Chapter 3  Clinical aspects of Ankylosing Spondylitis

I.E. van der Horst-Bruinsma, MD, PhD

Correspondence to:
I.E. van der Horst-Bruinsma, MD, PhD
Vrije Universiteit Medical Centre
Department of Rheumatology, room 4A-42
PO Box 7057, 1007 MB Amsterdam, The Netherlands
Phone  +31204443432
Fax      +31204442138
E-mail: IE.vanderHorst@vumc.nl
Disease characteristics of Ankylosing Spondylitis

Definition of the disease

Ankylosing spondylitis (AS) is a relatively common chronic inflammatory disorder that more often manifests in young males than in females. The disease presents with low back pain and morning stiffness due to a chronic inflammation of the sacroiliac (SI) joints and vertebral column. This inflammatory process can result in destruction of the vertebral column leading to postural deformities, like ankylosis of the cervical spine and kyphosis of the thoracic spine. Extraspinal manifestations of the disease consist of arthritis of the peripheral joints (especially knees, shoulders and hips), resulting in joint destruction that sometimes necessitates joint replacement, anterior uveitis, enthesitis, cardiac and pulmonary complications. \(^1\,^2\)

The diagnosis of definite AS requires fulfilment of the modified New York criteria\(^3\): obligatory are signs of a bilateral sacroiliitis grade 2-4 or unilateral sacroiliitis grade 3 or 4 plus at least one criterion out of 3 (inflammatory back pain, limited lumbar spinal motion in sagittal and frontal planes and decreased chest expansion relative to normal).

The onset of complaints is often gradual and the mean delay is 8 years to the time of diagnosis. Until recently, the prevalence was estimated 0.2% in the Caucasian population but later a prevalence up to 0.9% and even 1.4% in northern Norwegians was reported\(^4\,^5\).

AS belongs to a group of diseases which are referred to as Spondylarthropathies (SpA). The group of SpA includes rheumatoid factor negative patients with inflammatory back pain and/or asymmetrical synovitis, like psoriatic arthritis, arthritis accompanying inflammatory bowel disease (e.g.Crohn’s disease) and reactive arthritis. The prevalence of SpA is estimated at 1% in the Caucasian population, which equals the prevalence of Rheumatoid Arthritis (RA)\(^5\). SpA is diagnosed according to the criteria of the European Spondylarthropathy Study Group (ESSG)\(^6\), which require inflammatory spinal pain or synovitis plus a positive family
history of psoriasis or inflammatory bowel disease or alternate buttock pain or enthesiopathy or sacroiliitis.

Etiology

The cause of AS is multifactorial, as in many autoimmune diseases, and based on endogenous factors, such as the very strong genetic influences of HLA-B27 and exogeneous factors, such as bacterial infections.

Endogenous factors

The etiology of this chronic, familial disease is unknown. Heredity does play a major role. Familial recurrence of the disease is high and many patients belong to multi case families. Twin-studies suggest that up to 97% of the susceptibility to AS can be attributed to genetic factors. The main genetic component is the increased prevalence of the Human Leukocyte Antigen (HLA)-B27 gene, located at chromosome 6. More than 95% of the primary Caucasian AS patients are HLA-B27 positive, whereas HLA-B27 is only present in 8% in most of the Caucasian populations. HLA-B27 positive first-degree relatives of patients with AS have been estimated to be 10 times more at risk to develop AS than B27 positive individuals without such family history. However, genome scanning has shown that the major histocompatibility complex (MHC), including HLA-B27, contributes less than 40% to the recurrence risk ratio in AS.

Other potential candidates for genetic influences are the genes that encode for the production of pro-inflammatory cytokines, like interleukine1 (located at chromosome 2q14), like Interleukin 1 alfa and beta polymorphisms, as well as the polymorphisms of its functional antagonist the interleukin 1 receptor antagonist gene. Another gene, CARD 15, which plays an important role in the susceptibility to Crohn’s disease, a disease which is clinically related
to AS\textsuperscript{11-14} and the gene encoding for the human Transforming Growth Factor B1 (TGFB1) is interesting because this cytokine is a regulator of osteoblast proliferation and plays a role in the development of osteoporosis and fibrosis, two manifestations of long standing AS\textsuperscript{15,16}.

**Exogenous factors**

Apart from genetic factors, environmental factors also seem to play a role in the multifactorial causes of AS. The innate immunity could be disturbed, like in some polymorphisms of the \textit{TLR4} and \textit{CD14} genes, and make individuals prone to abnormal reactions after bacterial infections. The pathogenetic role of bacteria can be illustrated by the onset of another subtype of SpA, reactive arthritis. In this disease the symptoms manifest after bacterial infections, especially gastrointestinal (with Salmonella, Shigella, Yersinia or Campylobacter) or urogenital (with Chlamydia trachomatis). These infections provoke the onset of reactive arthritis, but their role in the onset of AS is still under debate. However, it was suggested that HLA-B27 interferes with the elimination of bacteria and might support the onset of persistent infection\textsuperscript{17}.

The role of one of these bacteria, Chlamydia trachomatis, in the pathogenesis of AS is interesting. This micro-organism was detected in 15-20\% of the urethra swabs of male, German, AS patients\textsuperscript{18} although a recent study did not reveal an increased prevalence of Chlamydia Trachomatis infections in Dutch AS males compared with a group of healthy men\textsuperscript{19}.

**Clinical characteristics**

**Age at onset**

Most often the disease begins in late adolescence or early adulthood with an average age of onset at 28 years\textsuperscript{20}, but also occurs in children (juvenile onset). The juvenile presentation is
dominated by peripheral arthritis. Onset after the age of 45 years is very uncommon. The minority of patients is diagnosed after 40 years of age (6%)\textsuperscript{21}. However, at an early stage the diagnosis can be difficult because the of complaints in AS are often gradual. This results in a mean delay of 8 years from the first symptoms to the time of diagnosis\textsuperscript{2}. A survey of 3000 German AS patients also confirmed that the majority (90%) had the first spondylitis symptoms between 15-40 years\textsuperscript{21}. A small subset of patients (15%) have a juvenile onset (before age of 16 years), but in developing countries this form of AS is more common (40%)\textsuperscript{22}.

\textit{Male vs female pattern}

The disease is more common in males than females with a male-to-female ratio of approximately 3:1\textsuperscript{23,24}. The age of onset might be slightly higher in females than males but the initial complaints are the same\textsuperscript{25}. Overall disease manifestations in men are most commonly located in the spine and pelvis, whereas women have more symptoms in the peripheral joints and pelvis\textsuperscript{26-28}. The disease tends to be more severe in men. In men, a higher incidence of uveitis was observed, which lasted longer and more often resulted in visual loss than women\textsuperscript{27}. Also complete obliteration of the sacroiliac joints occurs more often in men than in women as well as a extensive spinal ankylosis\textsuperscript{25,29}. In females, radiological changes of the cervical spine are more commonly reported than in men, as well as symphysitis\textsuperscript{29}. Although a more benign disease outcome in females is often quoted, the results are contradictory.

Fertility in females with AS did not differ from the fertility rate of healthy controls\textsuperscript{30}. Pregnancy was reported as a precipitating factor for AS with a disease onset during pregnancy in 21% within six months after delivery\textsuperscript{30}. 
Disease activity during pregnancy improved in only 30% of the patients, which is in contradiction with rheumatoid arthritis in which more than 70% of the patients show an improvement of the disease during pregnancy\textsuperscript{31}. Episodes of knee joint arthritis and acute anterior uveitis occurred, especially during the first and second trimester and within 4-12 weeks post-partum in 87% of patients. Pregnancy outcome, like complications during pregnancy and delivery and fetal outcome, like still birth and spontaneous abortion, were not worse compared with healthy controls\textsuperscript{30,32}. Drugs used during pregnancy included intra-articular corticosteroid injections, low dose prednisone, NSAIDs until gestational week 32 and sulfasalazine\textsuperscript{33}.

\textit{Spinal versus extraspinal manifestations}

The clinical features of AS can be divided in spinal and extraspinal features. The spinal characteristics include sacroiliitis and spondylitis and skeletal complications like vertebral fractures, pseudoarthrosis, etc. The extraspinal manifestations comprise peripheral arthritis, enthesitis, uveitis, cardiovascular and pulmonary involvement, cauda equina syndrome, enteric mucosal lesions, amyloidosis, a.o.

\textit{Spinal features}

The spinal involvement results in complaints of chronic inflammatory back pain (as is defined later in this Chapter) with morning stiffness. This morning stiffness lasts at least one hour, but often many hours, and improves with exercise but is not relieved by rest. The low back pain is caused by inflammation of the sacroiliac (SI) joints and vertebral column. Sacroiliitis is the most important characteristic of AS can be detected by a conventional radiograph of the pelvis which shows blurring of the distal part of the SI-joints, progressing to joint space narrowing and finally sclerosis of the joints. At an early stage of the disease Magnetic...
Resonance Imaging (MRI) or Computed Tomography (CT) is more sensitive to reveal signs of SI-inflammation compared with conventional radiographs\textsuperscript{34,35}. Pain at the cervical region and of the thoracic spine, especially with chest expansion, is caused by involvement of the cervical and costovertbral joints. The spinal inflammation coincides with the formation of syndesmophytes and squaring of the vertebrae, sometimes evolving into the classical bamboo spine (\textit{FOTO}), can lead to spinal ankylosis with a limited chest expansion, limited neck motion, flattening of the lumbar spine and thoracic kyphosis. These deformities, which often evolve after more than 10 years of the disease, result in a characteristic stooped forward posture and difficulties in looking forwards\textsuperscript{36}.

In a progressed disease, atlanto-axial subluxation might occur due to erosions of the transverse ligaments or other cervical structures, such as the odontoid process, resulting in neurological complaints due to myelum compression with quadriplegia even after a minor trauma of the neck\textsuperscript{37,38}.

Another possible complication of the spine is due to the decreased bone mineral density, in which case the osteoporotic spine is prone to fractures, especially of the cervical spine, even after a minor trauma\textsuperscript{39,40}. Osteoporosis is more common in patients with syndesmophytes, cervical fusion and peripheral joint involvement. Studies on bone mass density (BMD) measurement in AS focus on the generalized loss of bone measured in the lumbar spine or femoral neck, with incidence between 18 and 62\% of the AS patients\textsuperscript{41}. BMD measurement at the hip is more reliable in AS because the interpretation of the BMD measured at the anteroposterior lumbar spine BMD is difficult because of the para spinal ossification and syndesmophyte formation in more advanced disease\textsuperscript{42,43}. Most AS patients, even after a short disease duration, show a decreased BMD, which might be explained by the chronic inflammation that could be an important determinant of bone mass loss due to the effect of
osteolytic cytokines. In contrast, women with AS seem to show less severe losses of bone mass compared with male AS patients, which could be explained by protective hormonal influences in case premenopausal women or a lower disease activity\textsuperscript{44,45}.

Apart from the increased risk of osteoporosis, AS patients also have an increased risk of vertebral fractures (Standard Morbidity ratio of 7.6)\textsuperscript{46-48}. The risk of a vertebral compression fracture occurring over a 30 year period following the diagnosis of As is 14\% compared with 3.4\% for population controls\textsuperscript{41}. The increased risk of a vertebral fracture seems to be related to a longer disease duration\textsuperscript{46}.

On the other hand, the risk of limb fractures, such as the hip, distal forearm, proximal humerus and pelvis, was not significantly increased in association with AS\textsuperscript{48}.

The vulnerability of the spine in AS can be explained partly due to the low bone mass, but also to the rigidity of the spine which makes it prone to a fracture even after a minor trauma. Important to note is that vertebral fractures may occur silently and that the diagnosis of fractures can sometimes be difficult because the extra spinal bone formation may obscure them. Together with the possible neurological complications due to dislocation, like complete spinal cord lesions, incomplete lesions of the acute cervical central cord syndrome type, root lesion and an incomplete quadriplegia, these fractures may result in a poor outcome\textsuperscript{48}.

Patients should be aware of this risk and adapt their lifestyle by avoiding dangerous activities. Osteoporosis should be treated in AS, even despite the male predominance and relatively young age of the patients. The treatment should be considered including exercise and the prescription of bisphosphanates, despite the fact that proper placebo-controlled trial of the efficacy on bisphosphonates in AS are missing\textsuperscript{41}.

Physicians should be aware of the increased risk of fractures even after a minor trauma and radiography of the spine should be performed at an early stage to detect these fractures and treat them adequately. Apart from conventional radiography, CT scanning and MRI is advised
in case of a neck trauma because otherwise cord contusion and epidural hematoma can be missed.

Another spinal complication is non-infectious spondylodiscitis (Andersson lesion), which occurs in approximately 8% of the AS patients, predominantly at the lumbar and thoracic level, but multiple level lesions are not uncommon. Occasionally, a cervical discitis was described presenting with cervical pain in a previously quiescent, long-standing disease without a history of a preceding trauma. This sterile, destructive process in one intervertebral disc and the adjoining vertebral bodies, must be discriminated from an infectious discitis or osteomyelitis. The symptoms are renewed spinal pain, usually sharply localized and exacerbated by exercise, but most patients do not report symptoms localized to the lesion. In case of suspicion of spondylodiscitis MRI-scanning can detect the lesions. Important to realize is that bacterial cultures of this process should be obtained in order to exclude an infection and confirm the diagnosis of a sterile spondylodiscitis.

Extraspinal features

Arthritis

Peripheral arthritis occurs in approximately one third of the patients, especially in the knees, hips and shoulders. Hip involvement is usually bilateral, very common in the juvenile-onset AS and occurs mainly in the first ten years of the disease. The hip joints are prone to a flexion contracture and destruction which might make total joint replacement necessary at a relatively young age. The shoulders are also frequently involved. Arthritis of more peripheral joints is often located in the knees, wrists, elbows and feet usually in an asymmetrical pattern. The radiographic features of the inflamed joints can be similar to rheumatoid arthritis, showing
erosions, but in AS bony ankylosis of the wrists, tarsal bones, hips and small joints of the fingers and toes more often occurs.

**Enthesitis**

Many patients suffer from pain due to enthesitis, an extra-articular bony tenderness caused by local inflammation. Many sites can be involved, like costosternal junctions, spinous processes, iliac crests, great trochanters, ischial tuberosities, tibial tubercles or tendons insertions, like the Achilles tendons\(^54\). Recently, a feasible and validated enthesitis score was published, the Mases-score which included 13 numbers of enthesis: the left and right first and sevenths costochondral joints, anterior and posterior superior iliac spine, iliac crest, and proximal insertion of the Achilles tendon and the fifth lumbar spinous process\(^55\). This MASES score (range 0-13) was at least as reliable as the older Mander enthesitis index, which included 66 sites and more feasible in clinical practice and follow up of clinical trials.

**Ocular**

Acute anterior uveitis (previously called “iritocyclitis”) occurs in 25-30% of the patients and can be the first presenting symptom of the disease. In a recent study among 433 patients with different types of uveitis, 44 cases (almost 10%) of spondylarthropathy were detected\(^56\) (Lindner J, Rheumatology 2004), whereas others showed a number of 50% of previously undiagnosed cases of spondylarthropathy among uveitis patients\(^57,58\).

The occurrence of acute anterior uveitis is increased in the HLA-B27 positive population, with a lifetime cumulative incidence of 0.2 % in the general population compared with 1% in the HLA-B27 positive population\(^59\).

The attacks of uveitis are unilateral and recurrent and cause sudden ocular pain with redness and photophobia. These attacks might lead to inflammatory debris accumulating in the
anterior chamber which may cause papillary and lens dysfunction and blurring of vision. In some cases glaucoma and even blindness may occur if adequate treatment is delayed, but most of the time the uveites subsides spontaneously within 3 months. It can be treated by local corticosteroids or TNF-blocking agents, like infliximab, which seems to be successful in refractory uveitis. The efficacy of etanercept, another TNF-blocking agent, on uveitis seems to be controversial, because it does not seem to prevent a relapse in combination with methotrexate and it was suggested that this drug might even trigger a attack of uveitis. However, a comparison of three randomised studies with etanercept in AS showed a lower number of cases with uveitis in the etanercept-treated patients compared with placebo.

Gastro-intestinal

Asymptomatic inflammatory bowel disease is described in a high percentage of patients with spondylarthropathy (60%) and can be detected by endoscopy of the colon and terminal ileum. These lesions can be divided in acute lesions, resembling acute bacterial infections and chronic lesions that bear features of inflammatory bowel disease. The chronic lesions are more often seen in association with AS and although most of the time these enteric mucosal lesions are clinically silent, patients with chronic lesions experience significantly more episodes of diarrhea. During follow up studies it appeared that up to 25% of these AS patients with peripheral arthritis and chronic gut inflammation eventually develop Crohn’s disease. On the other hand, Crohns disease and ulcerative colitis (inflammatory bowel diseases, IBD) can manifest with sacroiliitis and peripheral arthritis, resembling AS.

Cardiovascular

Cardiac involvement can occur in long standing AS with aortic valve incompetence, due to aortitis of the ascending aorta and conduction abnormalities, caused by involvement of the
atrioventricular node. Conduction disturbances in AS are due to inflammation and fibrosis of the membraneous portion of the interventricular septum, thereby affecting the atrioventricular node.\textsuperscript{70} The latter sometimes requiring pacemaker implantation in case of a complete heart block. The occurrence of conduction disturbances in patients with AS varies from 1-33\%, of aortic insufficiency from 1-10\% and increases with age, disease duration, and presence of peripheral arthritis.\textsuperscript{71,72} Aortic insufficiency develops because the aortic inflammatory process affects the aortic wall directly behind and above the sinuses of Valsava. This leads to scarred, fibrotic thicket, shortened aortic valve cusps, to inwards rolling of the edges of the cusps and also to a dilatated aortic root resulting in aortic regurgitation.\textsuperscript{73-75} Aortic regurgitation and or variable degrees of atrioventricular or bundle branch block occur in approximately 5\% of the patients. Mitral regurgitation also occurs but less often.\textsuperscript{76} The course of aortic valve incompetence often leads to heart failure in several years and the only effective therapy is valvular replacement.\textsuperscript{77,78} The incidence of atrioventricular or bundle branch block is increased among the HLA-B27 positive population, independently of the diagnosis AS.\textsuperscript{79,80} Other less common cardiovascular manifestations associated with AS are pericarditis, cardiomyopathy and mitral valve disease.\textsuperscript{81} Besides these characteristic cardiovascular lesions associated with AS, myocardial involvement may also occur, especially left ventricular dysfunction. Left ventricular dilatation, as well as a poorly contracting left ventricle and abnormal systolic time intervals, were reported in five of 28 patients with AS\textsuperscript{82} and diastolic function of the left ventricle was significantly more often disturbed in AS compared with healthy controls.\textsuperscript{83} These finding were confirmed at necropsy in another group of AS patients\textsuperscript{73} which reported an excess of connective tissue in the myocardium.

In conclusion, AS is associated with well known characteristic cardiovascular manifestations, particularly conduction disturbances and aortic insufficiency. Moreover, there are some
suggestions for a higher prevalence of left ventricular dysfunction and ischaemic heart disease in AS.

Pulmonary

Pulmonary complications are infrequent and can be caused by rigidity of the chest wall and apical pulmonary fibrosis. In a retrospective study, an incidence of apical pulmonary fibrosis in AS was reported in 7%, based on plain radiography. This complication occurs, on average, two decades after the onset of AS, but recent studies with high resolution computed tomography (HRCT) detected interstitial lung disease in 50 –70 % of the patients with early AS, defined as a duration of < 10 years. The changes detected with HRCT, in a small study of 26 outpatients with AS without respiratory symptoms, included signs of interstitial lung disease (n = 16) and a few showed signs of emphysema (4 patients), apical fibrosis (2 cases) or a mycetoma (n=1). Plain radiography was abnormal in only four of these patients. Cavities in these fibrotic parts can be infected by bacteria and fungi, like Aspergillus. These cavitations may mimic tuberculosis in one thirds of the patients. Chronic aspergillus colonization is reported in 50-65% of patients with AS, whereas 10-30% develop an aspergillosis infection. Treatment is based on the administration of antifungal drugs in combination with surgical resection of the cavity and removal of the fungal ball.

(CT-SCAN Aspergillus Throns)

The inflammation of costovertebral and costotransverse joints do not seem to reduce the pulmonary function. The total lung and vital capacities are seldom reduced in AS patients, despite the diminished chest expansion, because the diaphragmatic function is not impaired.
Therefore, the exercise tolerance is not reduced in most patients if the patients are encouraged to maintain cardiorespiratory fitness\textsuperscript{99,100}.

\textit{Renal}

The incidence of renal abnormalities varies\textsuperscript{101,102} between 10-18\%. Secondary renal amyloidosis is the most common cause of renal involvement in AS (62\%), followed by IgA-nephropathy (30\%), mesangioproliferative glomerulonephritis (5\%), as well as membranous nephropathy (1\%), focal segmental glomerulosclerosis (1\%) and focal proliferative glomerulonephritis (1\%)\textsuperscript{103,104}. However, renal amyloidosis is a very rare complication of AS (1-3\% in European patients), but should be considered in case of proteinuria and or renal failure in AS\textsuperscript{105,106}. In 7\% of unselected AS patients, amyloid can be found in abdominal fat or rectal biopsies, but most do not develop clinically significant disease\textsuperscript{107-109}. Proteinuria or impaired renal function can indicate IgA-nephropathy, which is interesting because of the increased serum IgA levels in AS patients\textsuperscript{102,110,111}. Also, cases of IgA multiple myeloma have been reported\textsuperscript{112}.

\textit{Neurological}

Vertebral fractures, especially of the cervical spine, and cervical spine dislocations can cause neurological deficits after minor trauma, as was mentioned previously.

A slowly progressive cauda equina syndrome might occur late in the disease course as a rare complication, first described by Browie and Hauge in 1961\textsuperscript{113,114}. The symptoms are a sensory loss in the lumbar and sacral dermatomes, less often weakness and pain in the legs and loss of urinary and rectal sphincter tone\textsuperscript{115,116}. MRI can demonstrate arachnoiditis, with characteristic enlarged dural sacs and arachnoid diverticula and exclude are causes of myelopathies\textsuperscript{117}. One study with CT-scan also showed dural calcification, showed on\textsuperscript{118}. Treatment with NSAIDs or
corticosteroids alone is inappropriate to improve the neurological deficit and often surgical
treatment of the dural ectasia, by lumboperitoneal shunting or laminectomy, is necessary\textsuperscript{119}.

Hormonal

The elevated susceptibility for AS in men compared with women did suggest an etiological
role for sex steroids in AS. In male patients, elevated serum testosterone and in
premenopausal females lower 17β–estradiol levels were reported\textsuperscript{120,121}. It was even suggested
that anti-androgenic treatment would be beneficial for AS patients\textsuperscript{122}. However, more recent
studies revealed that serum testosterone levels are not elevated in male AS patients, but
previous found elevations might be explained due to the use of phenylbutazone\textsuperscript{123}. Therefore,
no basis is provided for anti-androgenic treatment. Also, the 17β-estradiol levels in later
studies did not differ between AS patients and controls\textsuperscript{124,125}.

The influence of hormones like prolactin and growth hormone, which might have a pro-
inflammatory effect, were recently studied in men with AS and RA. No unregulated responses
of these hormones were found after stimulation with insulin hypoglycaemia, in comparison
with healthy controls\textsuperscript{126}.

Diagnostic procedures

Symptoms

An important clue to the diagnosis of AS is a positive family history of AS or other associated
spondylartropathies. Familial aggregation of AS has been known for many years and a
positive family history can be found in 15-20\% of the cases\textsuperscript{2,127,128}. A positive family history
is one of the important clues to detect early cases of spondylarthritis in patients with
inflammatory back pain\textsuperscript{128}. 
One of the major symptoms is typical pain in the buttock and lower lumbar region which is accompanied by a few hours morning stiffness and improves with activity. The worse complaints are often at night and early in the morning. The inflammatory back pain can be insidious at onset but usually becomes persistent within a few months. Inflammatory back pain is defined as: onset before 40 years of age, insidious onset, duration of the back pain longer than 3 months, morning stiffness and improvement of the symptoms with exercise. Sacroiliitis causes unilateral pain in the buttock, that sometimes radiates down the thighs but not below the knee. Impaired movement of the back and neck occurs later in the disease.

In other patients bone pain, caused by enthesitis, is the first symptom which often presents in the heel pain, due to inflammation at the Achilles tendon insertion to the calcaneus. Other enthesitis lesions are the plantar fascia, sternal and costochondral sites and the large tendon insertions of extremities.

Thoracic pain, increased by deep breathing, coughing or laughter, can be caused by inflammation of the costovertebral joints. Thoracic spine involvement can also cause anterior chest pain with a shortness of breath on activity, caused by a limited respiratory excursion in a progressed disease.

In patients with severe involvement and rigidity of the spine, spinal fractures can occur even after a minor trauma, due to osteoporosis of the spine. The signs of this fracture can be acute pain in the vertebral column or increased mobility of a previously immobilized spine. The spinal fracture can also result in neurological deficit with long-tract signs, including quadriplegia.

Asymmetrical pain and swelling of the knee, hip ankle or shoulder or metatarsal joints often occur, caused by oligoarthritis. Sometimes the temporomandibular joints may be effected, leading to a reduced mouth opening and discomfort on chewing, but this is more common in patients with rheumatoid arthritis. Dactylitis, with pain and a sausage like swelling of a finger
or toe, can be caused by an inflammation of the Proximal Interphalangeal (PIP) and Distal Interphalangeal (DIP) joints can be found in AS but is more common in psoriatic arthritis. Fatigue is common and is partly caused by a disturbed sleep pattern due to pain and stiffness. Other constitutional features include fever and weight loss. Ocular features can present as attacks of acute pain, redness of the eye and blurred vision in case of acute anterior uveitis, which occur in one third of the patients. Altered bowel habits with diarrhoea and abdominal distension require investigation, because 60% of the AS patients suffers from sub clinical inflammatory changes of the small or large bowel and NSAIDs will be less well tolerated because they can also induce bowel inflammation. Shortness of breath on exertion can, apart from thoracic stiffness, also be caused by cardiac or pulmonary complications of AS. Cardiovascular involvement includes cardiac conduction abnormalities or aortitis with dilatation of the aortic valve ring. Pulmonary involvement, with progressive upper lobe fibrosis can also cause breathlessness.

Physical examination
Physical examination should include measurement of the blood pressure to exclude hypertension in case or renal involvement (or aortic insufficiency) and pulse frequency to detect bradycardia in case of atrioventricular conduction disturbances. The skin and nails should be overlooked to detect psoriatic lesions, especially in the ears, scalp, natal region, extension surfaces of the elbows and knees and pitting lesions of the nails. The eyes should be inspected to detect redness which might be caused by conjunctivitis or even an attack of acute anterior uveitis, in case of pain and a blurred vision. An irregular pupil could be the result of an attack of uveitis in the past with synechiae to the cornea or lens, which might cause glaucoma on the long run.
Examination of the heart can detect a murmur caused by aortic insufficiency or bradycardia due to conduction abnormalities. The chest might show signs of a limited chest expansion and signs of apical fibrosis, although these lung deformities often can only be detected by radiographic procedures. The abdomen should also be examined, but signs of inflammatory bowel disease most often are detected only with ileocolonoscopy.

Physical examination of the spine involves the cervical, thoracic and lumbar region. Cervical involvement, which often occurs late in the disease, can result in a limited flexion, extension, rotation or lateral flexion, but limitation in several directions often occur. The stooping of the neck can be measured by the occiput-to-wall distance. The patient stands with the back and heels against the wall and the distance between the back of the head and the wall is measured. Another method is the tragus-wall test which measures the distance between the tragus of the ear and the wall. Loss of lateral rotation also occurs and eventually the neck may lose all motion and become fixed in a flexed position.

The thoracic spine can be tested the chest expansion, which normally exceeds 5 cm, but is age- and sex-dependent, with lower expansion in females compared with males and decreasing with age. It is measured at the fourth intercostal space and in women just below the breasts. The patient should be asked to force a maximal inspiration and expiration and the difference in chest expansion is measured. A chest expansion of less than 5 cm is suspicious and < 2.5 cm is abnormal and raises the possibility of AS unless there is another reason for it, like emphysema. In progressed AS, the anterior chest wall becomes flattened, shoulders become stooped, the abdomen becomes protuberant and the breathing diaphragmatic. The normal thoracic kyphosis of the dorsal spine becomes accentuated.
The costovertebral, costotransverse and manubriosternal joints should be palpated to detect inflammation which causes pain on palpitation.

The lumbar spine can be tested by the ability of the patient bending forward to touch the floor with the fingertips with the knees fully extended. However, this test can be less reliable in case of limitations in the motion of the hips. A more appropriate test to detect limitation of the forward flexion of the lumbar spine is the Schober’s test. This is performed by making a mark between the posterior superior iliac spines (“dimples of Venus”) at the 5th lumbar spinous process. A second mark is placed 10 cm above the first one and the patient is asked to bend forward with extended knees. The distance between the two marks increases from 10 to at least 15 cm in normal people, but only to 13 or less in case of AS. Lumbar lateral flexion can be tested by the patient standing erect with the arms along side the body and by moving laterally with the fingers over the lateral side of the leg. The distance between the fingertips and the floor can be measured and the measurement can be repeated on the other side.

Tests to detect active sacroiliitis by palpation or other manoeuvres, like hyperextension of the lumbar spine or hyperextension of one hip joint, are not very specific because the pain caused by these tests could also result from enthesitis or arthritis of the hip, and therefore are not recommended.

All peripheral joints should all be investigated to look for signs of synovitis (pain, tenderness, swelling and limited motion). The hips and shoulder are most often involved, in one-third of the patients, and any limitations in function should be recorded early in the disease in order to detect progression later. Other joints often involved are the knees, wrists, elbows and feet.

The presentation is usually asymmetric and often monoarticular or oligoarticular.

Enthesitis lesion can be detected by palpation of the locations described above in the MASES-index.
**Laboratory tests**

Only 50-70% of the patients with an active disease show an elevated erythrocyte sedimentation rate (ESR) or a raised C reactive protein (CRP)\textsuperscript{129-131}. These acute phase reactants seem to show a higher correlation with peripheral involvement of AS than with spinal disease activity.

In contrast with rheumatoid arthritis, these acute phase reactants do not have a high correlation with the disease activity of AS, and elevation is more often observed in case of extraspinal manifestations than in case of more axial involvement. Therefore, their value as an outcome parameter for disease activity in therapeutic trials in AS is limited.

The platelet count may also be slightly elevated and a mild normochromic, normocytic anaemia, due to a chronic disease, is common in 15% of the patients.

Positive tests for the rheumatoid factor and ANA do not occur more often than in healthy controls\textsuperscript{2,132}.

The HLA-B27-antigen is present in the majority of the AS patients, but this test is inappropriate to confirm the diagnosis, which is primarily based on history, physical examination and radiographic evidence of sacroiliitis. In adolescent patients, where the radiographic confirmation of sacroiliitis can be difficult, HLA-B27 testing could be helpful to establish the diagnosis.

Raised alkaline phosphatase, primarily derived from bone, and serum IgA levels are common in AS. The urine might show protein or erythrocytes in case of renal involvement.

**Radiology**

The radiograph of the pelvis is necessary to assess the sacroiliac joints (SI), which might show signs of sacroiliitis, an obligatory sign for the diagnosis of AS. The severity of this
sacroiliitis can be graded from 0 (no abnormalities) to grade 4 (complete ankylosis of the SI-joints). At early stages of the disease, signs of sacroiliitis can be detected with CT and MRI before the abnormalities are present at the plain radiograph of the pelvis\textsuperscript{34,35}.

Also, the vertebral column often shows characteristic changes, like bony sclerosis with squaring of the vertebral bodies and ossification of the annulus fibrosis with syndesmophytes. This might lead to fusion of the vertebral column with a classical Bamboo-spine aspect on the radiograph of the lumbar region.

Involvement of the hip and shoulder joints with joint space narrowing can be detected by conventional X-rays.

**Differential Diagnosis**

The diagnosis of AS can be confirmed by the modified New York criteria as mentioned above. AS belongs to the group of diseases called Spondylarthropathies, which have the inflammatory back pain as a common feature and are defined by the ESSG-criteria, as described previously. The other types of SpA include psoriatic arthritis, inflammatory bowel disease (IBD) like ulcerative colitis and Crohns disease, reactive arthritis, juvenile spondylarthropathy and a group of undifferentiated spondylarthropathies. The majority of affected individuals with SpA possess the HLA-B27 antigen.

Psoriatic arthritis occurs in 5-7\% of the people with psoriasis. The psoriatic arthritis can present as a mono-/oligoarthritis resembling, the reactive arthritis pattern, or as an symmetrical polyarthritis, resembling rheumatoid arthritis (RA), but with involvement of the DIP-joints (in stead of the PIP-joints in RA) and without a positive rheumatoid factor.

Axial disease occurs in about 5\% of the psoriasis patients. Axial involvement may occur independent from peripheral arthritis and is often a symptomatic, but symptoms of
inflammatory back pain or chest wall pain may be present. Sacroiliitis is observed in one-third of the patients and frequently asymmetric. Spondylitis may occur without sacroiliitis and may result in fusion of the spine. Enthesitis is common, especially in the oligoarticular form of the disease. The radiographic features if the spine in case of psoriatic spondylitis show more or less random syndesmophyte formation, whereas in AS, syndesmophytes form in a more ascending fashion.\textsuperscript{133}

In 10-20\% of patients with IBD, like ulcerative colitis and Crohn's disease, peripheral arthritis occurs. Most often the knees, ankles and feet are affected. Large-joint effusions, especially of the knee, are common. In 10\% of the patients with IBD sacroiliitis or spondylitis occur and is often asymptomatic.\textsuperscript{134} The course of the spondylitis is independent of the active bowel inflammation.

Reactive arthritis refers to a mono-or oligoarthritis, which occurs after an infection of the genitourinary (with Clamydia trachomatis), gastrointestinal tract (with Salmonella, Shigella, Yersina or Campylobacter bacteria) or sometimes after a respiratory infection with Chlamydia pneumonialae. The arthritis usually occurs two to four weeks after the primary infection, presenting as an urethritis or a period of diarrhoea. Conjunctivitis, with crusting of the eyelids in the morning, can accompany the urethritis, but an acute anterior uveitis might also occur. The combination of arthritis, conjunctivitis and urethritis is also known as the Reiter's syndrome. The joint involvement is asymmetrical and located predominantly in the knees, ankles, and small joints of the feet, but joints of the upper extremities (wrists, elbows and hand joints) can also be effected. The large joints show signs of synovitis whereas the small joints of the hands and feet present as sausage digits or dactylitis. The course of reactive arthritis is self limiting with 3 to 12 months in the majority of the patients and the treatment consists of
non-steroidal anti-inflammatory drugs (NSAIDs) whereas antibiotic treatment is not indicated.

Rheumatoid arthritis (RA) can manifest with a mono-or oligo-articular onset, but has most often a symmetrical polyarthritis. RA can be distinguished from AS by the absence of inflammatory back pain, and the presence of the positive rheumatoid factor, in 60-70% of the patients and because it is more often associated with an increased ESR or CRP. The radiological features of RA, with erosions of the small joints of hands and feet, differ from AS.

Juvenile spondylarthropathy applies to a diagnosis made before the age of 16 and belongs to the group of Juvenile Idiopathic Arthritis (JIA). Most patients are boys and HLA-B27 positive and the tests for the rheumatoid factor and anti-nuclear antibodies (ANA) are usually negative. The symptoms mainly involve arthritis of the large joints of the lower extremities, especially the hip joint, which predicts a severe course of the disease. Enthesitis is common, as well as lower back or buttock pain. Acute anterior uveitis occurs in 5-10% of the patients. Plain radiographs of the sacroiliac joints and the lumbar spine often do not show abnormalities for many years. Treatment is based on NSAIDs and sulfasalazine is added in case of persistent arthritis 135,136.

Diagnoses resembling the complaints of AS are other syndromes or diseases that effect the spine, like a prolapsed intervertebral disc, fibromyalgia, spinal tumours, like chordoma or ependymoma, bone tumours, like osteoid osteoma, plasmacytoma, bone metastases or leukemic infiltration and infections of the spinal or sacroiliac joints like tuberculosis and brucellosis. Metabolic bone diseases like osteomalacia, hypophosphatemia and rickets can
also cause back pain. The noninflammatory back pain is, in most cases, aggravated by activity and relieved by rest and is not associated with a limited chest expansion or a limited lateral flexion of the lumbar spine.

Diffuse idiopathic skeletal hyperostosis (DISH or Forestier’s disease) can resemble AS because of the stiffness of the spine due to hyperostosis of the anterior longitudinal ligaments and bony attachments of the tendons. Occasionally the SI-joints show hyperostotic changes resembling sacroiliitis, but in most cases of DISH this feature is absent. However, in contrast with AS, the onset of the disease is at a later age (over 50), there is no association with HLA-B27 and there are more flowing ligamentous ossifications but less syndesmophyte formations.

Radiographic signs of sacroiliitis must be distinguished from osteitis condensans illii, which consists of a symmetric sclerosis on the iliac sides of both sacroiliac joints without erosions seen in women who have born children\(^5^3\).

**Disease outcome**
In many cases the disease outcome is favorably, but approximately one third of the patients develop disabling deformities\(^2\) . A few studies showed that the outcome of AS can be predicted by several disease characteristics during the first ten years of AS\(^1^3^7-1^4^0\). Predictors of a severe outcome are hip arthritis, an increased erythrocyte sedimentation rate, (ESR > 30 mm/h), peripheral arthritis and a juvenile onset (≤16 years). The rate of radiological progression appears to be constant during the several decades of the disease duration and is not higher in the first decade as was previously thought\(^1^4^1\). However, most patients who have mild spinal restriction after the first decade of their disease do not progress to severe spinal involvement during later years. Because AS starts at a young age, the socioeconomic consequences are high. Apart from the physical complaints, many patients struggle with work
disability. This subject was recently studied by Boonen in the Netherlands\textsuperscript{142}. The age and sex adjusted risk of work withdrawal was 3 times higher in AS compared with the figures of the general Dutch population.

The stage of the disease at the time of diagnosis and the delay of appropriate treatment also influence the outcome of the disease. Women appear to have a later age of onset and a milder disease compared with men\textsuperscript{24-30}.

The majority of AS patients possess the HLA-B27 antigen (> 95%), which is found to be associated with the onset of the disease. The relationship of this antigen with disease severity of AS is less obvious. In HLA-B27-negative patients a later age of onset, and less frequent occurrence of acute anterior uveitis and less familial aggregation was described\textsuperscript{143}. Also, HLA-B27 homozygous individuals seem to develop a more severe disease compared with HLA-B27 heterozygotes\textsuperscript{144}.

There are conflicting data regarding mortality in patients with AS. One population-based study, showed no difference in mortality between males with AS and the general male population\textsuperscript{145}. Other studies indicated that mortality in AS patients seen at referral centers, was higher than expected with standardized mortality ratio’s (SMR) of approximately 1.7 (range 1.5-1.9) \textsuperscript{146-149}. This might be due to a linear relation observed between disease severity\textsuperscript{149} and mortality as well as associations found between disease duration and mortality\textsuperscript{150,151}. Among older patients X-ray treatment, which was used until 1960, might be a factor in the increased mortality risk of 4.8 due to leukemia and other types of cancer among these patients\textsuperscript{151}. 
Treatment

Non Steroidal Anti-Inflammatory Drugs (NSAIDs) and physical therapy seem to improve the long-term outcome of AS\textsuperscript{152,153}. However, the effect of Disease Modifying Antirheumatic Drugs (DMARDs) is less impressive compared with their effect in rheumatoid arthritis. In placebo-controlled trials, sulfasalazine showed some improvement of disease activity, especially in SpA patients with peripheral arthritis\textsuperscript{154,155}. Altogether the number of therapeutic options for AS is limited and other drugs, such as methotrexate, leflunomide or thalidomide, will be explored further in placebo-controlled trials\textsuperscript{156}.

However, the therapeutic possibilities in AS have changed since the introduction of biologicals, especially drugs that block the effect of the pro-inflammatory cytokine Tumor Necrosis Factor (TNF) alfa. After a few successful pilot studies with anti-TNF therapy (infliximab and etanercept) in AS, large placebo-controlled trials\textsuperscript{157,158} confirmed the efficacy of the biologicals in these patients in disease activity, as well as in regression of MRI-changes\textsuperscript{159}. These new therapies will undoubtedly change the outcome and prognosis of AS dramatically in the forthcoming years.
References


