# Axial spondyloarthritis

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## Abstract

In Europe and the USA, axial spondyloarthritis (AxSpA) affects approximately 1% of the general population. The term encompasses a wide spectrum of disease from modest sacroiliac inflammation only detectable by magnetic resonance imaging (MRI) to devastating disease with bony ankylosis. With characteristic X-ray changes, the term 'ankylosing spondylitis' (AS) is used. AS affects men three times more often than women, but AxSpA without X-ray changes affects men and women equally. Symptoms usually begin in the third decade of life with inflammatory back pain. The key pathological element is enthesitis, although the main diagnostic feature is sacroiliitis. Approximately one-third of patients develop peripheral lesions including oligoarthritis, heel enthesitis, iritis, inflammatory bowel disease and psoriasis. Vertebral osteoporosis is not uncommon, and cardiovascular disease and renal impairment can complicate severe AS. The diagnosis of AxSpA can be made on the basis of imaging or on clinical features alone. The cause(s) of AxSpA remain unknown, but genetic factors, including HLA-B27 and the interleukin (IL)-23 receptor, confer susceptibility; and a link with gut inflammation and microbiota is suspected. Treatment includes regular exercises and non-steroidal anti-inflammatory drugs; tumour necrosis factor (TNF) and IL-17 inhibitor drugs provide dramatic improvements in symptoms, function and quality of life.

**Keywords** Ankylosing spondylitis; axial spondyloarthritis; biologic therapy; diagnostic criteria; enthesitis; MRCP; treatment

## Key points

- The spectrum of axial spondyloarthritis, ranging from non-radiographic disease to severe ankylosing spondylitis, is now well recognized
- Enthesitis and osteitis, both of which are demonstrable on MRI, are the key pathological lesions representing active disease. Emerging evidence supports early recognition and treatment to improve long-term outcomes
- MRI scanning, using selected fat-suppressed (STIR) and T1 sequences offers the best objective guide to early diagnosis
- A variety of patient- and physician-reported disease activity scoring systems exist and should be used regularly to monitor progress and response to treatment; these include the Ankylosing Spondylitis Disease Activity Score, which provides useful gradations of disease activity
- Genome-wide association studies have identified multiple genetic loci, notably *ERAP1* and *IL23R*, that contribute to the development of ankylosing spondylitis in addition to HLA-B27
- Mechanisms of pathogenesis probably include roles for the gut microbiota and local mucosal immunity, a novel population of interleukin (IL)-23-dependent T cells resident in entheses, HLA-B27 metabolism, and the IL-23—IL-17 axis
- Tumour necrosis factor-inhibitor drugs are the mainstay of treatment of severe AS. IL-17 inhibition with secukinumab is equally effective, and new drugs, including both biologic agents and oral 'small molecules', are currently in clinical trials

## Introduction

Axial spondyloarthritis (AxSpA) is an aseptic inflammatory condition primarily affecting entheses and synovial joints in the spine, producing pain, fatigue and progressive spinal stiffness. Involvement of extraspinal sites is also common and can be especially disabling.

It is now recognized that AxSpA occupies a spectrum. Many patients have inflammation at the sacroiliac joints or elsewhere in the spine that is detectable by magnetic resonance imaging (MRI), but approximately half of these will develop radiographic sacroiliac joint and/or spinal changes. When radiographic changes at the sacroiliac joints are present, the term 'ankylosing spondylitis' (AS) is used. It is a life-long condition of adults that substantially impairs quality of life and work capacity, and can shorten life.

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AxSpA is a member of the spondyloarthritis (SpA) family, whose members share similar clinico-pathological features and genetic predisposition, notably an association with the HLA-B27 and other genes. Other members of this group are psoriatic arthritis, reactive arthritis and enteropathic arthritis. Undifferentiated forms of SpA also occur in both children and adults, although involvement of the spine tends not to occur until the late teenage years. The prevalence of AxSpA varies in different populations, according to the background prevalence of HLA-B27, being higher in some circumpolar regions and lower in some black African populations. The prevalence of AxSpA in the USA has been defined as 1.0—1.4%, and that of AS 0.52—0.55%.[1]

## Clinical features

AxSpA usually begins in the late teens or 20s, typically presenting with inflammatory back pain (Table 1).[2] Back pain and stiffness are usually worse after inactivity and can awaken the sufferer from sleep. Symptoms improve with movement, so exercise is usually helpful. Sacroiliitis often causes buttock pain that can radiate down the back or front of either or both thighs but not below the knee. Typically, symptoms affect one side for a period of weeks or months and then subside, only to be followed





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**Inflammatory spinal pain**[2]

**ASAS definition – spinal pain ≥3 months plus:**

- Onset <40 years of age
- Insidious onset
- Improvement with exercise
- No improvement with rest
- Pain at night (with improvement on getting up)

The criteria are fulfilled if four or five parameters are met.

**Table 1**

by similar symptoms on the other side. This is known as alternating buttock pain. In up to one-third of patients, the peripheral skeleton is affected.

Extra-articular sites, including the entheses and eyes, can also be involved; both can precede the spinal symptoms. Chest wall pain is also common, resulting from either costochondritis or referred pain from the thoracic spine. Fatigue is often a disabling symptom.

Male predominance is the rule when radiographic changes are present (ratio of 3:1), but in non-radiographic AxSpA (nrAxSpA), the sex ratio is equal. Morbidity in nrAxSpA is similar to that in established AS.

Poor quality of life and socioeconomic consequences are critically important. In AxSpA, reduced work capacity is associated with both personal and societal costs, and many sufferers have substantial difficulties with personal relationships and recreation.[3]

## Musculoskeletal features

**Enthesitis:** the key pathological lesion of AxSpA is enthesitis. Entheses are complex and variable structures at the junction between ligaments, joint capsules or tendons and bone. In the spine, entheses are affected at the attachment of joint capsules around facet joints and sacroiliac joints, at the discovertebral junctions and at the attachments of the interspinous ligaments.

Initially, inflammatory entheseal lesions may be detectable by MRI – although this is not always of sufficient sensitivity – as areas with a high water signal on fat-suppressed sequences (e.g.short tau inversion recovery (STIR)). Later, radiographs may show areas of decalcification ('erosions') that subsequently give place to new bone formation. Ultrasound scanning is increasingly used to identify peripheral entheseal lesions. Ossification of entheseal lesions leads to the process of ankylosis.

Peripheral enthesitis is a characteristic feature of AxSpA. Most commonly, the heel is involved. Achilles tendon enthesitis occurs at the point of attachment, in marked contrast to the thickening and pain higher up the tendon that is seen in athletes. Enthesitis is often associated with formation of an Achilles tendon bursa, seen best from behind with the patient standing. Involvement of the plantar fascia is also characteristic, with troublesome pain and the formation of a fluffy bony spur on X-ray. These changes can be impossible to distinguish from degenerative plantar fasciitis. Evaluation of the entheseal lesions can be performed using the Maastricht Ankylosing Spondylitis Enthesis Score (MASES) or the Leeds Enthesitis Index (LEI).

Dactylitis, usually affecting a single toe ('sausage toe'), results from multiple entheseal lesions, often with associated synovitis, and is highly suggestive of SpA (see Jacques and McGonagle in Further reading).

**Sacroiliitis:** this is often the cause of the presenting symptoms of buttock and/or thigh pain. It must be distinguished from mechanical pain referred to the same areas from the lumbosacral spine. Clinical signs are unreliable, and the diagnosis is best made by MRI; however, the sensitivity of MRI is limited by the relatively dynamic bone marrow changes, and distinction from degenerative change can be difficult. Typical appearances are of juxta-articular bone marrow oedema best seen on a STIR (or similar) sequence, with later fatty change also seen on T1 sequences. Diagnostic appearances are defined and well illustrated in the Assessment of SpondyloArthritis International Society (ASAS) handbook.[3]

Radiographic changes of sacroiliitis are graded as 0–4, but such changes take several months or years to become diagnostic. MRI scanning may allow detection of pre-radiographic change and hence facilitate early diagnosis.

**Spinal lesions:** radiographic changes occur late, but are highly specific, whereas MRI changes may be detected earlier but are less specific. Inflammatory lesions at the corners of vertebral bodies are characteristic; these appear as bone oedema or fatty change on MRI and as sclerotic 'shiny corners' on X-ray. In older adults, such changes of osteitis are relatively non-specific, although osteitis at the pedicle is strongly linked with AxSpA. Osteitis can occur around the facet joints and vertebral spines. Such changes can lead to new bone formation that is eventually visible on radiographs as syndesmophytes or bony obscuration of the facet and sacroiliac joints.[3] Spinal deformity with pronounced thoracolumbar kyphosis is not unusual among those severely affected, and the flexed posture can be aggravated by hip involvement. Deformity often leads to personal isolation as well as practical difficulties.

**Peripheral arthritis:** up to 30% of patients with AxSpA also develop peripheral arthritis. This is usually asymmetrical oligoarthritis affecting the hip, knee and metatarsophalangeal joints, in contrast to the symmetrical changes in rheumatoid disease. Synovitis is histologically non-specific, but MRI may demonstrate extensive entheseal lesions within the joint area.

## Extra-articular manifestations

The SpA family of conditions is characterized not only by the clustering of spinal and peripheral skeletal lesions but also by the co-occurrence of acute anterior uveitis (AAU; iritis), inflammatory bowel disease (IBD) and cutaneous and mucosal psoriasis. The link with these lesions is probably explained by common genetic factors.

**Uveitis:** AAU occurs in around 30% of people with AxSpA at some stage but is usually asynchronous with the clinical activity of other lesions. In unselected patients presenting with AAU, up to 50% have or develop other features of SpA. AAU is typically unilateral, causing pain, redness of the eye and photophobia. Onset is acute and, unless treatment is rapid, blindness can ensue. Prompt treatment normally leads to full resolution. In most instances, topical corticosteroid treatment is effective but in



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