Spondyloarthropathies constitute a cluster of interrelated and overlapping chronic inflammatory rheumatic diseases that include ankylosing spondylitis (the prototype of spondyloarthropathies), reactive arthritis (including Reiter’s syndrome), psoriatic arthritis, enteropathic arthritis, and pauciarticular late-onset arthritis, a form of juvenile idiopathic arthritis [1–5]. These diseases are not associated with rheumatoid factor. They occur in genetically predisposed individuals and show a strong association with HLA-B27; however, the strength of the association with HLA-B27 varies markedly among the patients with the various forms of spondyloarthropathies, and also among many racial and ethnic groups [6–9]. Bacterial infections have long been suspected as the environmental triggers for many of these diseases, but the cellular and molecular mechanisms of inflammation are not yet fully understood. Chlamydial and many enterobacterial infections can trigger reactive arthritis, but an infectious trigger for ankylosing spondylitis has not yet been established [2].

Substantial evidence strongly favors a direct role for HLA-B27 in enhancing genetic susceptibility, and a few additional genetic factors may also influence the susceptibility, disease expression, or severity [9–16]. Some of these additional genetic predisposing factors may include some of the putative disease-predisposing genes for psoriasis and inflammatory bowel disease.

Spondyloarthropathies are more prevalent among males than females. The patients are usually in their late teens and early twenties at the time of disease onset, although spondyloarthropathies may sometimes present at an older age [2,17,18]. The primary pathologic sites include the entheses, which are the sites of bony insertion of ligaments and tendon, the sacroiliac joints and the axial skeleton, the limb joints, and some nonarticular structures, such as the gut, skin, eye, and aortic valve [19–21]. The initial clinical features may result from enthesitis (inflammatory lesions of the entheses), dactylitis, or oligoarthritis, and in some cases may progress to sacroiliitis and spondylitis, with or without extra-articular features such as acute anterior uveitis or mucocutaneous lesions.

It may not always be possible to differentiate clearly among the various forms of spondyloarthropathies in early stages because these diseases generally share many clinical features. Moreover, the clinical spectrum is much wider than previously realized, and the clinical features typical of spondyloarthropathies may occur in different combinations so that the previously established criteria for disease classification may be inappropriate for a large subset of such patients [17,18].

Some additional less clearly defined categories are being recognized, and some of them are grouped under the label of “undifferentiated” spondyloarthropathies [2,3,17,18,22,23]. The frequently underdiagnosed “undifferentiated” forms of spondyloarthropathies include isolated clinical syndromes, such as HLA-B27-associated seronegative oligoarthritis or polyarthritis, mostly of the lower extremities, without a recognizable preceding bacterial infectious trigger and any extra-articular clinical features, or associated inflammatory bowel disease or psoriasis. Some patients present with dactylitis (“sausage digits”) or enthesitis, especially at the heel (Achilles tendonitis and plantar fasciitis) (acute iritis) [2,18,21–25]. These may occur even in early childhood or in persons over age 50 [2,5,18].

Approximately 50% of white patients with acute anterior uveitis are HLA-B27–positive, and well over half of the patients with HLA-B27–positive acute anterior uveitis have some form of spondyloarthropathy [24,25]. An HLA-B27–associated syndrome of aortic incompetence plus heart block has also been described [26]. These extra-articular manifestations may occur in individuals with no signs of arthritis or may accompany the onset of spondyloarthropathy or occur many years later. A clear differentiation between the various forms of spondyloarthropathies, especially in their early stages, may not always be possible due to their overlapping clinical features.

Studies from Western Europe indicate that ankylosing spondylitis in its full spectrum is much more common than previously realized, and its overall prevalence may be similar to that of rheumatoid arthritis [2,27–29]. Moreover, the prevalence figure for spondyloarthropathies as a whole may be approximately twice as high; this is especially the case in the Eskimo and the Inuit populations that have a 25% to 40% prevalence of HLA-B27 in the
Amor (countries in association with the high prevalence of HIV infection [31]. Spondyloarthropathies has been observed recently in sub-Saharan African prevalence of HLA-B27 [30]. A sharp increase in the prevalence of seem to lack association with ankylosing spondylitis [10,37–39].

There are 25 different currently known natural variants of the HLA-B27 molecule. They show different ethnic distributions, and some of them may also show differences in disease association [7,10,15]. For example, HLA-B*2706 in Southeast Asians and HLA-B*2709 in Sardinian Italians seem to lack association with ankylosing spondylitis [10,37–39].

Ankylosing spondylitis is generally considered to be the most common and most typical form of spondyloarthropathy. It is a chronic systemic inflammatory disorder of undetermined etiology, usually beginning in early adulthood, primarily affecting the axial skeleton (sacroiliitis being its hallmark), but it can also exhibit some extra-articular features [2,3,40]. The inflammation appears to originate in ligamentous and capsular sites of attachment to bones (enthesitis), juxta-articular ligamentous structures, and the synovium, articular cartilage, and subchondral bones of involved joints [19–21,41–46]. The site of enthesitis is infiltrated by lymphocytes, plasma cells, and polymorphonuclear cells, and there is also edema and infiltration of the adjacent marrow space. A striking feature is a high frequency of axial enthesitis and synovitis that can result in fibrous and later bony ankylosis of the sacroiliac joints and the spine. It is two to three times more common in males than females, and the clinical and roentgenographic features seem to evolve more slowly in females. The characteristic early symptom is insidious onset of chronic low back pain and stiffness, beginning usually in late adolescence or early adulthood (mean age of onset, 24 years), but a variety of presentations may antedate back symptoms in some patients [2,40]. It is rare for ankylosing spondylitis to begin after 45 years of age [18,36], but there are many patients whose disease gets diagnosed at an older age, in part because they may have had minimal symptoms over the years.

The pain resulting from sacroiliitis is dull in character, difficult to localize, and felt somewhere deep in the gluteal region. It may be unilateral or intermittent at first; however, within a few months it generally becomes persistent and bilateral, and the lower lumbar spine area also becomes painful. Sometimes pain in the lumbar area may be the initial presentation. The symptoms typically worsen with prolonged inactivity or on waking up in the morning (“morning stiffness”), and improve with physical activity and a hot shower.

The diagnosis of ankylosing spondylitis is clinical, but the historic features suggestive of chronic inflammatory back pain, ie, its insidious onset before the age of 40, its worsening with inactivity and improvement on physical exercise, are not very specific on their own [4,47,48]. A history of acute anterior uveitis, a positive family history for ankylosing spondylitis or related spondyloarthropathies, or the presence of impaired spinal mobility or chest expansion further supports the clinical diagnosis. So does the presence of enthesitis with resultant tenderness over the sacroiliac joints and the spine, and sometimes at other sites, such as the heels, iliac crest, and the anterior chest wall. The modified New York criteria for ankylosing spondylitis are now commonly used for disease classification [49,50].

Reactive arthritis is defined as an episode of aseptic asymmetric peripheral arthritis, predominantly of the lower limbs, occurring within a month of a primary infection elsewhere in the body, usually genitourinary infection with Chlamydia trachomatis or an enteritis due to certain gram-negative enterobacteria [51–56]. It is frequently associated with one or more characteristic extra-articular features, such as ocular inflammation (conjunctivitis or acute iritis), enthesitis (Achilles tendonitis and plantar fasciitis), dactylitis (“sausage” digits), tenosynovitis, mucocutaneous lesions, urethritis, and, on rare occasions, carditis. The enteritis results from infection with bacteria such as Shigella, Salmonella, Yersinia, or Campylobacter (see Fig. 5–32). The reactive arthritis can also follow local injection of Bacille Calmette-Guérin (BCG) into the bladder as cancer therapy [57], but not with BCG inoculation that is used in some countries to decrease the risk of tuberculosis. It has been suggested that respiratory tract infections by Chlamydia pneumoniae may also trigger reactive arthritis [58]. The disease is most commonly seen in young sexually active adults, mostly men, when it is triggered by C. trachomatis. However, reactive arthritis is underdiagnosed in women due to the frequently subclinical or asymptomatic chlamydial infection among them and the infrequent performance of pelvic examinations by physicians to look for the presence of cervicitis. Postenteritic reactive arthritis affects children and adults, including the elderly, of both genders.

Urethritis and cervicitis can accompany arthritis after acute bacterial diarrhea; and, conversely, the psoriasiform lesions over the external genitalia (circinate balanitis and circinate vulvitis) do not directly relate to the presence of genitourinary infection. In about one quarter of all cases the triggering organism remains unknown.

A history of a preceding or associated diarrhea, urethral discharge, urinary frequency, dysuria, lower abdominal discomfort, tender enlarged prostate, circinate balanitis, conjunctivitis, mucosal lesions, onycholysis, or keratoderma blennorrhagica should suggest the possibility of reactive arthritis [55,59,60]. Septic arthritis should be ruled out by joint aspiration, Gram's stain, and culture of any accessible joint fluid. Conjunctivitis occurs in one third of patients with reactive arthritis, usually in synchrony with flares of arthritis, and some patients experience one or more episodes of acute anterior uveitis. The triad of arthritis, conjunctivitis, and urethritis has been called Reiter's syndrome, but most patients with reactive arthritis do not present with this triad. The full clinical spectrum of reactive arthritis has been broadened considerably, and “incomplete” forms are
observed much more commonly than the classic triad. Some patients may not demonstrate any recognized antecedent infection or may have asymptomatic triggering infection, and reactive arthritis–associated bacteria may trigger some forms of the undifferentiated spondyloarthropathies and juvenile arthritis.

The average duration of the arthritis is 4 to 5 months, but many patients have mild musculoskeletal symptoms persisting for more than a year. HLA-B27–positive patients tend to have more severe and more prolonged joint symptoms [53,55,60]. Recurrent attacks are more common in those with chlamydia-induced reactive arthritis. Approximately 15% to 30% develop chronic or recurrent arthritis or sacroiliitis and spondylitis, and these patients are mostly those with a positive family history or are positive for HLA-B27, and often have severe and more chronic disease.

Severe arthritis, or an illness resembling typical reactive arthritis, psoriatic arthritis, or undifferentiated spondyloarthropathy, can occur in some patients infected with HIV [31,61–63], but it seems to have become less common in developed countries due to the availability of more effective antiviral therapies. Since the advent of the current HIV epidemic, reactive arthritis, psoriasis, psoriatic arthritis, and related spondyloarthropathies, except ankylosing spondylitis, are becoming more prevalent in sub-Saharan Africa, where these diseases used to be extremely rare [31]. For example, the prevalence of spondyloarthropathies in Lusaka, the capital of Zambia, now has been calculated to be approximately 180 per 100,000 in HIV-infected individuals, 12 times higher than in the population uninfected with HIV [31,63]. Such patients are also prone to bone and joint infections due to their low CD4+ T-cell count.

Psoriasis is a common skin disease among whites (1% to 3% prevalence), and is even more common (5% to 10%) in northernmost regions of Norway and Russia, but it is uncommon in some other racial groups, such as blacks and native Americans (0% to 0.3%) [64]. More than 10% (range, 5% to 42%) of patients with psoriasis have associated inflammatory arthritis, including sacroiliitis and spondylitis [65]. Psoriasis usually antedates the appearance of arthritis by one to two decades. The arthritis usually begins between 30 and 50 years of age, but it can also begin in childhood. A search for psoriasis in an arthritis patient suspected to have psoriatic arthritis should not be limited to the extremities but also should include the scalp, ears, umbilicus, pelvic area, perineum, natal cleft (perianal area), palms, soles, and nails.

Psoriatic arthritis is defined as an inflammatory arthritis associated with psoriasis, occurring in the absence of rheumatoid nodules and serum rheumatoid factor [64–67]. Different subtypes of psoriatic arthritis have been proposed: monoarthritis and oligoarthritis, polyarthritis, arthritis of distal interphalangeal joints with nail changes, arthritis mutilans, and spondylitis. However, psoriatic arthritis runs a very variable course, and the distinction between these subtypes becomes less distinct with time and there are no universal criteria for its diagnosis. A subset of patients may show peripheral enthesitis without arthritis. The exact prevalence of each of these various forms is difficult to establish because the pattern in some patients may change with time, and some may show overlapping features.

The evolution of a mild psoriasis to a widespread erythrodermic pattern with an associated flare-up of arthritis may raise the possibility of an associated HIV infection. There has been a dramatic increase of psoriasis and psoriatic arthritis in sub-Saharan Africa, associated with the current epidemic of HIV infection [31,61–63]. Among a cohort of 702 patients with inflammatory arthritis in Zambia, 28 had psoriatic arthritis and all but one (96%) were HIV positive [63], suggesting that every patient with newly diagnosed psoriatic arthritis in sub-Saharan Africa should be tested for possible HIV infection.

The term enteropathic arthritis implies the occurrence of inflammatory arthritis in patients with ulcerative colitis and Crohn’s disease. It is more common than previously reported; 39% of 103 patients with ulcerative colitis or Crohn’s disease, irrespective of the extent of the bowel disease, had enteropathic arthritis [68]. Inflammatory back pain was present in 30% of these 103 patients, and 10% fulfilled the criteria for ankylosing spondylitis. The inflammatory arthritis of peripheral (limb) joints tends to occur much more frequently in enteropathic arthritis than with primary ankylosing spondylitis, but it tends to be self-limited and nondeforming, and correlates with flare-up of bowel disease, especially in the case of ulcerative colitis. The axial disease (sacroiliitis alone or with classic clinical and radiographic features of ankylosing spondylitis) does not fluctuate with bowel disease activity.

An increased frequency of subclinical inflammatory lesions in the gut (20% to 70%) is observed on colonoscopic mucosal biopsy in patients with spondyloarthropathy who have no gastrointestinal symptoms or clinically obvious inflammatory bowel disease [69,70]. Follow-up studies of such patients indicate that 6% of them will develop inflammatory bowel disease, and among those with histologically “chronic” inflammatory gut lesions, between 15% and 25% will develop clinically obvious Crohn’s disease. This suggests that the latter group of patients had initially a subclinical form of Crohn’s disease when they presented with arthritis [69,70].

Juvenile spondyloarthropathy begins before the age of 16, mostly in boys aged 9 years or older, and the common presentation is that of a seronegative oligoarthritis of the lower extremities, frequently with enthesitis [5,71]. Recent epidemiologic studies suggest that this disease may be much more prevalent than previously realized. There may be no clinically or roentgenographically identifiable involvement of the sacroiliac joints or the spine in these patients, and they may also lack any inflammatory back symptoms, mucocutaneous lesions, or gastrointestinal problems in early stages. Therefore, they may be misclassified as having a late-onset form of pauciarticular juvenile chronic arthritis.
FIGURE 5-1. The concept of spondyloarthropathy. The clinical spectrum of the rheumatologic diseases included under the term spondyloarthropathies consists of ankylosing spondylitis, reactive arthritis or Reiter’s syndrome, spondyloarthritides associated with psoriasis and chronic inflammatory bowel diseases, and a form of juvenile chronic arthritis (pauciarticular, late-onset type) [1–5]. All forms of the spondyloarthropathies are associated with the histocompatibility antigen HLA-B27, although the strength of this association varies markedly not only among the various disease forms but also among the various ethnic and racial groups worldwide [6–10]. These diseases tend to occur more often among young men who are in their late teens and early twenties and may start with features such as enthesitis (inflammatory lesions of the entheses, i.e., sites of ligamentous or tendinous attachments to bone) or dactylitis (sausage digits). The disease may progress to sacroiliitis and spondylitis, with or without extra-articular features such as acute anterior uveitis or mucocutaneous lesions [2,17,18]. The clinical features typical of the spondyloarthropathies may occur in different combinations so that the existing classification criteria may be inappropriate for a subset of such patients. For example, there are now well-defined HLA-B27–associated clinical syndromes such as seronegative oligoarthritis or polyarthritis (mostly affecting joints of the lower extremities), dactylitis, and enthesitis (plantar fasciitis or calcaneal periostitis, Achilles tendonitis, and tenderness of tibial tubercles). The overall prevalence of this form of undifferentiated spondyloarthropathy may be higher than that of reactive arthritis in some parts of the world [2,17,18,22,23].

FIGURE 5-2. Criteria for spondyloarthropathy. Features typical of the spondyloarthropathies may occur in various combinations, and it was recognized a few years ago that the available disease criteria are inadequate for many patients. Therefore, new classification criteria were proposed by the European Spondyloarthropathy Study Group to encompass the currently recognized wider spectrum [32]. These criteria have a high degree of sensitivity and specificity, but they cannot be used to help in identifying patients who have either an isolated peripheral arthritis, dactylitis, enthesitis, inflammatory spinal pain, acute anterior uveitis, or aortic insufficiency with heart block as the only clinical manifestation of the disease.
**AMOR CRITERIA FOR SPONDYLOARTHROPATHY**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Clinical symptoms or past history of</td>
<td></td>
</tr>
<tr>
<td>1. Lumbar or dorsal pain at night or morning stiffness of lumbar or dorsal region</td>
<td>1</td>
</tr>
<tr>
<td>2. Asymmetric oligoarthritis</td>
<td>2</td>
</tr>
<tr>
<td>3. Buttock pain</td>
<td>1</td>
</tr>
<tr>
<td>if alternate buttock pain</td>
<td>2</td>
</tr>
<tr>
<td>4. Sausage-like toe or digit</td>
<td>2</td>
</tr>
<tr>
<td>5. Heel pain or other well-defined enthesiopathic pain</td>
<td>2</td>
</tr>
<tr>
<td>6. Iritis</td>
<td>2</td>
</tr>
<tr>
<td>7. Nongonococcal urethritis or cervicitis within 1 mo before the onset of arthritis</td>
<td>1</td>
</tr>
<tr>
<td>8. Acute diarrhea within 1 mo before the onset of arthritis</td>
<td>1</td>
</tr>
<tr>
<td>9. Psoriasis, balanitis, or IBD (ulcerative colitis or Crohn’s disease)</td>
<td>2</td>
</tr>
<tr>
<td>B. Radiologic findings</td>
<td></td>
</tr>
<tr>
<td>10. Sacroiliitis (bilateral grade 2 or unilateral grade 3)</td>
<td>2</td>
</tr>
<tr>
<td>C. Genetic background</td>
<td></td>
</tr>
<tr>
<td>11. Presence of HLA-B27 or family history of ankylosing spondylitis, reactive arthritis, uveitis, psoriasis, or IBD</td>
<td>2</td>
</tr>
<tr>
<td>D. Response to treatment</td>
<td></td>
</tr>
<tr>
<td>12. Clear-cut improvement within 48 h after NSAID intake or rapid relapse of the pain after their discontinuation</td>
<td>2</td>
</tr>
</tbody>
</table>

A patient is considered to be suffering from a spondyloarthropathy if the sum is ≥ 6.

**FIGURE 5-3.** Amor criteria for spondyloarthropathy. The Amor multiple entry criteria system has one advantage over the European Spondyloarthropathy Study Group (ESSG) criteria in that the patients with undifferentiated spondyloarthropathy without arthritis or inflammatory back pain can be classified as having a form of spondyloarthropathy with the Amor criteria but not the European criteria [71]. No single item in the criteria list can contribute the six points needed to classify the patient as having spondyloarthropathy. Relief of pain within 24 to 48 hours after initiating treatment with a nonsteroidal anti-inflammatory drug (NSAID) or recurrence of pain within 24 to 48 hours after discontinuation of this treatment is of greater clinical usefulness (two points). For this component to be valid, the dosage of the NSAID should be large enough (ie, anti-inflammatory dose) and the dosage regimen sufficient to have appropriate therapeutic anti-inflammatory blood levels in the morning. IBD—Inflammatory bowel disease.

**RECENT PREVALENCE STUDIES OF ANKYLOSING SPONDYLITIS AND RELATED SPONDYLOARTHROPATHIES**

<table>
<thead>
<tr>
<th>Populations</th>
<th>B27 Frequency, %</th>
<th>Prevalence of AS, % General Population</th>
<th>B27(+) Population</th>
<th>Prevalence of SpA (including AS), % General Population</th>
<th>B27(+) Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eskimos (Alaska)</td>
<td>40</td>
<td>0.4</td>
<td>1.6</td>
<td>2.5</td>
<td>4.2</td>
</tr>
<tr>
<td>Eskimos (Alaska and Siberia)</td>
<td>25-40</td>
<td>1.8</td>
<td>6.8</td>
<td>2-3.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Saamis (Lapland)</td>
<td>24</td>
<td>1.4</td>
<td>6.7</td>
<td>1.9</td>
<td>13.6</td>
</tr>
<tr>
<td>Northern Norway</td>
<td>14</td>
<td>0.5</td>
<td>2</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>Mordovia</td>
<td>16</td>
<td>0.2</td>
<td>2</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>Holland</td>
<td>8</td>
<td>0.86</td>
<td>6.4</td>
<td>1.9</td>
<td>13.6</td>
</tr>
<tr>
<td>Germany</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 5-5.** Prevalence studies of ankylosing spondylitis (AS) and related spondyloarthropathies (SpA). Recent studies in the native populations of Siberia (Chukchi and Eskimo) and Alaska (Inupiaq and Yupik Eskimo) that have a very high prevalence of HLA-B27 (25% to 40%) show an overall prevalence of spondyloarthropathies (between 2% and 3.4%) [72]. This figure similarly lists the data derived from the recent epidemiologic studies in other populations [3,72].
# Ankylosing Spondylitis

## Clinical Features

### Classifications for Ankylosing Spondylitis

**Rome, 1961**

- **Clinical criteria**
  1. Low back pain and stiffness for more than 3 mo, not relieved by rest
  2. Pain and stiffness in the thoracic region
  3. Limited motion in the lumbar spine
  4. Limited chest expansion
  5. History or evidence of iritis or its sequelae

- **Radiologic criterion**
  1. Roentgenogram showing bilateral sacroiliac changes characteristic of ankylosing spondylitis (this would exclude bilateral osteoarthritis of the sacroiliac joints)

**Definite ankylosing spondylitis if:**
- Grade 3–4 bilateral sacroiliitis with at least one clinical criterion
- At least four clinical criteria

**New York, 1966**

- **Clinical criteria**
  1. Limitation of motion of the lumbar spine in all three planes: anterior flexion, lateral flexion, and extension
  2. Pain at the dorsolumbar junction or in the lumbar spine
  3. Limitation of chest expansion to 2.5 cm or less measured at the level of the fourth intercostal space

- **Grading of radiographs**
  - Normal, 0; suspicious, 1; minimal sacroiliitis, 2; moderate sacroiliitis, 3; ankylosis, 4

**Definite ankylosing spondylitis if:**
- Grade 3–4 bilateral sacroiliitis with at least one clinical criterion
- Grade 3–4 unilateral or grade 2 bilateral sacroiliitis with clinical criterion 1 or with both clinical criteria 2 and 3

**Probable ankylosing spondylitis if:**
- Grade 3–4 bilateral sacroiliitis with no clinical criteria

**Modified New York, 1984**

- **Clinical criteria**
  1. Low back pain of at least 3 mo duration improved by exercise and not relieved by rest
  2. Limitation of lumbar spine in sagittal and frontal planes
  3. Chest expansion decreased relative to normal values for age and sex
  4. Bilateral sacroiliitis grade 2-4
  5. Unilateral sacroiliitis grade 3-4

**Definite ankylosing spondylitis if:**
- Unilateral grade 3 or 4, or bilateral grade 2-4 sacroiliitis and any clinical criterion

**Probable ankylosing spondylitis if:**
- Three clinical criteria present; or radiologic criterion present with no clinical criteria

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**Clinical Features of Ankylosing Spondylitis**

**Skeletal**
- Axial arthritis, such as sacroiliitis and spondylitis
- Arthritis of “girdle joints” (hips and shoulders)
- Peripheral arthritis (uncommon)
- Others: enthesopathy, osteoporosis, vertebral fractures, spondylodiskitis, pseudoarthrosis

**Extraskeletal**
- Acute anterior uveitis
- Cardiovascular involvement
- Pulmonary involvement
- Cauda equina syndrome
- Enteric mucosal lesions
- Amyloidosis, miscellaneous

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**Figure 5-6.** Classification criteria for ankylosing spondylitis. These are the widely used diagnostic criteria for ankylosing spondylitis; they greatly depend on the radiographic evidence of sacroiliitis, which is the best nonclinical indicator of the disease presence. However, the status of the sacroiliac joints on routine pelvis radiographs may not always be easy to interpret in the early phase of the disease because of slow evolution in some patients and in adolescent patients. (Data modified from van der Linden [73].)

**Figure 5-7.** Clinical features of ankylosing spondylitis. Ankylosing spondylitis is a chronic systemic inflammatory disorder of undetermined etiology, usually beginning in early adulthood, primarily affecting the axial skeleton (sacroiliitis being its hallmark), but can also exhibit some extra-articular features [40]. Patients with ankylosing spondylitis are more prone to osteoporosis [74]. Acute anterior uveitis is the most common extra-articular feature, occurring in 25% to 40% of patients. It occurs relatively more commonly in HLA-B27-positive patients with ankylosing spondylitis than in those who lack this gene [75,76]. The other much less common features include aortic incompetence, heart block, apical pulmonary fibrosis and cavitation, amyloidosis, and IgA nephropathy [2,40]. The marked muscle wasting seen in some patients with advanced disease results from disuse atrophy. Neurologic involvement may occur owing to fracture or dislocation, atlantoaxial subluxation, or cauda equina syndrome [2,77–81].
FIGURE 5-8. Sites of inflammation. The inflammation primarily affects the axial skeleton and appears to originate in ligamentous and capsular sites of attachment to bones (enthesitis), juxta-articular ligamentous structures, and the synovium, articular cartilage, and subchondral bones of involved joints [19–21,40,41]. The site of enthesitis is infiltrated by lymphocytes, plasma cells, and polymorphonuclear cells; edema and infiltration of the adjacent marrow space are present. A striking feature is a high frequency of axial enthesitis and synovitis that can result in fibrous and later bony ankylosis of the sacroiliac joints and the spine [45].

Extra-articular or juxta-articular bony tenderness due to enthesitis at costosternal junctions, spinous processes, iliac crests, ischial tuberosities, or heels (arrows) may be an early feature of the disease. Stiffness and pain in the cervical spine and tenderness of the spinous processes may occur in early stages of the disease in some patients, but generally this tends to occur after some years. Back symptoms may be absent or very mild in an occasional patient, whereas others may complain only of back stiffness, fleeting muscle aches, or musculotendinous tender spots. These symptoms may be worsened on exposure to cold or dampness, and such patients may occasionally be misdiagnosed as having fibrositis (fibromyalgia). Some may have mild constitutional symptoms such as anorexia, malaise, or mild fever in early disease, and this may be more common among patients with juvenile onset, especially in developing countries. Involvement of the costovertebral and the costotransverse joints and occurrence of enthesitis at costosternal areas may cause chest pain that may be accentuated on coughing or sneezing. Some patients may note their inability to fully expand their chest on inspiration, but moderate to severe pulmonary restriction mostly occurs after long-standing disease.

FIGURE 5-9. Early symptoms and progression of ankylosing spondylitis (AS). A, The characteristic early symptom is insidious onset of chronic low-back pain and stiffness, beginning usually in late adolescence or early adulthood (mean age of onset, 24 years). The pain due to sacroiliitis is dull in character, difficult to localize, and felt somewhere deep in the gluteal region. It may be unilateral or intermittent at first; however, within a few months it generally becomes persistent and bilateral, and the lower lumbar spine area also becomes painful. Sometimes pain in the lumbar area may be the initial presentation. The symptoms typically worsen with prolonged inactivity or on waking up in the morning (“morning stiffness”), and improve with physical activity and a hot shower. The back pain and stiffness may awaken some patients from sleep and some may experience considerable difficulty in getting out of bed in the morning. Others may find it necessary to wake up at night to move about or exercise for a few minutes before returning to bed. Some patients may complain of easy fatigability, perhaps resulting, in part, from their disturbed sleep pattern. B, Progression of AS over a period of 26 years; the patient underwent bilateral total hip arthroplasties in 1973. (B from Little et al. [82]; with permission.)
Ankylosing spondylitis is diagnosed based on clinical history and physical findings, and the diagnosis is supported by radiographic evidence of sacroiliitis [40,47].

Most patients will have decreased spinal mobility (on hyperextension, forward and lateral flexion, and axial rotation). There is often tenderness of the sacroiliac joints or the spine at a relatively early stage of the disease, and there is gradual development of flattening of the lumbar spine (owing to loss of the normal lumbar lordosis). Decreased lumbar spinal flexibility is determined by modified Schober’s test (E) in which a mark is placed on the skin in the midline of the back at the level of the superior iliac spine. A second mark is placed 10 cm above in midline with the patient standing erect with knees fully extended (E,F). The patient is then asked to maximally bend forward without bending the knees. The distance between the two skin marks is stretched to 14 cm or more if spinal flexibility is normal.

(Continued on next page)
FIGURE 5-10. (Continued) **F**, Occiput to wall distance due to forwardly stooped deformity of cervical spine. Chest expansion is diminished due to costovertebral joint involvement. **G**, There is progressive kyphosis in advanced stages of disease. **H** and **I**, Test for eliciting sacroiliac pain by putting physical stress on the sacroiliac joints by application of downward pressure on the flexed knee, when the hip joint is flexed, abducted, and externally rotated; or by compression of the pelvis with the patient lying on one side (**H**). Two other procedures involve the application of direct pressure on anterior superior iliac spines, along with attempts to force them laterally apart, away from each other; and by forced flexion of one hip joint maximally toward the opposite shoulder, with hyperextension of the contralateral hip joint (**I**). (A–C courtesy of Heinz Baumberger.)
FIGURE 5-11. Hip and shoulder involvement. The reported frequency of hip joint involvement (A,B) varies from 17% to 36%; it is usually bilateral, insidious in onset, and potentially more crippling than involvement of any other joint of the extremities. It is relatively more common in patients with juvenile onset of ankylosing spondylitis. Flexion contractions of the hip are not uncommon at later stages of the disease and can be easily detected by having the patient lie on a very firm examining table and flexing one hip joint maximally to bring out the contracture in the contralateral hip joint. C, Shoulder joint involvement is generally relatively mild, but resulting limitation of motion can be easily detected by asking the patient to scratch his or her upper back. Involvement of peripheral joints other than hips and shoulders in “primary” disease (ie, unassociated with psoriasis, inflammatory bowel disease, or reactive arthritis) is infrequent, rarely persistent or erosive, and tends to resolve without any residual joint deformity. Intermittent knee effusions may occasionally be the presenting manifestation of juvenile ankylosing spondylitis. Ten percent of the patients may show episodes of temporomandibular joint inflammation, which can result in limitation of jaw motion in some patients.
FIGURE 5-12. A, Uveitis. Acute anterior uveitis occurs in 25% to 30% of patients at some time in the course of their disease and is relatively more common among B27-positive than B27-negative patients [24,25,75,76]. The acute inflammation is typically unilateral, but it can recur in either eye. The patient presents with unilateral left ocular pain, redness, lacrimation, and photophobia evolving over a few days, which results in blurred vision owing to accumulation of inflammatory cells in the anterior chamber and abnormal accommodation of the ciliary muscles secondary to inflammation. There is circumcorneal congestion, and on slit-lamp examination, increased numbers of white blood cells are seen in the aqueous humor of the inflamed eye.

The other extra-articular manifestations are relatively uncommon and can include aortitis (B,C) (leading to slowly progressive aortic valve incompetency and conduction abnormalities, sometimes requiring a pacemaker) and myocardial diastolic dysfunction [2,26,78]. Apical pulmonary fibrosis (fibrocystic disease) is a rare complication of ankylosing spondylitis. Another rare complication is cauda equina syndrome (D,E). D, CT scan (left) showing erosions of the lamina of the fourth vertebra caused by arachnoid diverticula characteristic of cauda equina syndrome in ankylosing spondylitis (arrowhead). The CT scan on the right is at the same level in normal control. E, Lateral spinal view T1-weighted sagittal image of arachnoid diverticulitis showing fluid-filled arachnoid diverticuli (arrows). (C–E from the American College of Rheumatology [83]; with permission.)
FIGURE 5-13. Demonstration of sacroiliitis. Schematic drawing (A) showing the location of the sacroiliac joint; the red line depicts sacroiliitis. The anteroposterior roentgenographic views in different patients (B, C) of the pelvis show bilateral sacroiliitis in ankylosing spondylitis (AS). There are erosions and blurring of the subchondral bone plate and reactive bone sclerosis that are more prominent on the iliac side of the joint.

D. A lateral view of the lumbar spine of patient with AS shows reactive bony sclerosis of the corner (“shiny corners”) of two adjacent vertebral bodies, and bone resorption of the anterior corners of the vertebral bodies that has resulted in vertebral “squaring.” Spondylodiscitis is present at the vertebral disk between the T12 and L1 vertebrae.
When sacroiliitis is clinically suspected

Conventional radiograph (AP view)

Multiple sacroiliac joints

Diagnosis of sacroiliitis established

Radiograph normal or equivocal, but high clinical suspicion of sacroiliitis

Radiograph normal and low clinical suspicion. No further workup

Low clinical suspicion of infection

Clinical suspicion of infection of sacroiliac joint

CT or MRI in selected clinical situations

If suspicion of infection

+ or uptake less than bone scan

Low likelihood of infection

In selected cases, CT scan for aspiration, culture, and drainage

CT scan horizontal cut across the sacroiliac joints showing bilateral sacroiliitis.

MRI gives excellent results and without radiation; it can show abnormalities of the periarticular bone marrow and subchondral bone, but at a greater cost. These two imaging modalities, however, are often not needed for the diagnosis of ankylosing spondylitis in most patients. MRI is very helpful in early detection of inflammation in sacroiliac joints and can predict the later occurrence of radiographically detectable sacroiliitis [4,84].

Short-T1 inversion recovery (STIR) fat saturation technique is useful for detecting bone marrow edema. Dynamic MRI using gadolinium detects inflammation. B, C, and D represent different patients. (From Khan [40]; with permission.)

**FIGURE 5-14.** Imaging evaluation. A, Algorithm for characteristic evaluation of sacral ileitis due to spondyloarthropathies or infections.

Ankylosing spondylitis may sometimes evolve over many years, but changes are usually present by the time the patient seeks medical attention. They are primarily seen in the axial skeleton, especially in the sacroiliac joints. Radiographic evidence of sacroiliitis is required for definitive diagnosis and is the most consistent finding: a simple anteroposterior (AP) roentgenogram is usually sufficient for its detection, and oblique views should not be requested. In patients with early disease in whom standard roentgenography of the sacroiliac joints may be normal or show equivocal changes, quantitative bone scintigraphy (B) may be too nonspecific to be useful [46,47]. CT is more sensitive but equally specific when compared with conventional roentgenography.
FIGURE 5-15.  A and B, Schematic drawings of lumbar spine, lateral view (A) and antero-posterior view (B). The inflammation of the superficial layers of the anulus fibrosus and at their sites of attachment to the corners of the vertebral bodies results in reactive bony sclerosis ("shiny corners") and subsequent bone resorption (erosions). Ultimately, this leads to "squaring" of the vertebral bodies (arrows; best visualized on lateral radiography of the spine) (see Fig 5-13D) and a gradual formation of intervertebral bony "bridgings" called syndesmophytes (C). There are often concomitant inflammatory changes in the apophyseal joints that may lead to ankylosis, and ossification of the interspinous ligaments may also occur (D). There can be a complete fusion of the vertebral column ("bamboo spine") in patients with severe ankylosing spondylitis of long duration. Spinal osteoporosis, although usually seen in patients with long-standing ankylosing spondylitis, can sometimes develop in a relatively early stage of the disease. Some patients can develop severe kyphosis (E).

(C from Berens [85]; with permission.)
Spondyloarthropathies

Figure 5-17. Spinal fracture. A through D. Spinal fracture can follow a relatively minor trauma in patients with long-standing severe ankylosing spondylitis. The spine is prone to fractures, usually occurring in the lower cervical spine. Quadriplegia is the most dreaded complication because of its high mortality rate. Isolated or multiple vertebral compression fractures may also occur. The pain associated with spinal fractures may be overlooked or wrongly attributed to exacerbation of the spondylitic process and could lead to diskovertebral destruction (spinal pseudoarthrosis) [79-81,84,86]. A, Bone scan showing lower cervical spine fracture. B and C, Firm bracing with the use of a halo-vest is needed to allow the cervical spinal fracture to heal. D, Skeleton of spondylitic patient showing lumbar fracture and resultant pseudoarthrosis. Imaging evaluation is necessary for evaluation of pseudoarthrosis (E).

The best early clinical clues to spinal fracture may be a history of acute or unexplained episode of back pain that is aggravated by movement, even in the absence of obvious physical trauma. It may sometimes be associated with localized spinal tenderness. Some patients may develop aseptic spondylodiskitis, mostly in the midthoracic spine. It is usually asymptomatic and without any physical trauma or infection and is relatively more common in the patients whose spondylitis also involves the cervical spine.

E. Imaging Evaluation for Pseudoarthrosis

<table>
<thead>
<tr>
<th>Clinical evidence of cord compression</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>Spine radiography (including flexion view)</td>
</tr>
<tr>
<td>MRI ⊗</td>
<td>⊗ Perform CT or sagittal tomography</td>
</tr>
<tr>
<td>Bone scan If positive, perform CT or sagittal tomography</td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 5-20. Family pedigree. This family shows marked familial aggregation of spondyloarthropathies. There is also presence of psoriasis in this family. Other families may show a presence of Crohn's disease or ulcerative colitis. Patients with psoriasis or inflammatory bowel disease are more likely to later develop ankylosing spondylitis than the rest of the population without these diseases, and the reverse is also true, i.e., patients with ankylosing spondylitis are more often found to have Crohn's disease, ulcerative colitis, or psoriasis. Ileocolonoscopic studies have disclosed the presence of subclinical bowel inflammation in a large number of patients with spondyloarthropathies who had no other evidence of inflammatory bowel disease [68–70]. Individuals affected with ankylosing spondylitis are shown as orange squares (males) and circles (females). Green squares and circles indicate related spondyloarthropathies, and red color indicates unaffected individuals. Segregation of HLA-A and –B haplotypes is also shown.
HLA-B27 as a common pathogenic pathway. Feltkamp [89] suggested a scheme with HLA-B27 acting as a common pathogenic pathway between several exogenous (environmental) and genetic factors and the phenotypic expression of spondyloarthropathies. Recent findings indicate that HLA-B27 mediates not only CD8+ T-cell responses but can also trigger CD4+ T-cell responses in vitro and in vivo [93]. HLA-B27-associated disease risk is enhanced by the presence of other genetic factors that play an important role in disease predisposition [10–16,90–93]. One of the reasons for the unilateral episode of acute anterior uveitis (AAU) and the often asymmetric peripheral arthritis of reactive arthritis (ReA) may be the randomness of the arrival of the exogenous antigenic inflammatory triggers at these sites. AS—ankylosing spondylitis. (Adapted from Feltkamp [89].)

Schematic ribbon diagram of the antigen-binding cleft of the HLA-B*2705 molecule, the most common subtype of HLA-B27 in caucasoid populations. A nonameric (nine amino acid long) antigenic peptide is shown anchored (bound) in the antigen-binding cleft of the molecule. The view is from above, as seen from the viewpoint of a T-cell receptor. The letters N and C indicate the amino (N) and carboxy (C) termini of the bound peptide. The arrow indicates the amino-terminus of the alpha (heavy) chain of the HLA-B27 molecule. The floor of the antigen-binding cleft is formed by the beta strands (broad arrows pointing away from the amino-terminus), and the margins are formed by alpha-helices shown as helical ribbons. The top alpha helix and the four beta strands to the left are from the alpha-1 domain of the heavy chain, and the bottom alpha helix and the four beta strands to the right are from the alpha-2 domain. The disulfide bond is shown as two connecting spheres. Not marked are the six side pockets (assigned the letters A, B, C, D, E, and F) on the surface of the antigen-binding cleft. Pockets A and F are highly conserved deep pockets at the two ends of the antigen-binding cleft. The residues that form pocket B are marked by black arrowheads (at positions 7, 9, 24, 34, 45, 63, 67, and 99). The side chain of the second amino acid (arginine) of the bound peptide is shown anchored into pocket B. There are at least 25 subtypes of HLA-B27, from B*2701 to B*2725 [15]. The various subtypes of HLA-B27 show different ethnic distributions, and some of them may also show differences in disease association. For example, the common subtypes in various world populations—B*2705, B*2702, and B*2704—are clearly associated with ankylosing spondylitis, whereas B*2709 in Sardinian Italians and B*2706 in Southeast Asians seem to lack such an association [10,36]. It is difficult to assess the disease association of the relatively uncommon subtypes at the population level. The two subtypes of HLA-B27 that are not associated with ankylosing spondylitis, that is, B*2706 and B*2709, differ from the other subtypes at residues 134 and 136, primarily affecting the conformation of pocket C/F. (Adapted from Khan [90].)
A. HLA-B27 FREQUENCY IN PATIENTS AND NORMAL CONTROLS

<table>
<thead>
<tr>
<th>Group</th>
<th>Whites</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>B27(+) %</td>
<td>n</td>
<td>B27(+) %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>485</td>
<td>8</td>
<td>60</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>140</td>
<td>92</td>
<td>36</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>54</td>
<td>72</td>
<td>20</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Reiter’s syndrome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B. PERCENT OF B27-POSITIVE PATIENTS AND NORMAL CONTROLS BY VARIOUS POPULATIONS

<table>
<thead>
<tr>
<th>Populations</th>
<th>Ankylosing Spondylitis</th>
<th>Normal Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients, n</td>
<td>B27 positive, %</td>
</tr>
<tr>
<td>Caucasoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>2022</td>
<td>79–100</td>
</tr>
<tr>
<td>Indians and Pakistanis</td>
<td>130</td>
<td>B3–100</td>
</tr>
<tr>
<td>Iranians</td>
<td>25</td>
<td>92</td>
</tr>
<tr>
<td>Arabs</td>
<td>32</td>
<td>81</td>
</tr>
<tr>
<td>Jews</td>
<td>31</td>
<td>81</td>
</tr>
<tr>
<td>Mongoloid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mainland China</td>
<td>196</td>
<td>89–91</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>77</td>
<td>99</td>
</tr>
<tr>
<td>Taiwan</td>
<td>76</td>
<td>95</td>
</tr>
<tr>
<td>Singapore</td>
<td>29</td>
<td>97</td>
</tr>
<tr>
<td>Japanese</td>
<td>72</td>
<td>82</td>
</tr>
<tr>
<td>Filipino</td>
<td>17</td>
<td>94</td>
</tr>
<tr>
<td>Thai</td>
<td>71</td>
<td>86</td>
</tr>
<tr>
<td>North American Indians</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haida</td>
<td>17</td>
<td>100</td>
</tr>
<tr>
<td>Navajo</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>Bella Colla</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>Pima</td>
<td>14</td>
<td>100</td>
</tr>
<tr>
<td>Zuni</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hopi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mestizo</td>
<td>239</td>
<td>69–81</td>
</tr>
<tr>
<td>South American Indians</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African blacks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central Africans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congo and Zambia</td>
<td>259</td>
<td>0</td>
</tr>
<tr>
<td>West Africans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mali</td>
<td>82</td>
<td>9.7</td>
</tr>
<tr>
<td>Gambia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Africans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>South Africa</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>American blacks</td>
<td>67</td>
<td>57</td>
</tr>
</tbody>
</table>

*Eskimos are not listed in the table; they have 25%-37% frequency of B27, and virtually all patients with ankylosing spondylitis are B27-positive [7]. Frequency of B27 is 9% in Indonesia and more than 25% in an isolated community in Papua New Guinea.
It is not a “routine” or “diagnostic” or “confirmatory” test.

Most patients with AS can be diagnosed clinically and do not need this test.

It cannot be used as a screening test for AS in the general population.

The sensitivity and specificity of the test depend on the racial and ethnic background of the patient.

The clinical usefulness of the test, like any other “imperfect” test, depends on the clinical setting in which it is performed, and requires Bayesian analysis to correctly interpret the clinical meaning of positive or negative test results.

The test can, in a similar manner, also be used as an aid to support the diagnosis of other B27-associated spondyloarthropathies besides AS.

The test does not help distinguish AS from other B27-associated spondyloarthropathies.

### C. IMPORTANT ASPECTS OF THE HLA-B27 TEST

- **Feature**
  - It is not a “routine” or “diagnostic” or “confirmatory” test.
  - Most patients with AS can be diagnosed clinically and do not need this test.
  - It cannot be used as a screening test for AS in the general population.
  - The sensitivity and specificity of the test depend on the racial and ethnic background of the patient.
  - The clinical usefulness of the test, like any other “imperfect” test, depends on the clinical setting in which it is performed, and requires Bayesian analysis to correctly interpret the clinical meaning of positive or negative test results.
  - The test can, in a similar manner, also be used as an aid to support the diagnosis of other B27-associated spondyloarthropathies besides AS.
  - The test does not help distinguish AS from other B27-associated spondyloarthropathies.

### D. CLINICAL FEATURES OF VARIOUS SPONDYLOARTHOPATHIES

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ankylosing Spondylitis</th>
<th>Reactive Arthritis (Reiter’s Syndrome)</th>
<th>Juvenile Spondyloarthritis</th>
<th>Psoriatic Arthropathy*</th>
<th>Enteropathic Arthropathy†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual age at onset</td>
<td>Young adult age &lt; 40</td>
<td>Young to middle-age adult</td>
<td>Childhood onset, ages 8–18</td>
<td>Young to middle-age adult</td>
<td>Young to middle-age adult</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>3× more common in males</td>
<td>Predominantly males</td>
<td>Predominantly males</td>
<td>Equally distributed</td>
<td>Equally distributed</td>
</tr>
<tr>
<td>Usual type of onset</td>
<td>Gradual</td>
<td>Acute</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Sacroiliitis or spondylitis</td>
<td>Virtually 100%</td>
<td>&lt; 50%</td>
<td>&lt; 50%</td>
<td>~ 20%</td>
<td>Gradual</td>
</tr>
<tr>
<td>Symmetry of sacroiliitis</td>
<td>Symmetric</td>
<td>Asymmetric</td>
<td>Asymmetric</td>
<td>Asymmetric</td>
<td>Symmetric</td>
</tr>
<tr>
<td>Peripheral joint involvement</td>
<td>~ 25%</td>
<td>~ 90%</td>
<td>~ 90%</td>
<td>~ 95%</td>
<td>~ 95%</td>
</tr>
<tr>
<td>HLA-B27 (in whites)</td>
<td>&gt; 90%</td>
<td>~ 75%</td>
<td>~ 50%</td>
<td>&lt; 50%§</td>
<td>~ 20%</td>
</tr>
<tr>
<td>Eye involvement‡</td>
<td>25% - 30%</td>
<td>~ 50%</td>
<td>~ 15%</td>
<td>~ 15%</td>
<td>~ 15%</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>1% - 4%</td>
<td>5% - 10%</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Skin, mucosal, or nail involvement</td>
<td>None</td>
<td>~ 40%</td>
<td>Uncommon</td>
<td>Virtually 100%</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

*About 5%–7% of patients with psoriasis develop arthritis, and psoriatic spondylitis accounts for about 5% of all patients with psoriatic arthritis.

†Associated with chronic inflammatory bowel disease.

‡B27 prevalence is higher in those with spondylitis or sacroiliitis.

§Predominantly conjunctivitis in reactive and psoriatic arthritis, and acute anterior uveitis in the other disorders listed above.

---

**FIGURE 5-25.** Suggested algorithm to help make an early diagnosis of ankylosing spondylitis (AS)/axial spondyloarthritis (SpA).

IBP—inflammatory back pain; NSAIDs—nonsteroidal anti-inflammatory drugs. (Adapted from Rudwaleit et al. [4] and Khan [40].)
Treatment of Ankylosing Spondylitis

SALIENT PRINCIPLES FOR MANAGEMENT OF ANKYLOSING SPONDYLITIS

No cure but most patients can be well managed with NSAIDs and regular exercise program; for those with more severe disease, preliminary results indicate significant efficacy of anti-TNF therapy.

A concerned (primary) physician providing continuity of care; consultation as needed by a rheumatologist, ophthalmologist, orthopedist, and others.

Education of the patient about the disease to help increase compliance.

Importance of early exercises to preserve good posture and minimize limitation of chest expansion; swimming is the best exercise; appropriate sports and recreations; sleeping on firm mattress; avoiding pillows under the head, if possible; avoidance of smoking; and prevention of spinal trauma.

Supportive measures and counseling with regard to social, sexual, and vocational aspects; importance of patient support groups.

Family counseling; thorough family history; physical examination of the relatives may disclose remarkable disease aggregation and many undiagnosed or misdiagnosed affected relatives in some families.

Surgical measures: arthroplasty, correction of deformity, and others.

Early diagnosis is important, as is the early recognition and treatment of extraskeletal manifestations, such as acute anterior uveitis (iritis), and of the associated disease or complications.

Anti-TNF therapy with infliximab is very effective for severe Crohn’s disease and also benefits any associated inflammatory arthritis [95].

FIGURE 5-26. Management of ankylosing spondylitis (AS). Many patients with AS can be well managed with nonsteroidal anti-inflammatory drugs (NSAIDs) along with physiotherapy and a lifelong regular exercise program [1,3,88]. There is currently no known method to cure or prevent the disease, and there is no special diet or any specific food that has a role in its initiation or exacerbation. Aspirin seldom provides an adequate therapeutic response, but other NSAIDs are more helpful and should be used in full therapeutic anti-inflammatory doses during active phases of the disease [1,3,88]. The patients should be informed about this because otherwise they may use the drugs occasionally and for their analgesic effect only. The responses by patients differ, as do the side effects, and it is worthwhile to search out the best alternative NSAID that works for each individual.

When the disease is not being adequately controlled by NSAIDs, the so-called disease-modifying antirheumatic drugs (DMARDs) used in the treatment of rheumatoid arthritis are not very effective: sulfasalazine may be moderately effective for peripheral arthritis, but has no significant beneficial effect on the typical axial disease, although its possible efficacy in early axial disease has not been studied [91,96,97]. Because of its efficacy in inflammatory bowel disease (IBD), sulfasalazine may be especially useful for AS associated with IBD. Some AS patients with peripheral joint involvement unresponsive to NSAIDs and sulfasalazine have responded to oral methotrexate therapy. However, a randomized double-blind, placebo-controlled study of 30 patients with severe AS has demonstrated no significant benefits in the group receiving oral methotrexate (10 mg weekly) for 24 weeks versus placebo, even in the subgroup with peripheral arthritis [95]. Oral corticosteroids have no therapeutic value in the long-term management of the musculoskeletal aspects of this disease because of their serious side effects, and the do not halt disease progression. Persistent synovitis may respond to a local corticosteroid injection, and uncontrolled studies of corticosteroid injection into the sacroiliac joints show that it may be helpful but the benefit lasts only a few months. Patients with severe spondyloarthropathies who were unresponsive to conventional therapies have now been treated with anti–tumor necrosis factor (TNF)-a therapy (ie, infliximab and etanercept), with rapid improvement of peripheral arthritis as well as axial symptoms and signs, including enthesitis as detected by MRI [94,94,98–104]. TNF blockers are also very effective in the treatment of psoriasis and psoriatic arthritis resistant to conventional therapy.

Infliximab, but not etanercept, is also effective in Crohn’s disease [95]. There is a case report of anti-TNF treatment for nephrotic syndrome in a patient with juvenile IBD-associated spondyloarthropathy complicated with amyloidosis and glomerulonephritis [104]. Consensus statements are being developed to establish criteria to be used in deciding the patient with spondyloarthropathy that may need this treatment and how to evaluate the therapeutic response [105,106]. The high cost of these new biologic agents and their major untoward effects, including opportunistic infections, reactivation of infections such as tuberculosis and histoplasmosis, and as yet unknown other possible side effects of long-term therapy, are, at present, the major deterrents. Experimental drugs under study for possible therapeutic effect in AS include panimadronate, a biphosphonate that needs intravenous infusion, and thalidomide [107–110]. However, no controlled studies have been reported.

The patient should walk erect, keeping the spine as straight as possible, and sleep on a firm mattress using as thin a pillow as possible. Physical activity that places prolonged strain on the back muscles such as prolonged stopping or bending, should be avoided. Self-help education, counseling, and health education for self-management are helpful in enhancing compliance with the recommended therapy [111–114]. Patient support groups enlist enthusiastic patient cooperation and provide information about the disease and advice about life and health insurance, jobs, working environment, wide-view mirrors, and other useful items [114]. Splints, braces, and corsets are generally not helpful and are not advised. Pregnancy does not usually affect the disease symptoms, and fertility, course of pregnancy, and childbirth have been reported to be normal. Regular exercise is of fundamental importance in preventing or minimizing deformity. Spinal extensions exercises and deep-breathing exercises should be done routinely once or twice daily, and smoking should be avoided [114]. Formal physical therapy is of value, especially in teaching the patient the proper posture, appropriate exercises, and recreational sports, and the need for maintaining the exercise program. Group exercise sessions that include hydrotherapy in warm water are helpful. Regular swimming is considered one of the best exercises for these patients. Some patients have difficulty driving their car because of the impaired neck mobility, and they may find special wide-view mirrors helpful.

Acute anterior uveitis requires prompt and vigorous treatment with dilation of the pupil and use of corticosteroid eye drops. The patient should be informed about the possibility of recurrence of acute iritis. Systemic steroids or immunosuppressives may be needed for rare patients with severe refractory uveitis, and recent data suggest that anti-TNF therapy is dramatically effective for these patients. Total hip arthroplasty gives very good results and prevents partial or total disability from severe hip disease. Vertebral wedge osteotomy may be needed for correction of severe kyphosis in some patients, although it carries a relatively high risk of paraplegia. Cardiac complications may require aortic valve replacement or pacemaker implantation. Apical pulmonary fibrosis and cavitary lung disease are not easy to manage; surgical resection may be rarely required.
**FIGURE 5-27.** Effects of infliximab therapy. The spinal MRI on the left part of the figure (lateral view) shows sites of enthesitis (arrows) that resolved (right part of figure) after infliximab therapy. The MRI on the right was taken after 1 year of treatment with infliximab. (Courtesy of J. Braun.)

**Reactive Arthritis**

**Clinical Presentation**

**FIGURE 5-28.** Presentation. **A–C,** Reactive arthritis, or Reiter’s syndrome, usually presents with acute oligoarticular arthritis, affecting more often the joints of the lower extremities. (Continued on next page)
FIGURE 5-28. (Continued) HLA-B27 predisposes the person exposed to the exogenous triggering agent. HLA-B27-negative patients who are exposed to the agent are much less likely to develop reactive arthritis. The arthritis usually resolves in about 3 months but can have recurrences or become chronic.

The patient can show arthritis, diarrhea, balanitis or cervicitis, conjunctivitis, acute anterior uveitis, psoriasiform rashes (keratoderma, or pustular psoriasiform lesion on palms and soles), painless superficial mucosal ulcerations (D, E), onycholysis without pitting of the nails, diffuse swelling digits ("sausage" digits; see Fig. 28C), Achilles tendonitis, and plantar fasciitis (F, G) can result in erosions and periosteal “whiskering” at sites of attachment of the Achilles tendon and the plantar fascia. G shows presence of plantar fasciitis as detected by gadolinium-enhanced MRI (left), which is better demonstrated on subsection imaging (right). (C courtesy of Khan and Sieper [55]; and G from Braun et al. [19]; with permission.)
FIGURE 5-29. **A** and **B**, Palmar and plantar skin lesions of keratoderma blennorrhagica. **C**, The left thumb in a patient with reactive arthritis shows onycholysis of thumb nail and dactylitis (“sausage digits”). The nails show no pitting or ridging that occurs in psoriatic arthritis (see Fig. 5-31F). (**A** and **B** from Koopman [115]; **C** from Khan and Skosey [116]; with permission.)

FIGURE 5-30. Asymmetric sacroiliitis. Anteroposterior roentgenographic view of the pelvis shows bilateral but somewhat asymmetric sacroiliitis in a patient with reactive arthritis.

FIGURE 5-31. Chronic reactive arthritis. Anteroposterior roentgenographic view of the pelvis and lumbar spine in a patient with chronic reactive arthritis shows asymmetric nonmarginal syndesmophytes that originate a little distance away from the corners of the vertebrae, in contradistinction to the marginal syndesmophytes of ankylosing spondylitis. Patients with psoriatic spondyloarthropathy are also more likely to develop similar nonmarginal syndesmophytes. Involvement of sacroiliac joints (sacroiliitis) is frequently observed and often asymmetric. There are no erosive changes of the sacroiliac joints in the patient's radiograph shown, although the right-sided joint is slightly indistinct. Similar radiologic findings can also be observed in patients with psoriatic spondylitis. (From Mustafa and Khan [117]; with permission.)
A. BACTERIAL INFECTIONS THAT CAN TRIGGER HLA-B27-ASSOCIATED REACTIVE ARTHRITIS

Gastrointestinal infection

Usual triggers
- Shigella flexneri
- Salmonella enteritidis and Salmonella typhimurium
- Yersinia enterocolitica and Yersinia pseudotuberculosis
- Campylobacter jejuni

Unusual triggers
- Shigella sonnei and Shigella dysenteriae
- Salmonella paratyphi
- Bacillus Calmette-Guérin
- Clostridium difficile

Urogenital infection

Usual triggers
- Chlamydia trachomatis

Unusual triggers
- Ureaplasma urealyticum

Respiratory infection

- Chlamydia pneumoniae

Mechanisms of reactive arthritis. A, Bacterial infections that trigger reactive arthritis. Reactive arthritis is an aseptic inflammatory arthritis developing in an immunologically sensitized host with nonproliferating antigens thought to be present in the joint. The sensitization is usually triggered by chlamydial urethritis, cervicitis, or enteric infection with Shigella, Yersinia, or Campylobacter in a genetically susceptible individual. HLA-B27 is the major currently known genetic risk factor. There has been a dramatic increase of reactive arthritis and related spondyloarthropathies in sub-Saharan Africa resulting from the current epidemic of HIV [31]. This is all the more remarkable given the almost complete absence of HLA-B27 in Bantu populations of Africa, and the fact that the HIV-associated reactive arthritis in Eurocaucasoid populations retains its strong association with HLA-B27. B, Schematic representation of the mechanism (pathogenesis) of reactive arthritis. In the figure, squares represent microbe-derived peptide, diamonds represent B27-derived peptide, and circles represent autoantigen.

(Reprinted by permission from Khan and Sieper [55].)
Diagnosis of Reactive Arthritis

The nonsteroidal anti-inflammatory drugs (NSAIDs) form the basis of therapy, and they should be used regularly in full therapeutic anti-inflammatory dose over an extended period [55,97]. The patient should be advised against using NSAIDs occasionally or for their analgesic effect only. Joint aspiration and intra-articular corticosteroid administration of triamcinolone may help obtain prompt and prolonged relief from severe and persistent synovitis, only after septic arthritis has been excluded. The differential diagnosis from septic arthritis may be sometimes difficult, and short hospitalization may be needed for patients with severe arthritis. Anti-inflammatory treatment should be initiated if true joint infection is not excluded. Joint rest and even temporary splinting may be needed in severe cases to alleviate pain, but should be used sparingly because it may result in muscle wasting. Physical therapy is valuable during convalescence to regain muscle strength and full range of joint motion. A comfortable pair of shoes and shoe inserts to alter weight bearing may help the patient with painful feet.

In a very severe case of acute reactive arthritis in which many joints are affected and NSAIDs alone have failed, a short course of oral corticosteroids may be needed, tapering down the dose according to improvement [55,97,118]. It is advisable to avoid prolonged low-dose oral corticosteroid therapy in chronic cases because it is rarely effective. Sulfasalazine may benefit patients with chronic disease; other “disease-modifying” drugs can be tried in some patients with persistent polyarthritis. Infliximab and etanercept have been found effective in treating severe reactive arthritis, psoriatic arthritis, recalcitrant enthesitis and dactylitis, as well as severe uveitis [119–123]. Skin lesions are treated with topical corticosteroids or keratolytic agents such as salicylic acid ointment. In severe cases, retinoids or methotrexate are most commonly used. Acute anterior uveitis must be diagnosed and treated promptly to prevent synchiae and other resultant complications; the inflammation may affect, on rare occasions, even the posterior uveal tract.

There is no benefit of antimicrobial treatment in patients with reactive arthritis and undifferentiated oligoarthritis. Antibiotic treatment of the triggering infection is only recommended if the presence of infection can still be identified after the onset of arthritis. For example, in Yersinia spp infections, the aim of such antibiotic therapy is to minimize the spread of infection within the family. However, a cautious approach should be exercised because antibiotic treatment may prolong the carrier state in some forms of enteritis, and short-term antibiotic treatment does not influence the course of postenteric reactive arthritis. It is obvious that once the trigger has been pulled, the chain of events takes its path anyway. Early treatment of patients with urogenital chlamydial infection in endemic areas has resulted in decreasing subsequent development of reactive arthritis, and vigorous antibiotic treatment of chlamydial reinfections significantly reduced relapses of reactive arthritis. In one study, a 3-month treatment with lymecycline showed some benefit for patients with chlamydial-induced reactive arthritis [55,97].

Recent studies indicate that prolonged antibiotic therapy is unlikely to be beneficial most patients, but a follow-up study of patients who 4 to 7 years previously had been treated with a 3-month course of ciprofloxacin or placebo indicates that the HLA-B27-positive subgroup of patients with reactive arthritis may benefit in the long run from ciprofloxacin therapy [121,122]. However, these promising findings from a small study need to be confirmed in future large studies.

Psoriatic Arthritis

Spondyloarthropathies
Psoriatic Arthritis

A. CLINICAL FEATURES OF PSORIATIC ARTHRITIS IN REPORTED SERIES

<table>
<thead>
<tr>
<th>Feature</th>
<th>Wright</th>
<th>Little</th>
<th>Roberts</th>
<th>Leonard</th>
<th>Krammer</th>
<th>Scarpa</th>
<th>Gladman</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymmetric oligoarthritis</td>
<td>53</td>
<td>?</td>
<td>?</td>
<td>63</td>
<td>54*</td>
<td>16.1</td>
<td>11†</td>
</tr>
<tr>
<td>Symmetric polyarthritis</td>
<td>31</td>
<td>?</td>
<td>79</td>
<td>23</td>
<td>25*</td>
<td>39</td>
<td>19‡</td>
</tr>
<tr>
<td>Distal</td>
<td>3</td>
<td>?</td>
<td>28*</td>
<td>3</td>
<td>?</td>
<td>7.5</td>
<td>12</td>
</tr>
<tr>
<td>Back</td>
<td>10</td>
<td>?</td>
<td>5*</td>
<td>7</td>
<td>21</td>
<td>21</td>
<td>2§</td>
</tr>
<tr>
<td>Mutilans</td>
<td>?</td>
<td>?</td>
<td>5*</td>
<td>3</td>
<td>?</td>
<td>2.3</td>
<td>16</td>
</tr>
<tr>
<td>Sacroiliitis</td>
<td>87</td>
<td>30</td>
<td>?</td>
<td>30</td>
<td>?</td>
<td>16</td>
<td>27</td>
</tr>
</tbody>
</table>

*Includes patients with only distal joints involved; includes more than one category.
† Includes symmetric oligoarthritis.
‡ Includes asymmetric polyarthritis.
§ Includes peripheral joint and back involvement.

FIGURE 5-34. Psoriatic arthritis is an inflammatory arthritis associated with psoriasis. The exact prevalence of each of its many forms has been difficult to establish (A; numbers in columns are percents). The disease pattern may change with time in an individual patient, and some patients may show overlapping features. Psoriasis and psoriatic arthritis are relatively more common in whites and are very uncommon among Africans, Chinese, and Native North Americans of unmixed ancestry. Distal interphalangeal joints are frequently affected in psoriatic arthritis (B–D). The nails often show pitting (E), discoloration, onycholysis (see Fig. 5-29C), thickening, and ridging. The fingers or toes may show diffused swelling (sausage digits) due to dactylitis resulting from tenosynovitis, arthritis, and periostitis (B,F,J).

(Continued on next page)
An asymmetric oligoarthritis is noted in 40% and asymmetric polyarthritis in 35%; this latter subgroup has the more erosive, deforming, and disabling disease (G,H). Radiographs of the involved joints in a patient with psoriatic arthritis show soft-tissue swelling, periostitis, juxta-articular hyperostosis, or mild erosions or severe joint destruction in some joints (D) and bony fusions in others (C). There is often lack of juxta-articular rarefaction (I). Sacroiliitis occurs in up to 20% of patients and 5% show predominant spondylitis with radiographic findings that can resemble those seen with reactive arthritis (see Fig. 5-31). G, Opera glass hand. There is marked resorption of thumb and index finger and to a lesser extent the fourth and fifth fingers, with sparing of middle finger. The resorption of thumb and index finger has resulted in the “telescoping” or “opera glass” deformity, characteristic of severe psoriatic arthritis. Psoriatic lesions on the palm are also evident along with the wrist swelling. Palmar and plantar skin lesions of psoriasis can sometimes resemble those seen in patients with reactive arthritis (see Figs. 5-20A and B). J, “Sausage digits” due to dactylitis. Achilles tendonitis and plantar fasciitis (due to enthesitis) can also occur, as is seen in some patients with reactive arthritis (see Figs. 5-20F and G) and other forms of spondyloarthropathies. (B from Perlman and Barth [124]; D, G, H, J from the American College of Rheumatology [83]; with permission.)

Histologic specimen of psoriasis. Psoriasis is a disease of abnormal keratinocyte proliferation (scale production) accompanied by an inflammatory component (redness, heat, itch) induced by T cells, but the precise cause is unknown. The activated T cells in the epidermis are predominantly CD8+, whereas those in the dermis are mostly CD4+. The infiltration of CD4+ cells precedes that of CD8+ cells. The epidermal CD8+ T cells possessing receptor are stimulated by a triggering factor (as yet unknown) and produce cytokines (including tumor necrosis factor) that stimulate keratinocytes and cause inflammation. These keratinocytes produce cytokines that in turn stimulate T cells.
spondylitis. (reactive arthritis, and so on. AS—ankylosing spondylitis, a strong association with spondyloarthropathies and with HLA-B27 even in the absence of any associated spondyloarthropathy. It is also associated with Crohn’s disease and ulcerative colitis, with or without associated (enteropathic) arthritis. AS—ankylosing spondylitis; RS—Reiter’s syndrome. (Adapted from Rosenbaum [125].)

**A. B27-ASSOCIATED “FORMES FRUSTES”**

- Chronic enthesitis (enthesopathies)
- Dactylitis (“sausage” digits)
- Keratoderma (pustular psoriasis)
- Aortic insufficiency with heart block
- Acute anterior uveitis (acute iritis)
- Symptomatic spondylitis without sacroiliitis

**B. SYMPTOMS AND SIGNS OF UNDIFFERENTIATED SPONDYLOARTHRopathies in Families of Patients with Ankylosing Spondylitis**

<table>
<thead>
<tr>
<th>Symptoms and Signs</th>
<th>Reference</th>
<th>Year</th>
<th>Relatives, n</th>
<th>Relative Frequencies, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacroiliitis without AS</td>
<td>Emery 1967</td>
<td>188</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Danoe 1977</td>
<td>37</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Christiansen 1977</td>
<td>63</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calin 1983</td>
<td>282</td>
<td>7*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LeClerc 1984</td>
<td>261</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>van der Linden 1984</td>
<td>101</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calin 1983</td>
<td>282</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory back pain</td>
<td>Khan 1985</td>
<td>100</td>
<td>9†</td>
<td></td>
</tr>
<tr>
<td>Khan 1985</td>
<td>86</td>
<td>15†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>van der Linden 1988</td>
<td>405</td>
<td>11†</td>
<td></td>
</tr>
</tbody>
</table>

* Minimal frequency, because only 70 (65%) of 107 symptomatic relatives were examined.
† Only individuals without radiographic changes.

**REPRESENTATIVE STUDIES ON THE LIKELIHOOD OF SPONDYLOARTHRopathies WITH ACUTE ANTERIOR UVEITIS**

<table>
<thead>
<tr>
<th>Study</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haar</td>
<td>34% of patients with acute iritis had AS</td>
</tr>
<tr>
<td>Beckingsale et al.</td>
<td>60% of patients with HLA-B27–associated iritis had significant back pain</td>
</tr>
<tr>
<td>Saari et al.</td>
<td>51% of patients with HLA-B27–associated acute anterior uveitis had rheumatic disease</td>
</tr>
<tr>
<td>Russell et al.</td>
<td>63% of patients with acute anterior uveitis had sacroiliitis by radionuclide scan</td>
</tr>
<tr>
<td>Stanworth and Sharp</td>
<td>42% of patients with nongranulomatous anterior uveitis had AS or RS</td>
</tr>
<tr>
<td>Pedersen</td>
<td>33% of patients with acute anterior uveitis had rheumatic disease</td>
</tr>
<tr>
<td>Vinje et al.</td>
<td>35% of patients with acute anterior uveitis had radiographic sacroiliitis</td>
</tr>
<tr>
<td>Linssen et al.</td>
<td>73% of HLA-B27–positive patients with acute anterior uveitis had rheumatic disease</td>
</tr>
<tr>
<td>Feltkamp</td>
<td>90% of patients with HLA-B27–associated acute anterior uveitis had definite or possible AS</td>
</tr>
<tr>
<td>Rosenbaum</td>
<td>84% of patients with HLA-B27–associated acute anterior uveitis had AS, RS, or incomplete RS</td>
</tr>
</tbody>
</table>

**FIGURE 5-37.** Rheumatic disease with iritis. Acute anterior uveitis has a strong association with spondyloarthropathies and with HLA-B27 even in the absence of any associated spondyloarthropathy. It is also associated with Crohn’s disease and ulcerative colitis, with or without associated (enteropathic) arthritis. AS—ankylosing spondylitis; RS—Reiter’s syndrome. (Adapted from Rosenbaum [125].)

**References**


