19.6 Spondyloarthritis and related conditions 4441

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Jürgen Braun and Joachim Sieper

ESSENTIALS The spondyloarthritides are a group of common inflammatory rheum- atic diseases with predominant involvement of axial and peripheral joints and entheses, together with other characteristic clinical fea- tures, including inflammatory back pain, sacroiliitis, peripheral arth- ritis (mainly in the legs), enthesitis, dactylitis, preceding infection of the urogenital/gastrointestinal tract, psoriatic skin lesions, Crohn-like gut lesions, anterior uveitis, and a family history of spondyloarthritis. Five subsets can be distinguished on clinical grounds: (1) axial spondyloarthritis, including ankylosing spondylitis; (2) reactive (spondylo)arthritis/Reiter's syndrome (see Chapter 19.8); (3) psori- atic (spondylo)arthritis; (4) (spondylo)arthritis associated with in- flammatory bowel diseases; and (5) undifferentiated peripheral spondyloarthritis. Prevalence in any population correlates roughly with that of HLA B27, but the relevance of this to pathogenesis is not known. Another more recent approach is to differentiate the spondyloarthritis on the basis of the predominant clinical manifest- ation: predominant axial and/or peripheral spondyloarthritis. Axial spondyloarthritis, including ankylosing spondylitis There are no diagnostic criteria, only classification criteria: the 2009 Assessment of SpondyloArthritis International Society criteria for axial and peripheral spondyloarthritis. Chronic back pain (>3 months) that has started before the age of 45 years is mandatory; then there should be either a positive imaging finding (conventional radiograph or magnetic resonance imaging of the sacroiliac joints) or a positive HLA B27 test; plus one (if imaging positive) or two (if HLA B27 posi- tive) more characteristic features. The historical modified New York classification criteria of 1984 required one of three clinical criteria—(1) inflammatory back pain; (2) limitation of spinal movement in three planes; or (3) deterioration of chest expansion—and radiological sacroiliac joint changes (bilat- eral grade 2 or unilateral grade

3/4). Sacroiliac radiographs may be normal in early disease when dynamic magnetic resonance imaging of the sacroiliac joints can be helpful in providing objective evidence of sacroiliitis in clinically suspicious cases. Age of onset of ankylosing spondylitis is commonly in the twenties, with male:female ratio of 2:1. Early in the course of disease there may be no limitation of spinal movement or chest expansion, but as it progresses there is restriction of lateral flexion, forward flexion, and extension. Treatment options include acute anti-inflammatory therapy with nonsteroidal anti-inflammatory drugs and local corticosteroids, disease-modifying drugs (sulphasalazine and methotrexate) and biologicals (antitumour necrosis factor), together with physiotherapy. There is no cure. Psoriatic arthritis Psoriasis precedes joint disease in most cases, but there is poor cor- relation between onset, severity, and activity of psoriatic skin lesions and arthritis. More than 80% of patients with psoriatic arthritis have nail dystrophy. The most characteristic features are dactylitis and osteoproliferative changes in radiographs of peripheral joints. The CASPAR classifica- tion criteria, which are both sensitive and specific, require established inflammatory articular disease with at least three points from the fol- lowing features: (1) current psoriasis (score 2); (2) a history of psoriasis (unless current psoriasis); (3) a family history of psoriasis (unless cur- rent psoriasis or history of psoriasis); (4) dactylitis; (5) juxta-articular new bone formation; (6) rheumatoid factor negativity; and (7) nail dystrophy. Many patients improve with the use of nonsteroidal anti- inflammtory drugs and intra-articular steroids, especially in the case of large joint involvement or flexor tenosynovitis. Those who do not improve need to be treated with disease-modifying drugs (sulpha- salazine, methotrexate). Arthritis associated with inflammatory bowel disease Similar to the other spondyloarthritides, the arthritis is mostly asym- metric and predominantly affects the legs. Flaring of gut symptoms is often associated with arthritis. Treatment with nonsteroidal anti- inflammtory drugs may be effective for arthritis and spondylitis but can exacerbate bowel disease: there are few data on the use of disease-modifying drugs. Peripheral, including undifferentiated peripheral spondyloathritis According to the above-mentioned Assessment of SpondyloArthritis International Society classification criteria, patients with predom- inant peripheral spondyloarthritis have as a primary symptom ei- ther (1) arthritis, (2) enthesitis or (3) dactylitis, and—in addition—at least one of (a) anterior uveitis, (b) psoriasis, (c) inflammatory bowel 19.6 Spondyloarthritis and related conditions Jürgen Braun and Joachim Sieper

section 19 Rheumatological disorders 4442 disease, (d) preceding infection, (e) HLA B27 and (f) sacroiliitis on magnetic resonance imaging. In addition, they may also have at least two of (a) arthritis, (b) enthesitis, (c) dactylitis, (d) inflamma- tory back pain, and (e) positive family history for spondyloarthritis. Classification of undifferentiated spondyloarthritis excludes the pres- ence of psoriasis, inflammatory bowel disease, or a preceding in- fection but includes the rest of the Assessment of SpondyloArthritis International Society criteria for peripheral spondyloarthritis. Nonspecific therapy is as for other arthritides, with nonsteroidal anti-inflammtory drugs and intraarticular and/or systemic gluco- corticoids. Sulfasalazine may be useful for peripheral and axial symptoms, but very few therapeutic trials with disease-modifying drugs have been performed. Methotrexate is often used but data are scarce. SAPHO syndrome There are no evaluated diagnostic criteria for the acronym of SAPHO syndrome (synovitis, acne, pustulosis palmaris et plantaris, hyperostosis, and osteitis). However, the combination of a classical skin symptom (such as pustolosis or significant acne) with a charac- teristic joint or bone lesion (such as arthritis of the sternoclavicular joint, osteitis, or hyperostosis in the anterior chest wall) is clinic- ally convincing. Analgesics, nonsteroidal anti-inflammtory drugs, and intra-articular steroids are usually effective.

Anti-TNF agents and bisphosphonates have been shown to be efficacious in more severe cases. Spondyloarthritides Introduction and definitions The spondyloarthritides are a heterogenous group of inflam- matory rheumatic diseases with predominant involvement of axial and peripheral joints and entheses. In addition to these, the spondyloarthritides share other characteristic clinical features (e.g. anterior uveitis, psoriasis, and colitis with mostly asymp- tomatic Crohn-like gut lesions). Clinical symptoms in subsets of spondyloarthritides can overlap, for example, with psoriatic skin lesions in reactive arthritis (keratoderma blenorrhagicum), espe- cially the subform formerly called ‘Reiter’s syndrome’ with the triad arthritis, urethritis, conjunctivitis, and patients can move from one subset to another, for example, from undifferentiated peripheral spondyloarthritis (SpA) to axial spondyloarthritis and ankylosing spondylitis (AS). The various names that have been and are still used for the spondyloarthritides include seronegative spondarthropathies, spondarthritis, spondylarthropathy, and spondyloarthritis. Importantly, the term spondyloarthritis means a category of inter- related rheumatic disease, it does not only mean axial involve- ment, as the asymmetric pattern of involvement of mainly the legs by oligoarthritis and enthesitis is also typical. The prefix sero- negative, referring to the general absence of rheumatoid factors in the spondyloarthritides, is historical and redundant. The term spondyloarthritis is now generally preferred. The spondyloarthritides are not ‘modern’ diseases, with anky- losing spondylitis first having been described in 1649 (Table 19.6.1). Epidemiology The mean age at onset of patients with axial spondyloarthritis is 20 to 30 years, with a slight preponderance of men. Next to rheumatoid arthritis, the spondyloarthritides are the most frequent inflamma- tory rheumatic diseases (Table 19.6.2), with ankylosing spondyl- itis, psoriatic spondyloarthritis, and undifferentiated peripheral spondyloarthritis being the most common subsets. The overall prevalence of spondyloarthritides in patients presenting with back pain to general practitioners’ surgeries in the United Kingdom has been estimated at 5%. The spondyloarthritides are associated with the major histo compatability complex class I antigen HLA B27, and the prevalence of spondyloarthritides in any population correlates roughly with that of HLA B27. The magnitude of association differs between the subsets (Table 19.6.3): it has been mainly shown for ankylosing spondylitis, but in Inuit populations reactive arthritis is more frequent. Pathogenesis The overall influence of genes in the pathogenesis of ankylosing spondylitis has been estimated to be 80 to 90%, leaving only 10 to 20% to other causative factors such as environmental influences, including infections. HLA B27 is responsible for less than one-third of the total genetic load: more than 150 subtypes are now recog- nized by polymerase chain reaction technology, two of which are not associated with ankylosing spondylitis: HLA B2706 (Thailand) and HLA B2709 (Sardinia). There is a weaker association of ankylosing Table 19.6.1 First historical descriptions of spondyloarthritis Spondyloarthritis Moll/Wright 1974, ESSG 1991 Ankylosing spondylitis Connors 1649, Brodie 1888 Reactive arthritis/Reiter’s syndrome Reiter 1916, Ahonen 1973 Psoriatic arthritis Wright 1959 Arthritis associated with inflammatory bowel diseases Bargen 1930 Enthesitis Niepel 1961 HLA B27 association Brewerton, Schlosstein 1973 (Undifferentiated) Spondylarthropathy ESSG 1991 (Nonradiographic) axial spondyloarthritis ASAS 2009 ASAS, Assessment of SpondyloArthritis international Society; ESSG, European Spondylarthropathy Study Group. Table 19.6.2 Prevalence of spondyloarthritis Disease Prevalence Spondyloarthritis 0.6–2.0% Ankylosing spondylitis 0.2–1.4% Undifferentiated spondyloarthritis 0.2–0.7% Reactive arthritis 0.01% Psoriasis 1.0–3.0% Psoriatic arthritis 0.3% Arthritis associated with inflammatory bowel disease 0.001%

19.6 Spondyloarthritis and related conditions 4443 spondylitis with HLA B60 and HLA DR1, and the interleukin 1 (IL1) gene cluster, while the association with tumour necrosis factor α (TNFα) polymorphisms is weak. Recently, ERAP-1, IL-23R have been identified as major genetic contributors to ankylosing spon- dylitis: in the case of ERAP-1 this works only together with HLA B27. Gene–gene interactions have now been demonstrated between ERAP1 variants and HLA-B 27 and HLA-B 40 in ankylosing spon- dylitis, HLA-Cw6 in psoriasis, and HLA-B 51 in Behçet's disease. Of note, the main genes responsible for psoriasis (Cw6) and IBD (NOD2) are not associated with ankylosing spondylitis. Non- MHC genes have also been genetically associated with ankylosing spondylitis. The relevance of HLA B27 to disease pathogenesis is unknown: several models have been proposed to explain tissue tropism, including the new bone formation, and the genetic associations of the spondyloarthritides (Table 19.6.4). The strongest argument in favour of a central involvement of the cellular immune system is the combined genetic association of the MHC class I molecule HLA B27 with ERAP-1. Another convincing finding has been the demonstra- tion of TNFα mRNA and protein in the sacroiliac joints of patients with ankylosing spondylitis. The classical arthritogenic peptide model is backed by the dem- onstration of HLA B27-restricted CD8+ T-cell clones in the synovial fluid of patients with reactive arthritis. Immunodominant peptide motifs and peptides have been described, but their pathogenetic relevance is not yet clear. Lipopolysaccharide and RNA of bacteria associated with reactive arthritis and a CD4+ T-cell response dir- ected against bacterial antigens have been detected in reactive arth- ritis, but it is not clear whether this immune response is beneficial or arthritogenic. At the humoral and the cellular level, molecular mimicry (partial sequence homologies at the protein and DNA level) between bacterial antigens and self structures (mainly the HLA B27 molecule) has been described. It also seems possible that patients with HLA B27+ SpA have deficient immune reactivity, for example, diminished ability to secrete TNFα, or a synovial Th2 re- sponse (secretion of too little interferon-γ, too much IL-4, IL-10), making elimination of bacteria difficult. Presentation of HLA B27-derived peptides themselves by HLA class II molecules, or even by HLA class I molecules, has been proposed as an explanation of the association of HLA B27 with disease. The 'HLA-B27 mis-folding hypothesis' suggests that HLA B27 has a tendency to mis-fold in the endoplasmic reticulum, it being a particular feature of HLA B27 that newly synthesized HLA B*2705 molecules fold and associate with β2-microglobulin (β(2)m) more slowly than other MHC class I molecules. As a consequence of this mis-folding, free HLA B27 heavy chains can form abnormal homodimers, which—as β(2)m-free HLA B27 homodimers and multimers—are expressed at the cell surface of leucocytes, dendritic, and other cells with the possible function of antigen presentation. There is also an increasing tendency to incriminate mechanical stress as an initiating factor in pathogenesis. Clinical features The characteristic clinical features of the spondyloarthritides (see Figs. 19.6.1–19.6.3) are listed in Table 19.6.5. Diagnosis Five subsets of spondyloarthritis can be distinguished on clinical grounds: axial spondyloarthritis including ankylosing spondyl- itis; reactive (spondylo)arthritis/; psoriatic (spondylo)arthritis; (spondylo)arthritis associated with inflammatory bowel diseases; and undifferentiated peripheral spondyloarthritis. Classification criteria for spondyloarthritides are shown in Box 19.6.1. Inflammatory back pain is one of the main clinical findings on which a diagnosis of axial spondyloarthritis can be based (Box 19.6.2 and Table 19.6.6). Patients younger than 45 with chronic back pain (defined as being present for more than three months), initially located to the buttocks (sometimes alter- nating), who have significant morning stiffness, who frequently wake up in the second half of the night because of pain, and who report relief by exercise but not by rest, are very likely to have axial spondyloarthritis. Other features of possible relevance in- clude other clinical signs of spondyloarthritis (enthesitis, arthritis,

Table 19.6.3 HLA B27 association of spondyloarthritis. Note that the prevalence of spondyloarthritis (mainly of the first four listed in Table 19.6.2) relates to the prevalence of HLA B27 in different populations Spondyloarthritis HLA B27 prevalence Ankylosing spondylitis 85–95% Reactive arthritis 30–80% Reiter's syndrome 60–90% Psoriatic arthritis Peripheral arthritis 10–30% Axial involvement 40–60% Arthritis associated with inflammatory bowel diseases Peripheral arthritis 10–30% Axial involvement 40–60% Undifferentiated spondyloarthritis 50–70% Population HLA B27 prevalence Native Americans 6–50% Inuit 15–25% North Europeans 10–25% Middle Europeans 6–9% North Americans 6–8% South Europeans 4–6% Africans 1–5% Table 19.6.4 Spondyloarthritis—pathogenetic models Model Mechanism Arthritogenic peptide model Bacterial protein processed/ presented by B27 to CD8+ T cells Deficient immune response Failure of B27+ cells to properly present and eliminate bacteria Molecular mimicry Similarity of bacterial and self structures, possibly resulting in autoimmunity Autoimmunity Self structures such as B27-derived peptides presented by class I or II molecules

section 19 Rheumatological disorders 4444 anterior uveitis, family history), elevated acute phase reactants (C-reactive protein, ESR), the presence of HLA B27, and a good response to nonsteroidal anti-inflammatory drugs (NSAIDs). HLA B27 contributes much more to the diagnosis of axial spondyloarthritis than do elevated acute phase reactants, but note that HLA B27 alone can never make a diagnosis, although it does increase the probability of an underlying spondyloarthritis by more than tenfold. Likelihood ratios have also been calculated for the other items. In combination with the leading symptom of chronic back pain starting before the age of 45, buttock pain, improvement by movement and psoriasis, HLA B27 is of value for identification of patients with spondyloarthritis in a primary care setting. Differential diagnosis The most important, because most frequent, differential diagnosis is nonspecific low back pain, especially if it exceeds 3 months duration in a patient younger than 45 years. The leading clinical symptom of inflammatory back pain may be associated with pain radiating from the lower back to the thighs. Hence an important initial dif- ferential diagnosis is sciatica, but this usually has an acute onset. Fig. 19.6.1 Enthesitis at the insertion of the Achilles tendon in a patient with reactive arthritis. Table 19.6.5 Characteristic clinical features of spondyloarthritides Clinical feature Details Inflammatory back pain See Box 19.6.2 Sacroiliitis Imaging Peripheral arthritis Affects predominantly but not exclusively the lower limbs; it is often asymmetric but may also involve both knees or ankles Enthesitis Inflammation at the insertion sites of tendons and ligaments to bone (00A0;19.6.1 and 19.6.2) Dactylitis Inflammatory involvement of a whole finger or toe (Fig. 19.6.3) with tendovaginitis and arthritis (sausage digit) Preceding infection In the urogenital/enteral tract 1–6 weeks before the onset of arthritis Psoriatic skin lesions Confirmed by a dermatologist Crohn-like gut lesions Confirmed by a gastroenterologist Anterior uveitis Confirmed by a ophthalmologist Family history of spondyloarthritis First-degree relatives Fig. 19.6.2 MRI showing inflammation of the plantar fascia in a patient with spondyloarthritis. Fig. 19.6.3 Dactylitis of the third finger of the right hand in a patient with undifferentiated spondyloarthritis.

19.6 Spondyloarthritis and related conditions 4445 In inflammatory back pain, radiation is more often bilateral than unilateral, rarely extends below the knees, almost never into the foot, and is not associated with paraesthesia, although cough impulse pain may be present. Diagnostic procedures for the detection of disc herniation by magnetic resonance imaging (MRI) or computed tomography (CT) can be misleading, as disc prolapses are found in as many as 30% of normal individuals. Diffuse idiopathic skeletal hyperostosis (DISH) or Forestier's dis- ease, an often-severe

radiographic spondylosis, can be difficult to distinguish from longstanding ankylosing spondylitis. The appear- ance and localization of the spondylophytes helps to differentiate DISH from syndesmophytes and ankylosing spondylitis. Scoliosis is not usually a marked feature of ankylosing spondylitis. Classification requires the presence of one major and one minor criterion (Table 19.6.6). Note that dactylitis, uveitis, and HLA B27 are not included. The peripheral arthritis does not have to be asym- metric, although it often is; both knees or ankles might well be in- volved. Inflammatory back pain is mostly due to sacroiliitis but can also be caused by enthesitis. For patients with axial spondyloarthritis who do not fulfil the criteria the term nonradiographic axial spondyloarthritis has been created, but at present this is only rele- vant for the approval status of biologics, since some are only ap- proved for ankylosing spondylitis. Since the threshold between nonradiographic axial spondyloarthritis and ankylosing spondylitis ('definite radiographic changes in the sacroiliac joints') is artificial and methodologically unreliable, it is recommended that only the term axial spondyloarthritis be used for this condition. Sacroiliitis occurs in several other rheumatic and infectious diseases, as shown in Table 19.6.7. The differential diagnosis of peripheral arthritis of the legs includes Lyme disease, sarcoidosis (Löfgren's syndrome), gout, and undifferentiated oligoarthritis. The differential diagnosis of enthesitis includes epicondylitis and fibromyalgia, and that of dactylitis is erysipela and infection. Prognosis The following seem to be poor prognostic factors for the develop- ment of new bone formation (more syndesmophytes, ankylosis) in patients with ankylosing spondylitis: male gender, the presence of syndesmophytes at presentation, elevated C-reactive protein (CRP), much inflammation on MRI, smoking, manual work and (perhaps) medication. Box 19.6.1 ASAS Classification Criteria for axial spondyloathritis

1. Patients must have ≥3 months back pain with age at onset less than 45 years PLUS
2. Sacroiliitis on imaging PLUS ≥1 spondyloarthritis feature, or HLA-B27 PLUS ≥2 other spondyloarthritis features Spondyloarthritis features: • IBP • arthritis • enthesitis heel • uveitis • dactylitis • psoriasis • Crohn's/colitis • good response to nonsteroidal anti-inflammatory drugs • family history for spondyloarthritis • HLA-B27 • elevated C-reactive protein Box 19.6.2 Features of inflammatory back pain • nature: chronic back pain for more than three months • age at onset: less than 45 years • location: buttocks • time characteristics: — morning stiffness for more than 30 minutes — wakening up in the second half of the night — slow onset • response to interventions: — improvement by movement, not by rest — improvement by nonsteriodal ani-inflammtory drugs within 48 hours • other features of spondyloarthritis Table 19.6.6 Diagnostic criteria for spondyloathritis (1991 European Spondylarthropathy Study Group criteria) Major criteria Inflammatory back pain Oligoarthritis (asymmetric) of the lower limbs Minor criteria Enthesitis Alternating buttock pain Preceding symptomatic infection Psoriasis Crohn-like gut lesions Family history Radiographic sacroiliitis Table 19.6.7 Differential diagnosis of sacroiliitis Axial spondyloarthritis Reactive arthritis Psoriatic arthritis Arthritis associated with inflammatory bowel disease SAPHO syndrome Other rheumatic diseases (rare) Rheumatoid arthritis Systemic lupus erythematosus Sjögren's syndrome Gout Osteoarthritis Paget's disease Hyper/hypoparathyroidism Infectious diseases and malignancies Septic sacroiliitis Acute (staphylococci, steptococci, others) Chronic (tuberculosis, brucellosis) Malignancies (lymphoma, metastasis)

 In reactive arthritis—a disease with a relatively good prognosis— HLA B27 is a risk factor for chronicity. Ankylosing spondylitis Ankylosing spondylitis is a

chronic inflammatory rheumatic disease that mainly affects the axial skeleton, starting in the sacroiliac joints and often progressing to the spine, but peripheral joints, enthesial structures, the anterior uvea, and the aorta can also become affected. The diagnosis is made on the basis of significant radiological changes in the sacroiliac joints and the spine, the typical clinical his- tory of inflammatory back pain and stiffness, and evidence of limited spinal movement and/or chest expansion on physical examination. Epidemiology The age of onset is commonly in the twenties, but ankylosing spon- dylitis can begin in childhood, or considerably later (at age >50). The male:female ratio is about 2:1. About 80–90% of white patients with ankylosing spondylitis are positive for HLA B27, the percentage may be a bit lower in axial spondyloarthritis. There is a strong tendency of ankylosing spondylitis to recur within families, with its heritability formally calculated to be more than 90%. The likelihood of getting ankylosing spondylitis in a sibling or first-degree relative of a patient with ankylosing spon- dylitis, compared with the prevalence in the general population, is 52–94 (the relative recurrence risk ratio). The recurrence risk ratio in ankylosing spondylitis drops rapidly with increasing dis- tance of relationship. Recurrence risk is also 6–16-fold higher in HLA-B27-positive first-degree relatives of patients with ankylosing spondylitis compared with the risk of HLA-B27-carriers in the gen- eral population. The non-MHC contribution has been more accur- ately quantified in studies of twins that show a concordance rate in monozygotic twins (about 63%) that is substantially higher than in dizygotic twins (about 12.5%), even when dizygotic twins are con- cordant for HLA-B27_ (about 27%). Disease activity (51%), func- tional impairment (68%) and radiographic change (62%) are also heritable in ankylosing spondylitis. There is a strong cofamiliality of ankylosing spondylitis with in- flammatory bowel disease and psoriasis. First-degree relatives of patients with ankylosing spondylitis are c.3-fold more likely to de- velop Crohn’s disease or ulcerative colitis than unrelated individ- uals. Psoriasis is at least threefold more common in patients with ankylosing spondylitis than in the general community. The dis- covery of multiple genes shared between these conditions has con- firmed that these diseases are closely related. Immunopathology and pathogenesis The leading features of ankylosing spondylitis are spinal inflamma- tion and ankylosis, but their cause is unknown. The association of ankylosing spondylitis with bacterial infections is unlike reactive arthritis. However, antibodies to Klebsiella pneumoniae have been more frequently detected in patients with ankylosing spondylitis than in healthy controls, but similarly often in patients with Crohn’s disease and first-degree relatives of those with ankylosing spon- dylitis. This finding is probably explained by increased gut perme- ability, and its predominant clinical association is with peripheral (not axial) arthritis. The sacroiliac joint is the structure most frequently involved in the initial phase of disease. If biopsy is performed, T cells and macrophages are seen to be the predominant infiltrating cells, with CD4+ and CD8+ T cells both present. The reason for this tropism is unclear. The fact that sacroiliac and spinal joints are affected in diseases caused by mycobac- teria and other microbes may argue for a pathogen-triggered patho- genesis in ankylosing spondylitis, but bacteria associated with reactive arthritis have not been detected in the sacroiliac joints. Clinical features The most common initial symptom is inflammatory back pain, com- monly in the lower back and the buttocks. Early in the course of disease there may be no limitation of spinal movement or chest ex- pansion. As it progresses, there is restriction of lateral flexion, for- ward flexion, and extension. There is often a flattening of the lumbar lordosis, or an inability to reverse this on forward flexion. With more advanced disease a thoracic kyphosis develops, with concomi- tant restriction of thoracic rotation and chest expansion due to in- flammation and ankylosis of the costovertebral and costotransverse joints. In severe cases movements of the cervical spine are also re- stricted in all planes, with dramatic limitation of lateral flexion. The combination of cervical stiffness and severe thoracic kyphosis can lead to

difficulties with forward vision. An example of a young pa- tient with severe progressive disease is shown in Fig. 19.6.4. Severe Fig. 19.6.4 Thirty-year-old man with rapidly progressive ankylosing spondylitis (disease of five years' duration).

19.6 Spondyloarthritis and related conditions 4447 spinal disease is more frequent in men than in women. There is no evidence that pregnancy has a significant impact on the course of the disease. Peripheral joint involvement occurs in 30 to 50% of cases at some time, with about 20 to 30% of patients having acute peripheral arthritis of the legs, often with joint effusions as the first symptom, this being especially marked in children. This situation is difficult to differentiate from reactive arthritis. Joint involvement is usu- ally oligoarticular and often asymmetrical. The joints most often involved are the knees, ankles, hips, shoulders, wrists, temporo- mandibular joints, sternoclavicular joints, manubriosternal joints, costovertebral joints, zygapophyseal joints, and symphysis pubis. Small joints are rarely affected. Enthesitis occurs at the heel at the insertion of the Achilles tendon (Fig. 19.6.1) and the plantar fascia (Fig. 19.6.2), and at the iliac crests, the ischial tuberosities, the greater trochanters, and other sites. The diagnosis is often difficult if no swelling is apparent, in which case ultrasound can be revealing. Dactylitis of fingers and toes is uncommon in ankylosing spondylitis, being seen most often in psoriatic arthritis. Physical examination of the spine and thoracic cage The physical examination is important in the evaluation of patients with ankylosing spondylitis—in particular to quantitate flexibility of the spine and thoracic cage. The following measurements are useful, but it should be stressed that the values expected of normal individ- uals are dependent on age and physical training. • Anterior and lateral spinal mobility (Schober test): ■ Ventral—with the patient standing upright, a horizontal line is drawn across the lumbar spine connecting the two posterior superior iliac spines. Marks are made in the midline over the spine 10 cm cranial (original version) and 5 cm caudal (modi- fied version) to the horizontal line. The patient then bends with legs straight and the distance is measured again. It nor- mally increases by more than 3 cm, and in younger people by more than 5 cm. The measure is age dependent. ■ Lateral—the distance between the tip of the longest finger and the floor is measured in the upright position. This is repeated when the patient tries to flex laterally towards the ground as far as possible, normally moving by more than 10 cm. • Chest expansion—the circumference of the thorax is measured in the fourth intercostal space after maximal inspiration and ex- piration. It normally alters by more than 3 cm, in younger people by more than 5 cm: again the measure is age dependent. In pa- tients with ankylosing spondylitis it indicates involvement of the costovertebral joints. • Occiput/wall distance—in the upright position the patient leans backwards against a wall. The distance between occiput and wall is measured: there is no gap (0 cm) in most young pa- tients; in patients with ankylosing spondylitis it usually indicates hyperkyphosis of the thoracic spine. • Chin/sternum distance—the chin is maximally bent towards the sternum, and should normally be able to touch it. • Cervical rotation—the head is rotated to the left and right sides, with the angles of rotation measured (normally >50°). • Intermalleolar distance—the patient tries to stand with their feet together and also to spread their legs maximally: the malleoli should normally touch and the distance of the spread feet usually exceeds 1 m. This measure is dependent on age, training, and the degree of osteoarthritis of the hip. Physical examination for extra-articular organ involvement Acute anterior uveitis can occur at any time in the course of disease and is seen in 20 to 30% of patients. It is typically unilateral, but ei- ther eye may be affected in separate episodes. Recurrent attacks are common. Aortic regurgitation secondary to aortitis occurs in about 1 to 2% of patients with ankylosing spondylitis, most frequently in advanced disease, and may be associated with

atrioventricular block. Probably on the basis of a restrictive pulmonary defect due to limited chest expansion, apical pulmonary fibrosis occurs in no more than 1% of patients, especially those with advanced disease. Cauda equina syn- drome caused by arachnoid cysts may complicate severe longstanding disease, with resultant disturbance of the bladder and bowel function. Lumbar diverticulae may be demonstrated by MRI. Diagnosis The 1984 modified New York criteria for ankylosing spondylitis are shown in Table 19.6.8. There is a significant diagnostic delay in women (8 years) and in men (5 years), the most probable reason being that back pain is a very frequent complaint, and that primary care and general physicians are often not trained to distinguish in- flammatory from other causes of back pain such that referral for spe- cialist opinion is delayed. Laboratory and radiological features The ESR and the C-reactive protein are raised in 30 to 50% of patients, with moderate correlation to overall disease activity. Less com- monly, serum IgA levels are raised. Mild to severe normochromic normocytic anaemia occurs in about 10 to 20% of patients. Note that other Spondyloarthritis-like symptoms and syndes mophytes are not part of these criteria. For a definite diagnosis of ankylosing spondylitis, the radiological criterion is essential and one clinical criterion required. If only clinical symptoms and findings are present, a diagnosis of probable ankylosing spondylitis may be made. Sacroiliac radiography Dependent on stage, severity, and duration of disease, there are sacro- iliac joint abnormalities in almost all patients. The radiological changes are graded from 0 (normal), to I (minimal changes), II (sclerosis, some erosions), III (severe erosions, pseudodilatation of joint space, limited ankylosis), and IV (ankylosis) (Fig. 19.6.5). They are crucial Table 19.6.8 Diagnostic criteria for ankylosing spondylitis Clinical parameters Inflammatory back pain Limitation of spinal movement in three planes Deterioration of chest expansion Radiological parameters Sacroiliac joint changes of at least: Bilateral grade 2 Unilateral grade 3 or 4

section 19 Rheumatological disorders 4448 for the diagnosis of ankylosing spondylitis and for the differentiation from undifferentiated spondyloarthritis, but it must be noted that significant inter- and intraobserver variability has been reported— particularly concerning grades I and II—which creates diagnostic problems and confusion. Sclerosis, joint space narrowing, and even synchondrosis occur in healthy elderly individuals. Oblique and other special views are generally not significantly better than normal anteroposterior pelvic radiographs, but can be helpful in a few cases. Sacroiliac magnetic resonance imaging and computed tomography Sacroiliac radiographs may be normal in early ankylosing spondyl- itis, and in clinically suspicious cases dynamic magnetic resonance imaging of the sacroiliac joints can be helpful in providing objective evidence of sacroiliitis. Active inflammation can be demonstrated by enhancement after application of a contrast agent (gadolinium DTPA) or by special magnetic resonance sequences, such as short tau inversion recovery (STIR) or other fat saturation techniques that op- timize the visualization of oedematous areas (Fig. 19.6.6). CT of the sacroiliac joints is superior to normal radiographs for documenting bony changes such as erosions and ankylosis. The sacroiliac joint is accessible to biopsy under CT guidance. Spinal radiography The characteristic spinal lesion, mostly occurring in more advanced disease, is the syndesmophyte—a bony proliferation originating from an inflammatory area at the ligamentous/discal attachment to the vertebral edge. This early ankylotic structure predominantly grows cranially to fuse with the next vertebral body and has to be distinguished from the spondylophyte, which mainly grows laterally and typically indicates degenerative vertebral disease. In ankylosing spondylitis, the earliest spinal lesions are frequently in the lower thoracic and upper lumbar spine, sometimes preceded by squaring of the vertebrae seen on lateral films. The zygapophyseal joints are frequently involved at all stages. Anterior

spondylitis is in- dicated by lateral spinal radiographs showing hypersclerotic corners (Romanus lesion, Fig. 19.6.7). Spondylodiscitis (Anderson lesion) is revealed by erosion of the disc and vertebra with a hypersclerotic lining. In later stages new bone formation and calcification of liga- ments occurs, eventually leading to bridging syndesmophytes and the characteristic ‘bamboo spine’ (Fig. 19.6.8). Spinal magnetic resonance imaging Early spinal inflammation (spondylitis, spondylodiscitis) can be de- tected by dynamic MRI, which can be useful for localizing inflam- mation in the spine in the early stages when plain radiographs are normal. Treatment Although there is no cure for ankylosing spondylitis, several treat- ments are available. The main therapeutic options are: • Acute anti-inflammatory therapy—NSAIDs and local cortico- steroids; systemic corticosteroids are not recommended Fig. 19.6.5 Radiographic sacroiliitis (stage IV in both joints) in a 28- year-old man with ankylosing spondylitis. Fig. 19.6.6 MRI showing right-sided active sacroiliitis. Fig. 19.6.7 Radiographic anterior spondylitis (arrow) in a 42-year-old man with ankylosing spondylitis.

 • Disease-modifying therapy—sulfasalazine for peripheral arth- ritis and possibly in early disease stages; methotrexate has limited value for peripheral arthritis but is clearly not useful for axial conditions. There is no evidence for the use of leflunomide, gold, or hydroxychloroquine • Antiresorptive therapy—bisphosphonates (disodium pamidronate) may have some value in selected patients (only one controlled trial, no approval) • Biologicals—anti-TNF therapy (infliximab, adalimumab, etanercept, certolizumab, golimumab) and anti-IL17A (secukinumab) Nonsteroidal anti-inflammtory drugs are better than analgesics and can be used in combination with them. Diclofenac (50–150 mg), meloxicam (7.5–15 mg), acemetacin and indometacin (50–150 mg) are frequently given. Thalidomide and phenylbutazone, which had been reserved for severe cases when other agents have failed, are now very rarely used (where available). The more novel COX-2 selective coxibs (celecoxib 100–200 mg, etoricoxib 90–120 mg) are also useful. The main risk of NSAIDs is gastrointestinal side effects: 25% of patients are affected, ranging from dyspepsia to peptic ulceration and (rarely) bleeding or perforation. It is important to identify pa- tients at risk and to provide them with proper information about possible symptoms. Prophylactic therapy with proton pump inhibi- tors is indicated in those at particularly high risk (older age, history of ulcer, disability, comorbidity). As most NSAIDs may be associ- ated with a slightly increased incidence of cardiovascular events over time, the individual risk profile of the patient also has to be taken into account. This might be of special clinical relevance, as patients with ankylosing spondylitis may have increased cardiovascular risk because of persistent inflammation. Most patients with ankylosing spondylitis do not respond to small doses of corticosteroids. Transient high-dose steroid treatment has been tried in extreme cases with additional symptoms of inflamma- tory bowel disease, with temporary and limited success. Sulfasalazine is given in a dosage of 2–3 g/day, when effects may be seen after 2 to 4 months. An influence on peripheral joint disease has been demonstrated, but not on axial symptoms, which may be due to the preferential study of patients with longstanding disease. It is therefore mainly indicated for patients with peripheral arthritis. Methotrexate is also often used in the absence of convincing data. The anti-TNFα antibodies infliximab (in a dosage of 5 mg/kg intra- venously every 6 to 8 weeks after an initial induction phase at weeks 0, 2, and 6), which has also been found to be effective in Crohn’s disease and rheumatoid arthritis, and adalimumab (40 mg subcuta- neously every 2 weeks), golimumab (50 mg subcutaneously every month) and certolizumab (200 mg subcutaneously every two weeks) have been shown in randomized placebo-controlled trials to have significant clinical efficacy in patients with persistently active axial spondyloarthritis, including

nonradiographic axial spondyloarthritis and ankylosing spondylitis, but regulatory approvals are complex and changing in both Europe and the United States. The TNF receptor antagonist etanercept (50 mg subcutaneously weekly, given either in one or two dosages) has similar clinical ef- ficacy for musculoskeletal symptoms, but is less or not effective for gut, skin, and eye symptoms associated with spondyloarthritis. Secukinumab (an anti-interleukin 17A monoclonal) has been ap- proved for patients with active ankylosing spondylitis by both the European and US regulatory agencies. The dosage of 150 mg sub- cutaneously every 4 weeks, after an initial saturation phase with every week dosing, is lower than that approved for psoriasis (300 mg subcutaneously every 4 weeks). The aim of physiotherapy is to maintain and enhance function by improving mobility and muscle strength. Patients affected by spinal stiffness should have physiotherapy on a regular daily basis. Hip replacement is indicated for those with severe hip involve- ment, and spinal osteotomy can be indicated in cases where visual problems have occurred that are due to severe kyphosis. Prognosis The established myth is that ‘patients with ankylosing spondylitis generally do well’. However, one-third are severely disabled and ex- perience intense pain and impairment of health comparable to those with rheumatoid arthritis. ankylosing spondylitis does not burn out: disease activity and pain are independent of its duration. As the disease usually starts in the second or third decade of life, pa- tients with ankylosing spondylitis typically suffer its effects for many years. Mortality may be slightly increased, possible causes of prema- ture death being amyloidosis, NSAID gastropathy (ulcers, bleeding), vertebral fractures, and cardiac or respiratory complications. Reactive arthritis/Reiter’s syndrome For further information see Chapter 19.8. Undifferentiated spondyloarthritis Definition The term undifferentiated spondyloarthritis was introduced and defined by the European Spondylarthropathy Study Group (ESSG) Fig. 19.6.8 Spinal radiograph showing classical bamboo spine.

 in 1991. Terms such as incomplete Reiter’s syndrome, syndrome of enthesopathy and arthritis, HLA B27-positive oligoarthritis (and others) had been used previously. The fact that patients with a clin- ical picture of peripheral oligoarthritis but without spinal symp- toms were also classified/diagnosed as spondyloarthritis had indeed been confusing for many rheumatologists. Now the terminology has again changed and only patients with predominant peripheral symptoms who do not have psoriasis, inflammatory bowel disease or a preceding infection are named ‘undifferentiated’. Patients with undifferentiated spondyloarthritis have the typ- ical clinical features of predominant peripheral spondyloarthritis but do not fit into any of the other defined categories as explained here. The condition may represent an early form of another spondyloarthritis subset (most often ankylosing spondylitis), or be a genuine spondyloarthritis subset of its own. The new Assessment of SpondyloArthritis International Society (ASAS) criteria for spondyloarthritis cover axial and peripheral spondyloarthritis, es- pecially axial spondyloarthritis is a possible predecessor of anky- losing spondylitis, since at least 50% of patients go on to develop this condition. Epidemiology The prevalence of peripheral undifferentiated spondyloarthritis is not known precisely, but the frequency is not much less than that of psoriatic arthritis, and it is more common in men. About 70% of patients are HLA B27-positive. In some contrast to other spondyloarthritides, late-onset disease has been reported. Clinical features The main clinical features are asymmetric peripheral arthritis, pre- dominantly of the lower limbs, enthesitis, dactylitis, anterior uveitis, and some patients do also report inflammatory back pain. Diagnosis The term undifferentiated spondyloarthritis is no longer used for patients with predominant axial symptoms but only for patients with predominant peripheral symptoms. The diagnosis of periph- eral undifferentiated spondyloarthritis requires peripheral

arthritis of the lower limbs and at least one other characteristic feature in addition—enthesitis, dactylitis, anterior uveitis, a positive family history for spondyloarthritis, or HLA B27. The classification criteria for peripheral spondyloarthritis have already been described. These include psoriasis, inflammatory bowel disease, and a preceding infection, but these features are now considered disease defining and hence are not present in undifferentiated spondyloarthritis. Radiographs are not essential for a diagnosis, but in clinically suspi- cious cases MRI of the sacroiliac joints may be helpful in providing objective evidence of sacroiliitis. The differential diagnosis of asymmetric peripheral arthritis of the lower limbs in spondyloarthritis comprises Lyme disease, sar- coidosis, gout, osteoarthritis, atypical rheumatoid arthritis, and con- nective tissue diseases and other rarer conditions. Treatment Nonspecific therapy with NSAIDs, intra-articular steroid injections, transient immobilization, ice packs, and physiotherapy is similar to that of other arthritides. Sulfasalazine may have some efficacy for peripheral and axial symptoms, but very few therapeutic trials with disease-modifying agents have been performed in undifferentiated spondyloarthritis. TNF blockers (so far mainly adalimumab) have been shown to work for peripheral spondyloarthritis. Prognosis The long-term prognosis of patients with peripheral undifferenti- ated spondyloarthritis is uncertain: there are no data available at present. Psoriatic arthritis Definition All kinds of arthritis occurring in association with psoriasis can be regarded as psoriatic arthritis, but it is clear that there can be con- siderable variability in arthritic manifestation. Many patients can be classified as having a spondyloarthritis, but some are affected in a manner more closely resembling rheumatoid arthritis, and there are other unique forms such as arthritis mutilans. Different forms of psoriasis may be associated with different form of arthritis. Epidemiology Psoriasis is common, with prevalence between 1 and 3% of the population. Arthritic symptoms occur in 20–40% of these, with the axial skeleton affected in 15–25%, such that the overall preva- lence of psoriatic arthritis is somewhere around 0.1–0.3%. The peak age of onset of psoriatic arthritis is between 20 and 40 years: ju- venile disease is rare. Both sexes are equally affected, but women more frequently get polyarthritis and men more often have spinal involvement. Pathogenesis Familial aggregation and high concordance rates in monozygotic (70%) compared with dizygotic twins (20%) suggest that there are important genetic factors in psoriasis and psoriatic arthritis. About 30% of patients give a clear history of affected first-degree rela- tives. The genetic impact is thought to be multifactorial. Psoriasis is associated with HLA B13, B17, B37, and HLA DR7, the strongest association being with Cw6 (RR = 24). HLA associations of psori- atic arthritis are with HLA B38 and B39 (peripheral arthritis), with HLA DR4 (symmetric polyarthritis) and HLA B27 (spondylitis). The importance of HLA genetic linkage may lie in determination of the immunological response to particular antigens, and there has been much interest in the possible role of streptococcal infection. A proliferative response of skin and synovial T cells to streptococcal antigens has been detected in psoriatic arthritis, but also in rheuma- toid arthritis, and the (immuno)histology is similar in the two con- ditions, although some differences have been described. Koebner’s phenomenon is described in psoriasis, when plaques arise at sites of skin injury, scratches, and scars, but the role of trauma in psoriatic arthritis is not clear. Drugs can exacerbate and trigger psoriasis: most well known are β-blockers, antimalarials, and lithium, and withdrawal of corticosteroids can induce a skin flare, but the relevance of these factors to psoriatic arthritis is uncertain. Clinical features The most characteristic features of psoriatic arthritis are dactylitis and osteoproliferative changes in radiographs of peripheral joints.

 The pattern of axial involvement is somewhat different from that in ankylosing spondylitis, and in contrast to rheumatoid arthritis, patients with

psoriatic arthritis may have involvement of the distal interphalangeal joints. It is possible that psoriatic arthritis can occur without skin involvement. Psoriatic arthritis has been divided into five subgroups: distal interphalangeal (overlapping, most common); asymmetrical (spondyloarthritis-like); symmetrical (rheumatoid arthritis-like); mutilans (unique, rare; see Fig. 19.6.9); and spinal (ankylosing spondylitis-like). It must be stressed, however, that these subgroups are not clearcut. In one study the initial classification pattern changed when patients were evaluated over a period of eight years: finally only two categories remained—peripheral disease without axial in- volvement (70%), and axial involvement with or without peripheral arthritis (30%). The latter was correlated with duration of the disease and magnitude of joint involvement. Erosions were found in 70% of the patients. Psoriasis precedes joint disease in most cases (70–80%); both occur simultaneously in 15%; and in about 10% arthritis comes first. There is poor correlation between onset, severity, and activity of psoriatic skin lesions and arthritis. More than 80% of patients with psoriatic arthritis have nail dystrophy, whereas this is the case in only 20% of those with uncomplicated skin disease. Nail dystrophy, ranging from some to many nail pits and horizontal (not longitu- dinal) ridging to onycholysis, occurs most often in those with distal interphalangeal involvement. In some patients the involvement of interphalangeal joints and nails is closely correlated, with both ap- pearing on the same finger(s). Acute anterior uveitis occurs mainly in those with radiological sacroiliitis and ankylosing spondylitis. Different types of psoriatic skin involvement lead to different types of arthropathy. Most frequent is the common psoriasis vulgaris, but a type of skin disease that frequently affects the palms of the hands and soles of the feet with many psoriatic plaques is also seen: pusto- losis palmaris et plantaris. This type is associated with SAPHO syn- drome, which is related to the spondyloarthritides but has unique features that justify the designation as a separate subset of these disorders. A severe form of psoriatic arthritis can occur in HIV-infected patients, although is not clear whether HIV increases the overall prevalence of psoriatic arthritis. Severe peripheral enthesitis (predominantly of the heel) and dactylitis are characteristic. Knee arthritis can be rapidly destructive. Axial inflammation is less frequent. There is an overlap between psoriatic arthritis and reactive arth- ritis in the form of keratoderma blennorrhagica, a desquamating psoriasis-like lesion mostly occurring on the soles of the feet in pa- tients with Reiter’s syndrome. Psoriatic arthritis often improves during pregnancy. There is no adverse effect of the disease on mother or child. Diagnosis Scaling erythematous papules and plaques on the scalp and ex- tensor aspects of the extremities, often surmounted by a silvery white micaceous scale that is easily removed, are suggestive of psor- iasis. Elbows and knees are often affected. The diagnosis of psoriatic arthritis is based on the presence of these characteristic skin lesions, which are not always obvious. Less accessible areas such as the navel, perineum, and scalp need to be examined carefully. The patient should be asked whether they have a family history of psoriasis or psoriatic arthritis. As psoriasis is a frequent disease, it must be remembered that a patient with psoriasis can have an attack of gout or another form of arthritis. The diagnosis of psoriatic arthritis should be considered in those without skin lesions if there is distal interphalangeal joint involvement, dactylitis, the involvement of a whole finger or toe, tendon sheaths and bone of an affected limb, and/or typical radio- graphic changes. The CASPAR (Classification criteria for psoriatic arthritis) criteria consist of established inflammatory articular disease with at least three points from the following features: current psoriasis (assigned a score of 2; all other features are assigned a score of 1), a history of psoriasis (unless current psoriasis is present), a family history of psoriasis (unless current psoriasis is present or there is a history of psoriasis), dactylitis, juxta-articular new bone formation, rheumatoid factor negativity, and nail dystrophy. These criteria are sensitive (0.914) and specific (0.987). Laboratory and radiological features Acute phase reactants are often raised.

HLA determinations including HLA B27 do not provide diagnostic help in those with psoriatic arthritis, but in HLA B27-negative patients who appear to have ankylosing spondylitis, psoriasis (and inflammatory bowel dis- ease) should always be sought. The presence of rheumatoid factor does not formally exclude a diagnosis of psoriatic arthritis, there being a background prevalence of rheumatoid factor positivity, but a positive result should always make the physician consider the diag- nosis carefully. The distribution of radiological changes reflects clinical involve- ment, with the interphalangeal joints involved earlier than larger joints. A characteristic lesion in advanced cases is the so-called pencil-in-cup deformity (Fig. 19.6.10), which evolves by resorption of the distal end of a phalanx or metacarpal with uniform deep ero- sion of the end of the corresponding distal phalanx. In some cases the joints can be completely destroyed and invisible on the radiograph. Radiological grounds for thinking the diagnosis more likely to be psoriatic arthritis than rheumatoid arthritis are distal interphalangeal joint involvement, asymmetric joint involvement, marginal erosions with adjacent bone proliferation (whiskering), osteolysis, periost- itis, proliferative new bone formation, and ankylosis. Radiological Fig. 19.6.9 Severe psoriatic arthritis (arthritis mutilans).

section 19 Rheumatological disorders 4452 sacroiliitis is a finding in 20 to 40% of patients. The axial disease in psoriatic arthritis can be indistinguishable from that in primary an- kylosing spondylitis, but in psoriatic arthritis the following are more likely: asymmetrical sacroiliitis; less zygapophyseal joint involve- ment; fewer, coarser, and asymmetric syndesmophytes; and bony bridging that is more often than not asymmetrical. Psoriatic arth- ritis syndesmophytes can be indistinguishable from spondylophytes typical of DISH (Forestier’s disease). When scintigraphy is used to detect the extent and localization of arthritis, an increased uptake of the isotope technetium-99 can frequently be detected in the sternoclavicular and manubriosternal joints, but this is not necessarily associated with clinical symptoms. Treatment Many patients improve with the use of NSAIDs and intra-articular steroids, especially in the case of large joint involvement or flexor tenosynovitis. However, 20 to 40% of patients will not improve and need to be treated with conventional disease-modifying antirheumatic drugs or biologics. Sulfasalazine 2 to 3 g daily is often effective against arthritis, especially in patients with limited skin disease. Methotrexate 7.5 to 25 mg orally or subcutaneously weekly is likely to also work for arthritis (limited data), and even better for the skin. Intramuscular gold and azathioprine have been tried. Antimalarials and penicillamine are not indicated; the former may exacerbate psoriasis. Ciclosporin may be given in severe cases, es- pecially with skin involvement. There is limited information on the use of combination therapies. Systemic corticosteroids are limited to extreme cases of arthritis: psoriasis usually flares when they are withdrawn. Intra-articular glucocorticoids are useful. Local skin therapy has no effect on joint symptoms. Fumaric acid is most frequently used as starting therapy in Northern Europe. Etretinate is not clearly beneficial for arthritis and may cause arthralgias and many other adverse reactions. Apremilast, a phosphodiesterase-4 inhibitor, has now been approved for psoriasis and psoriatic arthritis. The safety profile is pretty good, no labora- tory controls are necessary, and an effect on skin and joints has been demonstrated, but the effect size in comparison to other biologics is less impressive. All anti-TNF agents (see ankylosing spondylitis section) are ap- proved for psoriasis and psoriatic arthritis, also an IL12/IL-23 inhibiting agent (these cytokines share the p40 receptor). The role of physiotherapy is similar to that in other spondy loarthritides with predominant peripheral involvement, and there are no special considerations for surgical intervention in psoriatic arthritis, apart from the fact that the presence of florid skin lesions close to a joint is a relative contraindication to surgery. Prognosis Severe

psoriasis can lead to significant disability. There are only limited data from long-term studies in psoriatic arthritis, but in cross-sectional studies 10 to 20% of patients are in a poor functional class, and the HLA antigens HLA B27, HLA B39, and DQw3 have been associated with such an outcome. Arthritis associated with inflammatory bowel disease Definition An arthropathy with various clinical symptoms occurring in asso- ciation with Crohn's disease and ulcerative colitis is termed arth- ritis associated with inflammatory bowel disease. Other forms of arthropathy occurring in association with enteropathy are Whipple's disease, and arthritis after intestinal bypass surgery. Epidemiology A relationship between gut and joint disease was postulated in 1922 when Smith treated arthritis patients with segmental bowel surgery. Bargen and Hench in 1929 and 1935 described arthritis in associ- ation with ulcerative colitis and Crohn's disease. Moll and Wright included arthritis associated with inflammatory bowel disease in the concept of spondyloarthritis in 1973. Mielants and Veys described Crohn's-like gut lesions in all subsets of spondyloarthritis in 1984. The prevalence of Crohn's disease and ulcerative colitis is be- tween 0.05 and 0.1% of the population, generally higher in white and Jewish people. The peak occurrence of both diseases is between 15 and 35 years, but it may appear in every decade of life; both sexes are equally involved. Arthritis associated with inflammatory bowel disease occurs in 10 to 30% of patients with inflammatory bowel dis- ease, in general more frequently in Crohn's disease than in ulcerative colitis, and more often in patients with colonic involvement and in those with extensive bowel disease. There is a genetic predisposition for inflammatory bowel disease with documented familial aggregation for both Crohn's disease and ulcerative colitis. The association with HLA B16, HLA B18, and HLA B62 is not strong. The peripheral arthritis of inflammatory bowel disease is only weakly associated with HLA B27, but axial in- flammation is more strongly associated with it (50%). The patient with inflammatory bowel disease who is HLA B27-positive is at high risk of developing spondylitis. The relative frequency of sacroiliitis and ankylosing spondylitis in inflammatory bowel diseases varies Fig. 19.6.10 Radiograph of a hand showing destructive psoriatic arthritis.

 between 2 and 20% or more, partly depending on the sensitivity of the diagnostic imaging procedure. Only 4% of patients with ankylosing spondylitis develop overt inflammatory bowel disease, whereas 60% have microscopically detectable Crohn-like gut lesions. Pathogenesis The pathogenesis of inflammatory bowel disease and arthritis as- sociated with inflammatory bowel disease is not known. One hy- pothesis is of an aberrant immune response to gut bacteria, with gut inflammation leading to increased permeability, allowing bacteria to cross the mucosal border and get access to joints. There is some evidence from the HLA B27 transgenic rat model that gut and joints are closely linked: susceptible rats get both colitis and arthritis once they have left a germ-free environment. Clinical features Patients with ulcerative colitis and Crohn's disease typically pre- sent with bloody diarrhoea and abdominal pain, and in severe cases with fever, weight loss, and fatigue. For further details of gastrointestinal and other nonrheumatological presentations, and criteria for diagnosis, see Chapters 15.11 and 15.12. As with the other spondyloarthritides, the arthritis is mostly asymmetric and predominantly affects the legs. The arthritis is mi- gratory, often transient, but tends to recur. It does not frequently become chronic but may be associated with erosive disease in some patients. Flaring of gut symptoms is often associated with arthritis, especially in ulcerative colitis. Patients experience significantly fewer joint symptoms after colectomy. Two types of arthropathy were distinguished in a study of almost 1500 patients with inflammatory bowel disease, essentially on the basis of how many joints are involved and (importantly) without knowledge of spinal radiographs. Pauciarticular disease (type I, fewer than five joints involved) affected 3.6% of

patients with ulcera- tive colitis and 6% of those with Crohn’s disease and was acute and self-limiting, with episodes lasting four to five weeks, in 83 and 79% of the cases. Polyarticular disease (type II, five or more joints) af- fected 2.5% of patients with ulcerative colitis and 4% of those with Crohn’s disease and was associated with persistent symptoms in 87–89% of the cases. The onset of peripheral arthritis is associated with exacerbations of colitis, but there is no link between enteric and spinal symptoms. Acute anterior uveitis occurs in 10% of patients with inflamma- tory bowel disease. It is associated with axial involvement and with HLA B27. The type of uveitis is somewhat different in inflammatory bowel diseases to that in other spondyloarthritides: posterior uveitis and scleritis may occur. The most common skin lesion in arthritis associated with inflammatory bowel disease is erythema nodosum, occurring in association with exacerbation of enteritis. Diagnosis Most arthritic symptoms occurring in patients with inflammatory bowel disease can generally be attributed to spondyloarthritides. However, as in psoriasis, patients can have more than one dis- ease (osteoarthritis, and so on). As many as 50–60% of all patients with ankylosing spondylitis have gut lesions resembling those in Crohn’s disease, but most are asymptomatic. Clinically apparent ankylosing spondylitis often precedes Crohn-like symptoms. This spectrum of diseases clearly and typically belongs to the spectrum of spondyloarthritides. The differentiation (if needed) will rarely cause problems, as one disease is usually predominant. Along with psoriasis, inflammatory bowel disease should always be looked for in HLA B27-negative patients who appear to have ankylosing spondylitis. Treatment Treatment of inflammatory bowel disease is always the first consid- eration and will probably influence peripheral arthritis. Treatment with NSAIDs may be effective for arthritis and spondylitis but can exacerbate bowel disease. There are few data on the use of DMARDs. Sulfasalazine is effective in ulcerative colitis and other spondyloarthritides and may accordingly be used in arthritis asso- ciated with inflammatory bowel disease. Azathioprine is effective in Crohn’s disease and can be tried to treat severe and chronic joint disease. Corticosteroids are the therapy of choice in acute inflamma- tory bowel disease and will generally help arthritis, but they should not be used for mild and transient joint symptoms. As previously stated, NSAIDs tend to exacerbate gut symptoms, but etoricoxib did not cause more flares than placebo (both c.10%) in one controlled study. In more severe cases biologics are used to treat inflammatory bowel disease and this will usually also have an effect on joint or axial symptoms. Prognosis The prognosis of arthritis associated with inflammatory bowel dis- ease is generally good. Joint destruction is a rare event. Patients may have ankylosing spondylitis at presentation of inflammatory bowel disease, or develop this later. SAPHO syndrome Definition French workers proposed SAPHO (synovitis, acne, pustolosis palmaris et plantaris, hyperostosis, and osteitis) as a unifying diag- nosis for several idiopathic bone and skin diseases, thereby com- bining over 50 different terms published in the literature (including pustulotic arthro-osteitis, chronic multifocal osteomyelitis, Tietze syndrome (German), and acquired hyperostosis syndrome). Their description of the common symptoms and overlapping features of this heterogenous group of rheumatic joint, bone, and skin diseases has led to better recognition of the relatively rare condition. There is an argument that SAPHO simply represents a subset of psoriatic arthropathy, also that it might not really belong to the spondyloarthritides at all because only 43% of patients with SAPHO fulfilled the European Spondylarthropathy Study Group criteria, and only 1 in 19 was HLA B27-positive in one follow-up study. However, there are some clear similarities. Pathogenesis The pathogenesis of SAPHO syndrome is unclear. Some authors think that it is similar to that of reactive arthritis. Propionibacterium acnes, which can induce arthritis in animals, has been detected in acne lesions and grown from osteitic lesions in some cases. However, cultures are negative in most cases, and antibiotics are ineffective.

 Diagnosis There are no evaluated diagnostic criteria for SAPHO. Most con- vincing clinically is the combination of a classical skin symptom— such as pustolosis or significant acne (acne conglobata and acne fulminans or hidradenitis suppurativa)—with a characteristic joint or bone lesion such as arthritis of the sternoclavicular joint, osteitis, or hyperostosis in the anterior chest wall. Diagnosis is important to avoid unnecessary biopsy procedures, but can be very difficult, especially in those without typical skin le- sions. The most important differential diagnoses are bacterial osteo- myelitis and malignancy. The pattern of joints affected differs from other rheumatic diseases: the sternoclavicular joint (Figs. 19.6.11 and 19.6.12), the clavicle, the ribs, and the mandible are frequently involved by arthritis, osteitis, and/or hyperostosis. Sacroiliitis, mostly unilateral, occurs in one-third of patients. Treatment Analgesics, NSAIDs, and intra-articular steroids are usually ef- fective. In severe cases systemic corticosteroids should be con- sidered. Immunosuppressive agents can be added if the steroid dose cannot be tapered to less than 10 mg/day of prednisolone (or equivalent). Sulfasalzine, azathioprine, and methotrexate have been tried successfully in some cases. Radiation therapy can also be effective in refractory cases. No controlled studies have been performed. Patients with refractory disease might also respond to treatment with TNF blockers. There are positive case reports also for bisphosphonates. Prognosis The course of disease is very variable. Initially, occurrence of sev- eral flares per year is common. Further progress is usually favour- able, but complications such as axillary vein and C8 compression can occur. Some patients may develop ankylosis and a few progress to ankylosing spondylitis. Other enteric arthropathies Whipple’s disease Whipple’s disease is a rare systemic disease that usually involves the small intestine (see Chapter 15.10.6). The associated arthritis is often symmetric and polyarticular, and may antedate the intestinal com- plaints by years. It is not usually destructive. Axial involvement oc- curs but is not typical. Arthritis associated with coeliac disease For a description of coeliac disease (gluten-sensitive enteropathy) see Chapter 15.10.3. The joint manifestations show a striking re- sponse to a gluten-free diet, which strongly suggests a causal rela- tionship. The pattern of arthritis is very variable, and overt bowel symptoms are absent in half of cases, making diagnosis difficult. The lumbar spine, hips, knees, shoulders, elbows, wrists, and ankles are most frequently affected, often symmetrically. The arthritis is not de- structive. HLA B8 and DR3 are frequently found. The pathogenesis is unclear. Arthropathies associated with collagenous colitis Collagenous colitis is a chronic diarrhoeal disease character- ized by a normal or near-normal mucosa endoscopically and a thick subepithelial collagen layer. More than half of patients with this disorder have some form of arthritis and use NSAIDs regularly. Arthropathies associated with intestinal bypass surgery Arthritis has been reported in 5–50% of patients in the first three years after jejunoileal bypass surgery. A symmetric periph- eral polyarthritis involves the knees, wrists, metacarpophalangeal and metatarsophalangeal joints, elbows, proximal interphalangeal joints, and ankles and is usually nondestructive. Almost half of those affected also have vesicopustular skin lesions. No specific HLA association has been found, but two previously healthy HLA B27-positive patients developed spondylitis. Bacterial over- growth of the blind loop is critical for pathogenesis. Fig. 19.6.11 Arthritis/hyperostosis of the left sternoclavicular joint in a 52-year-old man with SAPHO syndrome. Fig. 19.6.12 Computed tomography scan showing severe osteitis of the left sternoclavicular joint in a 35-year-old woman with SAPHO syndrome.

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