. Obesity has an additional adverse impact on PsA disease activity and treatment response. Patients with psoriasis and PsA have increased rates of depression and suicidality compared to the general population. The prevalence of

malignancy in PsA is not increased, and mortality studies have shown conflicting results. ■ ■DIAGNOSIS The diagnosis of PsA is based on clinical features of cutaneous psoriasis with inflammatory musculoskeletal disease such as arthritis, dactylitis, enthesitis, or spondylitis. Presence of dactylitis is an important sign, and careful examination of feet is important since dactylitis of a single toe or enthesitis around the heel may be the only musculoskeletal man ifestation of PsA in a patient with psoriasis. Psoriasis may be hidden in areas such as the scalp, umbilicus, below breasts, or in the natal cleft, or it may be present in the nail only and should be looked for carefully. Typical involvement of the joints of the fingers or toes is in a “ray” dis tribution (involvement of all joints in a finger or toe), with one finger showing dactylitis, another with bony ankylosis, and the neighboring finger showing arthritis mutilans. The pattern of involvement in PsA is often asymmetric compared with RA, in which the pattern tends to be symmetric. The presence of spondylitis with asymmetric oligoarticular peripheral arthritis would virtually rule out RA and would make the diagnosis of PsA more likely. The diagnosis of PsA may sometimes be made even in the absence of psoriasis if the above characteristic features are present and if there is a family history of psoriasis or PsA. Laboratory tests only play a minor role in the diagnosis of PsA. Tests for acute-phase reactants such as ESR or CRP are abnormal in ~50% of patients despite clinically active disease. High levels of ESR or CRP are markers of severe disease and are predictors of radiographic damage and mortality. RF is typically negative, but low titer RF or low titer anticyclic citrullinated peptide antibody may be positive in <10% of patients. HLA-B27 is positive in 20% of all patients with PsA and 50% of patients with axial PsA. A patient with PsA may present with monoarticular arthritis of knee or ankle, and in this situation,

synovial fluid analysis will differentiate between infection (“septic arthritis”), crystal-induced arthritis, OA, or immune-mediated inflam matory arthritis such as PsA. White blood cell counts of >2000/mL of synovial fluid with no crystals and negative Gram stain and culture are diagnostic of inflammatory arthritis and, in this clinical scenario, should raise the suspicion of SpA such as PsA, reactive arthritis, or IBD-associated arthritis. Routine laboratory tests such as complete blood counts or kidney or liver function tests do not help in making the diagnosis of PsA but can be useful for monitoring treatment or assessing comorbidities. ■ ■IMAGING FEATURES Imaging is an important modality in the assessment of PsA and may help in confirming the diagnosis and determining disease severity. Radiographs of the hands, feet, pelvis, spine, and other affected joints should be performed to look for changes suggestive of PsA. In early disease, x-rays of the hands and feet show soft tissue swelling around the involved joints. Periarticular osteopenia is generally absent. Mar ginal erosions are markers of disease severity and predict further radio graphic progression, deformity, and disability. In PsA, erosions are often accompanied by “fluffy” new bone formation. The combination of ero sions at joint margins with new bone formation is characteristic of PsA (Fig. 374-6). New bone formation may also cause ankylosis of the joints. There also may be joint space narrowing, “pencil-in-cup” deformity, and in late stages, such as arthritis mutilans, total joint destruction or joint lysis and acro-osteolysis (resorption of the terminal phalanx) are seen. Certain characteristic radiographic features such as “pencil-in-cup” deformity, bony ankylosis in a ray distribution, or “fluffy” new bone formation close to sites of erosions can be pathognomonic of PsA. X-ray of the pelvis (anteroposterior view) may show changes of sac roiliitis. Sacroiliitis in PsA is more likely to be unilateral compared to axSpA, where it is usually bilateral. Axial involvement in PsA may show changes of shiny vertebral corners, erosions, squaring of vertebrae, and syndesmophyte formation on the lateral view of the spine. While this may mimic radiographic axSpA, often in PsA, the syndesmophytes are chunky and “nonmarginal” and develop

from sites away from the vertebral corners (Fig. 374-7). The presence of such syndesmophytes is characteristic of PsA. Cervical and lumbar vertebrae are frequently involved. Rarely, atlantoaxial subluxation develops with potentially serious consequences. Ultrasound combined with Doppler evaluation can help in differ entiating enthesitis from fibromyalgia tender points or in differenti ating mechanical versus inflammatory etiology. Ultrasound can also detect erosions before they appear on x-rays, especially in the hand joints. Some of the findings in inflammatory enthesitis in PsA include thickening of the tendon with loss of the regular fibrillar architecture, hypoechoic lesion, and neovascularization around insertions of ten dons, ligaments, and joint capsules at the bone. Bony irregularities and erosions would distinguish inflammatory from mechanical enthesitis. Ultrasound, however, is highly operator dependent and is useful in expert hands only, which remains a limitation. MRI with IV contrast of the peripheral joints can detect synovitis, and MRI without contrast in axial joints may show bone marrow edema (on the short tau inver sion recovery [STIR] image) suggestive of active inflammation before any abnormality is visualized on x-rays. MRI can also show erosions in the joints even before they are seen on plain x-rays. MRI is also very useful in visualizing enthesitis. CT scans are useful when an MRI is unavailable or contraindicated, although the risk of considerable radia tion exposure needs to be balanced with the benefits. Nuclear medicine bone scans are neither specific nor sensitive to diagnose PsA. Use of fluorodeoxyglucose positron emission tomography scans to assess inflammatory burden in PsA is experimental. ■ ■CLASSIFICATION CRITERIA The Classification of Psoriatic Arthritis (CASPAR) criteria (Table 374-6) have a specificity of 98.7% and sensitivity of 91.4%. To meet the CASPAR criteria for PsA, individuals must first have inflammatory articular dis ease (joint, spine, or entheseal) and must have at least three points from the five categories described in Table 374-6.

A FIGURE 374-6 A. X-ray of the feet in psoriatic arthritis. These images show erosions, loss of cartilage in bilateral first metatarsophalangeal (MTP) joints, bilateral interphalangeal joint of great toes, and right fifth MTP joint. There are changes of secondary osteoarthritis with sclerosis and osteophyte formation in these joints and early pencil-in-cup deformity in the left fifth MTP joint. B. X-ray of the hands in psoriatic arthritis. Left thumb interphalangeal joint showing early pencil-in-cup deformity (marked with **). Right third finger has dactylitis and shows periosteal new bone formation in the third proximal phalanx (white arrow), along with erosions in the proximal (marked with *) and distal interphalangeal joints (marked with *). This combination of periosteal new bone formation and erosions in “ray” distribution is typical of psoriatic arthritis. ■ ■DIFFERENTIAL DIAGNOSIS OA, the most common form of arthritis, occurs in ~5% of the popu lation, and it may coexist with psoriasis especially in the DIP joints. Thus, the presence of Heberden nodules in the context of patients with hand OA with concomitant psoriasis is an important differential diagnosis to be made. Psoriatic nail involvement would differentiate PsA from inflammatory OA of the DIP joints, along with imaging abnormalities such as on ultrasonography. Patients with “seronegative RA” should be carefully examined for presence of psoriasis in hidden areas (scalp, umbilicus, gluteal cleft, genitals, below breasts, and nails) and questioned about family history of psoriasis. Many patients with seronegative RA may have pSpA such as PsA, ReA, or IBD-associated arthritis. The high skin turnover in psoriasis can lead to hyperuri cemia, and gout can coexist with PsA. Flare of monoarticular PsA should be assessed with synovial fluid analysis to rule out gout or septic arthritis. PsA shares several clinical, laboratory, and imaging features with other SpA conditions such as ReA, IBD-associated FIGURE 374-7 X-ray of the lumbar spine anteroposterior view in psoriatic arthritis. The images show nonmarginal “chunky” syndesmophytes (marked with white arrows).

CHAPTER 374 Spondyloarthritis B arthritis, and axSpA, and patients may fulfill classification criteria of multiple SpAs simultaneously. Calcium pyrophosphate deposition disease (CPPD) arthritis affecting the MCP joints may coexist in the elderly with skin psoriasis. Chondrocalcinosis of the triangular fibrocartilage in the wrist, “hook-like” osteophytes in the MCP joints, and absence of erosions or fluffy new bone formation should rule out PsA. Synovitis, acne, pustulosis, SAPHO, and rarely hidradenitis sup purativa may mimic palmer plantar psoriasis and PsA. ■ ■ASSESSING DISEASE ACTIVITY IN

PSORIATIC ARTHRITIS Disease Activity in Psoriatic Arthritis (DAPSA) and Minimal Disease Activity (MDA) are the most common instruments used to assess dis ease activity in clinical practice. A simple scale used to assess plaque psoriasis is to ask the patient, “How many palms will be covered by the current psoriasis on your body?” With one palm of the patient counted as 1% body surface area (BSA), the total BSA involved by active psoriasis can be assessed. Nail psoriasis and dactylitis can be TABLE 374-6 Classification Criteria for Psoriatic Arthritis (CASPAR) Patients with Inflammatory Articular Disease (Joint, Spine, or Entheseal) Plus ≥3 Points Meet CASPAR Criteria for Psoriatic Arthritis CATEGORY DESCRIPTION POINT VALUE Psoriasisa Current psoriasis as determined by a rheumatologist or dermatologist

Personal history of psoriasis obtained from patient or qualified health care provider

A family history of psoriasis as reported by patient in a first- or second-degree relative

Nail changes Typical psoriatic nail dystrophy (onycholysis, pitting, and hyperkeratosis) present at assessment

Rheumatoid factor Rheumatoid factor negative

Dactylitis (swelling of entire digit) Current dactylitis or history of dactylitis recorded by a rheumatologist

Radiographic evidence Juxtaarticular new bone formation (excluding osteophyte formation) on plain radiograph of hand or foot; appears as illdefined ossification near joint margins

aPsoriasis should account for only one of the three descriptors. Source: Adapted from WJ Taylor et al: Arthritis Rheum 54: 2665, 2006.

assessed by simply counting the digits with affected fingernails or with dactylitis. A number of enthesitis indices have been developed, such as the Spondyloarthritis Research Consortium of Canada Index and the Leeds Enthesitis Index. Axial arthritis is assessed using tools borrowed from axSpA assessment.

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders TREATMENT Psoriatic Arthritis The treatment target is remission or low disease activity. This is achieved by nonpharmacologic and pharmacologic interven tions including novel advanced therapies. A multidisciplinary team consisting of rheumatologists, physical and occupational thera pists, dermatologists, and depending upon the domains involved, gastroenterologists, ophthalmologists, psychologists/psychiatrists, dieticians, endocrinologists, and cardiologists may be needed to

manage common comorbidities. All pharmacologic interventions need to be based on shared decision-making between the patient and their provider. The four main classes of pharmacotherapy used in the man agement of PsA include NSAIDs, conventional synthetic diseasemodifying antirheumatic drugs (csDMARDs), biologic DMARDs, and tsDMARDs. Biologic and tsDMARDs have revolutionized the management of PsA by effectively controlling signs and symptoms, decreasing joint damage progression, and improving health-related quality of life. Biologic DMARDs used in the man agement of PsA include TNFi (etanercept, adalimumab, inflix imab, certolizumab, or golimumab), antibodies against IL-12/23 (ustekinumab), IL-17A (secukinumab, ixekizumab), IL-17A and IL-17F (bimekizumab), IL-23 (guselkumab, risankizumab), and costimulatory blockade agent (abatacept). tsDMARDs include the phosphodiesterase-4 (PDE4) inhibitor apremilast; JAKis such as tofacitinib, baricitinib, and upadacitinib; and the tyrosine kinase 2 (TYK2) inhibitor deucravacitinib. The IL-17A and IL-17A+F inhibitor nanobodies izokibep and sonelokimab are currently undergoing clinical trials. TREATMENT RECOMMENDATIONS The ACR along with National Psoriasis Foundation (ACR-NPF), EULAR, and Group for the Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) have published separate recom mendations for the pharmacologic management of PsA, though there are many similarities. They all recommend that the treat ment should be tailored according to the disease activity assessed by level of symptoms and clinical findings in peripheral joints, skin, nails, axial skeleton, entheses, and presence of dactylitis. Individual clinical features (age, gender, concomitant medica tions, and psychosocial factors), comorbidities (especially IBD, uveitis, metabolic syndrome, and heart disease), prognostic indi cators, and patient preferences, values, and cultural background need to be considered in this shared decision-making process. Patients should be monitored at regular intervals and treatment adjusted as appropriate. Treatment is generally continued indefi nitely for this lifelong disease since there is high risk of flare once treatment is discontinued. Principles and recommendations for PsA management from these recommendations are summarized in Table 374-7. For musculoskeletal manifestations of PsA, TNFi and IL-17i have demonstrated comparable efficacy, whereas IL-17i, IL-12/23i, and IL-23i have shown superior efficacy in clearing skin psoriasis compared to TNFi in head-to-head studies. JAKis have comparable efficacy to TNFis for musculoskeletal manifestations of PsA. All biologics except abatacept, and JAKis have shown efficacy in reduc ing radiographic progression in PsA, but none of the csDMARDs, PDE-4 inhibitors, or TYK2 inhibitors have shown this. While there are no comparative studies on safety, IL-17i, IL-12/23i, IL-23i, PDE-4 inhibitors, and TYK2 inhibitors are perceived to be safer than TNFis in clinical practice.

REACTIVE ARTHRITIS The interrelation between infection and arthritic disease has been established for many decades. ReA refers to the development of arthri tis following urogenital or gastrointestinal infection involving welldefined triggering microorganisms that are normally not cultivable from the joints affected. Prototypical inducers of reactive arthritis include Yersinia, Campylobacter, Salmonella, Shigella, and Chlamydia. ■ ■CLINICAL FEATURES A crucial factor in the diagnosis relates to recognition of the clinical pic ture and the identification of causative organisms. A hallmark feature is the time delay between initial infection and onset of arthritis: the interval ranges between 1 day and 4 weeks after infection. Inflammatory mus culoskeletal disease (joint, spine, or entheseal) is essential for the diag nosis of ReA. The clinical spectrum may include a typical asymmetrical oligoarticular arthritis preferentially involving lower limbs, enthesitis, tendonitis, bursitis, dactylitis, inflammatory back pain, and sacroiliitis. Mucocutaneous lesions may also occur in addition to the musculoskel etal manifestations and include uveitis/conjunctivitis, erythema nodo sum, oral ulcers, circinate balanitis, and keratoderma blenorrhagica. ReA is strongly

associated with the presence of HLA-B27, with up to 50–80% of all reactive arthritis patients carrying HLA-B27. Accordingly, prevalence of ReA matches the prevalence of HLA-B27, which has a clear North-South gradient; e.g., the highest prevalence of HLA-B27 is observed in the Northern Hemisphere, which was reflected by historical large out breaks of ReA in, for example, Scandinavian regions. However, over the past decades, there has been a steady decline in the number of such out breaks with improved hygiene and changes in microbiota. Recent updates on incidence of reactive arthritis point to an overall incidence rate estimate of 3.4 cases per 100,000 person-years. Overall, the estimated percentage of cases to develop ReA following an enteric infection with Campylobacter, Salmonella, Shigella, or Yersinia is estimated around 2.6%. Expert consensus refers to ReA only if clinical picture and causative microbes are HLA-B27 and SpA related. Hence many other infections that trigger onset of arthritis fall outside of the SpA construct. These “infection-related arthritides” constitute all forms of arthritis associated with infections except septic arthritis. They include, among others, acute rheumatic fever, meningococcus, Mycoplasma genitalium, Ureaplasma urealyticum, Chlamydia pneumoniae, beta-hemolytic streptococci, and some live vaccines and COVID. These should not be described as ReA since the clinical pattern does not fit the SpA spectrum and is unrelated to HLA-B27. Thus, the term ReA should be restricted to an acute SpA that is linked to an acute genitourinary or gastrointestinal infection. The other forms should be referred to as postinfectious arthritides and will not be discussed further in this chapter. ■ ■DIAGNOSIS ReA is diagnosed based on clinical features and identification of an antecedent infection from medical history and laboratory tests and exclusion of other different diagnosis. While diagnostic procedures are focused around HLA-B27 and molecular testing for Chlamydia tracho matis infection, additional individualized diagnostic tests must also be considered to rule out other causes (e.g., postinfectious arthritides). Laboratory tests such as stool cultures to test for Salmonella, Shigella, Campylobacter, and Yersinia can sometimes confirm a preceding or concomitant infection with a causative pathogen, but since gastrointes tinal symptoms often have resolved when rheumatic features develop, pathogens may no longer be retrievable. Serology for enteric pathogens is used primarily in epidemiologic studies to test for preceding infec tions, but there are some questions on its utility in daily clinical prac tice given the overall low yield of positive results. All patients should be offered screening for Chlamydia. TREATMENT Reactive Arthritis Treatment of ReA is oriented to management of SpA features, but treatment guidelines for ReA do not exist currently. While antibiot ics are not used in the routine care of ReA, one study demonstrated

TABLE 374-7 Pharmacologic Management of Psoriatic Arthritis (PsA) PRINCIPLES AND RECOMMENDATIONS 1. The primary goal of treating patients with PsA is to maximize long-term health-related quality of life through control of symptoms, abrogation of inflammation, prevention of structural damage, normalization of function, and social participation. 2. PsA requires multidisciplinary treatment (rheumatologist, dermatologist, psychiatrist, gastroenterologist, ophthalmologist, dietician, endocrinologist, cardiologist, and physical/occupational therapists), and it should be based on a shared decision-making between the patient and the rheumatologist. 3. “Treat to target” is recommended, with the target being minimal disease activity or remission. Patients should be regularly monitored, and treatment should be adjusted appropriately to reach the target. 4. NSAIDs may be used as an initial short-term treatment to relieve symptoms related to peripheral arthritis, enthesitis, dactylitis, and axial disease. NSAIDs alone are very rarely sufficient to treat PsA but can be combined with cs-, b-, or tsDMARDs. 5. Local injections of glucocorticoids should be considered for active arthritis, enthesitis, and/or dactylitis. Glucocorticoid

injections around lower extremity weightbearing entheses should be avoided due to the risk of tendon rupture. 6. Systemic glucocorticoids should be avoided. In rare circumstances such as acute flares of arthritis, they may be used with caution at the lowest effective dose for the shortest period. 7. In patients with active disease with peripheral arthritis, enthesitis, and/or dactylitis, treatment with csDMARDs, such as methotrexate, sulfasalazine, or leflunomide, should be considered at an early stage. Methotrexate is preferred if clinically relevant psoriasis is present. 8. PDE-4 inhibitor or TYK-2 inhibitor may be considered as the initial treatment instead of csDMARD for active musculoskeletal disease (except axial disease) or active skin disease. 9. In patients with predominant axial disease, csDMARDs should be avoided, and either bDMARDs or JAKi should be considered after inadequate response to NSAIDs. 10. In rare circumstances, in patients with very active musculoskeletal disease (multiple swollen joints, structural damage in the presence of active inflammation, and/ or clinically relevant extraarticular manifestations such as IBD or uveitis) or extensive skin involvement, treatment with bDMARDs can be started before csDMARDs at the discretion of the treating provider. 11. The choice of initial biologic for active musculoskeletal disease (TNF, IL-12/23, IL-17, or IL-23 inhibitors) should be based on pros and cons of each therapy class, patients' comorbidities, and their comfort with risks/benefit. 12. For patients with predominant skin disease along with musculoskeletal disease, IL-12/23, IL-17, or IL-23 inhibitors are preferred over TNF inhibitors. 13. For PsA patients with comorbid IBD, monoclonal antibodies against TNF, IL-12/23 inhibitors, IL-23 inhibitors, or JAKi therapy is preferred. IL-17 inhibitors should be avoided in patients with active IBD but can be used in patients with history of IBD. 14. For PsA patients with comorbid uveitis, therapy with monoclonal antibodies against TNF is preferred. 15. JAKi should be used after failure of TNF inhibitors according to the black-box warning issued by regulatory authorities based on their CV risk. Comorbidities of metabolic syndrome and CV disease should be considered before JAKi treatment. 16. Combination of methotrexate with bDMARDs such as TNF inhibitors has not been shown to improve efficacy compared to bDMARDs alone. 17. Abatacept has no efficacy against the disease domains of skin, nail, and the axial skeleton. Its efficacy against peripheral arthritis is modest. 18. Agents that effectively treat skin and nail involvement (but with minimal efficacy on the musculoskeletal domains) include topical glucocorticoids such as clobetasol, retinoic acid derivatives, PUVA, and cyclosporin. 19. Biosimilars may be used in place of the original biologics. 20. Tapering of DMARDs in a PsA patient with long-term minimal disease activity or remission should be a shared decision. Stopping DMARD therapy is not recommended. Abbreviations: bDMARDs, biologic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; CV, cardiovascular; IBD, inflammatory bowel disease; IL, interleukin; JAKi, Janus kinase inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; PUVA, psoralene plus ultraviolet light A; TNF, tumor necrosis factor; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs. that a 6-month course of combination antibiotics (doxycycline or azithromycin, combined with rifampicin) yielded higher response rates then placebo in chronic Chlamydia-induced ReA. However, these results have not been replicated, and the routine use of longterm antibiotics to treat chronic ReA is not recommended. In acute ReA, management of joint symptoms include NSAIDs, intraarticular glucocorticoids for monoarthritis or oligoarthritis, and short-term low-dose systemic glucocorticoids for polyarticular joint involvement. While ReA is thought to be self-limiting and resolving in a large proportion of patients, ReA may also evolve into a chronic phase. The presence of HLA-B27 has been linked to the evolution into chronicity in part because HLA-B27 has been sug gested to promote intracellular survival of causative microorgan isms in infected macrophages, providing a roadmap to chronicity. In chronic forms of ReA (e.g., lasting longer than 6 months and with

inadequate response to management outline in acute ReA), DMARDs such as sulfasalazine and methotrexate and even TNFis can be considered. Overall, the management of chronic forms of ReA follows treatment principles of peripheral SpA. IBD-ASSOCIATED ARTHRITIS An intriguing relationship between bowel and joint inflammation has emanated for >50 years that points to a prominent role of barrier integ rity loss and dysbiosis in SpA, initially recognized by uncovering the

CHAPTER 374 Spondyloarthritis occurrence of arthritis in IBD patients. The link between gut and joint inflammation, however, is reciprocal. Hence, patients with a diagnosis of SpA but without associated gastrointestinal symptoms were also found to display histologic signs of inflammation in ileocolonoscopic studies, primarily in the terminal ileum. Here, two types of lesions were described: an acute type of inflammation resembling an infectious enterocolitis and a chronic type of inflammation with many features of Crohn's disease. Overall, the frequency of microscopic inflammatory lesions mounts up to 50% of new-onset treatment-naïve SpA patients and is associated with higher degrees of bone marrow edema in MRI of sacroiliac joints. Furthermore, the presence of chronic lesions rep resents a risk factor for evolution into full-blown Crohn's disease and progression to AS. These microscopic lesions are accompanied by elevated fecal calprotectin and CRP levels. Both ulcerative colitis and Crohn's disease are associated with SpA. AxSpA as well as pSpA commonly occur in both of them, with pSpA being the most prevalent form. R-axSpA develops in up to 10% of IBD patients, whereas prevalence of pSpA varies largely according to vari ous studies, ranging from 10 to 30%. Conversely, patients with axSpA have a substantially higher risk of developing IBD, with a prevalence varying between 5 and 10% and with an observed increase with disease duration. This reciprocal rela tionship between IBD and AS is reflected by a considerable overlap in the genetic predisposition between these diseases, including polymor phisms in genes linked to type 3 immunity (e.g., IL-23R, IL-12p40,

RORc), innate immunity (TNFAIP3, TLR4), and epithelial integrity (GPR35, PTGER4). However, HLA-B27 is not a risk factor for IBD.

■ ■CLINICAL FEATURES Axial skeletal involvement associated with IBD is clinically similar to idiopathic axSpA. There may be, however, a disconnect in time in the occurrence of both. Thus, axSpA may develop after diagnosis of IBD but, in other cases, precedes onset of IBD. Peripheral involvement in IBD resembles the clinical picture of peripheral SpA, which may include more acute forms of oligoarthritis that co-occur with relapses of IBD. More chronic forms of SpA may also occur that may cause substantial structural damage if not appropriately treated. A rare sym metric polyarticular arthritis that runs an independent course has also been described. PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders In addition to IBD patients with a firm diagnosis of SpA, a compara ble fraction of IBD patients have arthralgias or fibromyalgia symptoms. ■ ■DIAGNOSIS IBD-related arthritis is diagnosed based on clinical and imaging fea tures in patients with a history of IBD and follows the same diagnostic principles as other forms of SpA. It is important to note, however, that most patients with IBD-related arthritis are seen while being treated for IBD. Thus, special caution should be taken in interpretation of imag ing in patients treated with biologics, immune suppressive drugs, and glucocorticoids. TREATMENT IBD-Associated Arthritis Management of IBD-related arthritis follows the general prin ciples of axSpA and pSpA treatment with some special consid erations, given the observed disconnect that may occur between gut and joint symptoms with some targeted therapies. Within the targeted therapies, the monoclonal antibodies, but not the soluble receptor, blocking TNF-α are effective in IBD as well as

in both axial and peripheral SpA. Other biologics with efficacy in IBD that may have proven efficacy in peripheral SpA include ustekinumab (anti-IL12/23p40), guselkumab, and risankizumab (anti-IL23p19), but anti-IL17 therapy is contraindicated. The JAKi tofacitinib and upadacitinib are approved in ulcerative colitis and upadacitinib in Crohn's disease and are also effective in axSpA and pSpA. Other treatments for IBD include sulfasalazine and related drugs as well as systemic and local glucocorticoids. NSAIDs, especially COX2-selective formulations, are helpful for arthritis and generally well tolerated but may induce IBD flares, so they should be considered only for temporary use. Vedolizumab is a gut-selective integrin inhibitor approved for both Crohn's disease and ulcerative colitis. However, up to 15% of IBD patients treated with vedolizumab may develop new-onset disease or flare of axSpA or pSpA. UNDIFFERENTIATED PERIPHERAL SPONDYLOARTHRITIS The term "undifferentiated pSpA" is used to describe patients who do not fit into any of the above well-defined conditions such as axSpA, PsA, ReA, or IBD-associated arthritis but have the typical SpA phe notype (oligoarticular inflammatory arthritis, usually involving lower limbs, asymmetric, or peripheral enthesitis or dactylitis). The ASAS group developed classification criteria for pSpA in 2011 (Table 374-8). These criteria allow the classification of a patient with peripheral enthesitis or dactylitis but without peripheral arthritis. The prevalence and incidence of undifferentiated pSpA are not known since there are no epidemiologic studies available. Some of these patients are likely to have ReA, where the inciting infection is silent, and in some patients, features of psoriasis and/or IBD may develop later. Treatment of pSpA

TABLE 374-8 Assessment of Spondyloarthritis International Society (ASAS) Criteria for Peripheral Spondyloarthritis (SpA) Arthritis or enthesitis or dactylitis Plus ≥1 of:

- Psoriasis
- Inflammatory bowel disease
- Preceding infection
- HLA-B27
- Uveitis
- Sacroiliitis on imaging (radiographs Plus ≥2 of the remaining:
- Arthritis
- Enthesitis
- Dactylitis
- IBP in the past
- Positive family history for SpA or MRI) Note: Peripheral arthritis: usually lower limb, asymmetric arthritis; enthesitis: clinically assessed; dactylitis: clinically assessed. Abbreviations: IBP, Inflammatory back pain; MRI, magnetic resonance imaging. should be individualized based on the predominant musculoskeletal manifestation. SPONDYLOARTHRITIS ASSOCIATED WITH SAPHO SYNDROME AND HIDRADENITIS SUPPURATIVA SAPHO is a clinical entity that is sometimes associated with Propioni bacterium acne infection on bone biopsies. It is included under SpA since some patients have asymmetric inflammatory arthritis (typi cally sternoclavicular joints and chest wall costochondral junctions), sacroiliitis, and spinal hyperostosis. The skin manifestations include acne conglobate and palmoplantar pustular lesions that are patho logically identical to psoriasis. Some consider SAPHO as the adult phenotype of juvenile chronic recurrent multifocal osteomyelitis (CRMO), where the osteomyelitis is sterile. Apart from TNFi, IL-17i, and JAKi, there are case reports of pamidronate, a bisphosphonate, being

effective in treatment. Hidradenitis suppurativa patients may develop a SpA phenotype of musculoskeletal involvement, including asymmetric sacroiliitis. ■ ■FURTHER READING Coates L et al: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): Updated treatment recommendations for psoriatic arthritis 2021. Nat Rev Rheumatol 18:465, 2022. Danve A et al: Treatment of axial spondyloarthritis: An update. Nat Rev Rheumatol 18:205, 2022. Gracey E et al. Revisiting the gut-joint axis: Links between gut inflam mation and spondyloarthritis. Nat Rev Rheumatol 16:415, 2020. Gracey E et al: Tendon and ligament mechanical loading in the pathogenesis of inflammatory arthritis. Nat Rev Rheumatol 16:193,

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