



ANKYLOSING SPONDYLITIS

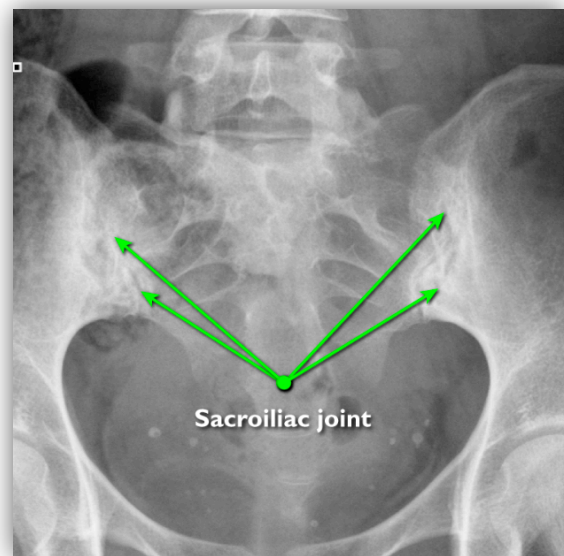
What is Ankylosing Spondylitis

Ankylosing Spondylitis (AS) is an inflammatory rheumatic condition that is one of a number of diseases that are characterised by inflammation of the spine termed Spondyloarthritis. The inflammation that occurs particularly affects the sites at which tendons or ligaments join onto bone. The most commonly affected region is the sacroiliac joints, which is where the spine joins onto the pelvis. However, any joint can be affected and, in addition, sites where tendons join onto bone are also commonly involved, such as the insertion of the Achilles tendon into the calcaneus (heel bone). Furthermore, inflammation can occur at other organs in addition to the musculoskeletal system, such as at the eye, intestines, and lungs.

“Ankylosing Spondylitis is the most common of the Spondyloarthritides”

AS afflicts a small proportion of the population, estimated at about 0.5%, but is commonly under recognized in those suffering with back pain. Consequently, the average time to diagnosis can be quite long, which some have estimated to be as long as 5-7 years. The ability to diagnose this condition early continues to be a significant challenge despite the fact that the disease has been present in humans for thousands of years, as shown in the remains of three Egyptian pharaohs, and the first specific description of the disease being published in 1693. Therefore, a current focus in Ankylosing Spondylitis is how to identify those suffering with the condition at an earlier point in their disease

course, at which time the condition is termed axial Spondyloarthritis.



X-ray of the sacroiliac joints showing joint space narrowing, erosive change and indistinct margins, due to sacroiliitis. Image courtesy of Anatomate-Apps

Spondyloarthritis encompasses a group of conditions that share the common clinical manifestation of inflammatory back pain. These conditions include Ankylosing Spondylitis, Reactive Arthritis, Psoriatic Arthritis, and Enteropathic-associated arthritis. There are differences between these conditions that may not be evident early in the disease and only become apparent overtime. However, the emphasis in this early phase of the condition is to determine the presence of an inflammatory spinal disease, rather than differentiating between these specific conditions.

Ankylosing Spondylitis is the most common of the Spondyloarthritides. The condition is symptomatically more common in men, with the usual age of onset being in the 3rd and



4th decades of life (average age at onset is 26 years). It is unusual for the disease to commence after the age of 50. Overall, AS is more common in the Caucasian population. There is a familial predisposition to the disease, whereby the risk of developing AS is increased if a first-degree relative is affected, especially if HLA B27 (a genetically determined cellular marker) is present.

“Ankylos – Greek (Gr) for stiffening; Spondylos – vertebra (Gr); itis – inflammation (Gr)”

The consequence of the inflammation present within the spine and other musculoskeletal structures is subsequent uncontrolled increase in bone formation that results in stiffening and ultimately fusion of the joints. It is this process that gives the condition its name of *Ankylos* – Greek (Gr) for stiffening; *Spondylos* – vertebra (Gr); *itis* – inflammation (Gr). The fusion that occurs in the spine commonly causes the affected to have a stooped (flexed hip) posture that ultimately has a significant impact upon their ability to look forward and walk.

What causes Ankylosing Spondylitis?

The exact cause of Ankylosing Spondylitis has not yet been specifically established. However, a genetic component seems to be particularly important. This relates to the presence of Human Leukocyte Antigen (HLA) B27 in a high proportion of patients with Ankylosing Spondylitis. HLA B27 is a protein that is present on the surface of certain cells, where it has an important role in the action of the immune system. The function of HLA B27 is to display antigenic peptides, which is in effect debris from oneself

or from external insults (such as infection), to T cells that are very important in determining what immune response is necessary to these potential threats. The type of HLA present is genetically determined by chromosome 6.



X-ray of the lumbar spine (anterior view) showing fusion of the vertebrae, also called bamboo spine. Image courtesy of Anatomate-Apps.

HLA B27 is strongly associated with Ankylosing Spondylitis and to a lesser extent the other Spondyloarthritides. However, the exact mechanism relating HLA B27 with these diseases has not been determined. Although, interestingly, those who are HLA B27 positive are more likely to develop iritis, have an earlier onset of disease, and be diagnosed earlier with AS compared to their counterparts who are HLA B27 negative.



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Nevertheless, this marker is present in 90-95% of those with AS, which is higher compared to those with Reactive arthritis, Enteropathic spondyloarthritis or Psoriatic spondyloarthritis where HLA B27 is present in 75%, 60%, and 50% respectively. The difficulty in understanding the role of HLA B27 is the fact that it is present in a significant proportion of the population who never develop an inflammatory spinal disease.

The prevalence of HLA B27 varies significantly, depending upon the population studied. In the Australian context, 8-12% of the population is HLA B27 positive, compared to 0.1-0.5% in the Japanese and up to 24% in the northern Scandinavian communities. It appears that the prevalence of HLA B27 in a community is related to the distance from the equator, with the highest rate furthest away such as in Northern Europeans with the least in sub-Saharan Africa.

However, as previously mentioned, the prevalence of AS in Australia is at most about 0.5%, highlighting that only a small proportion of those who are HLA B27 positive proceed on to develop the disease. That is, only 5-8% of those with HLA B27 will develop AS, so it seems that HLA B27 in itself is not the sole mediator in the development of the disease. As a result, the utility of testing for the presence of HLA B27 has been questioned, since neither a positive or negative test will be definitive in ruling the disease in or out. However, in a population with the early manifestations of an inflammatory spinal disease, assessing whether HLA B27 is present is thought to be useful and has therefore been included in the criteria for identifying axial Spondyloarthritis.

Although HLA B27 is the most important genetic aspect of the disease, there is active interest in other genetic factors. The most interesting of these identified at present is the Interleukin-1 (IL-1) gene cluster, which relates to a very important messenger that promotes inflammation called Interleukin-1. The CYP 2D6 gene is another genetic factor, but this seems to be only weakly associated with the disease.



X-ray of the lumbar spine (lateral view) showing bony projections called syndesmophytes (bridging and non-bridging). Image courtesy of Anatomate-Apps.

Familial studies have confirmed the importance of genetics in the development of AS, since the risk of developing the disease is significantly increased if a first-degree relative is affected. That risk has been estimated from 12-20%.

Although, the susceptibility for AS has a strong genetic component, other factors are necessary for the development of the disease. The nature of these other factors has not been definitively proven, but the most likely environmental agent



thought responsible is infection. However, it is not known which specific infection triggers the onset of AS. The most likely culprit is either an intestinal or urinary pathogen (bacteria). The sexually transmitted infections, Chlamydia Trachomatis and Neisseria Gonorrhoeae are the common organisms responsible for Reactive arthritis, which is related to AS.

Therefore, the concluding remark regarding the cause of Ankylosing Spondylitis as we understand it at present is that it likely relates to an unknown environmental trigger, most likely an infection, occurring in a genetically predisposed host.

How is Ankylosing Spondylitis diagnosed?

There is no one single test that is able to diagnose AS. Instead the diagnosis is derived from a combination of clinical and radiological features. This has led to a number of criteria that have aimed to be most specific in identifying those affected with the disease. The most commonly used criteria were created in New York, which were modified in 1984. The criteria includes:

1. Clinical criteria

- a. Low back pain and stiffness for more than 3 months which improves with exercise, but is not relieved by rest
- b. Limitation of motion of the lumbar spine in both the sagittal (front-back) and frontal planes (side-side) – which refers to the direction of movement
- c. Limitation of chest expansion relative to normal values corrected for age and sex – which reflects the degree of movement in the midback where it joins onto the rib cage.

2. Radiologic criteria

Sacroiliitis on radiographs

Definite AS is diagnosed if the radiologic criteria is satisfied with the presence of at least 1 clinical criterion.

Probable AS is diagnosed if;

- I. Three clinical criteria are present
- II. Radiologic criterion present without any signs or symptoms satisfying the clinical criteria

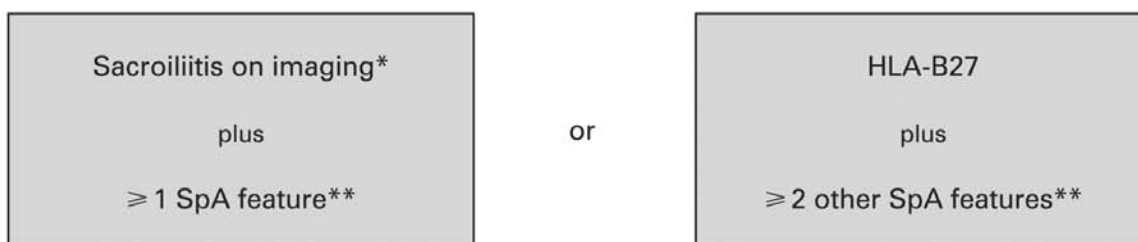
The main aim of these diagnostic criteria, such as the modified New York criteria, is to ensure a uniform population of patients with AS for the purpose of research. Consequently, such an approach to diagnosis is unlikely to identify patients with early disease because of the need to have limitation of motion and the presence of radiological change, both of which often requires a significant amount of time to develop. Therefore, recent interest has focused on how to identify patients in the early phase of their illness.

In this regard the Assessment of SpondyloArthritis international Society (ASAS) developed criteria for the diagnosis of Axial Spondyloarthritis, which defines the scenario when an inflammatory spinal disease is present that does not fulfill the criteria for a specific subtype. The criteria is presented below (Published by Rudweleit et al 2009 *Annals of Rheumatic disease* 68: 777-783);



ASAS classification criteria for axial SpA

(in patients with back pain \geq 3 months and age at onset < 45 years)



** SpA features:

- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's disease/ulcerative colitis
- Good response to NSAIDs
- Family history for SpA
- HLA-B27
- Elevated CRP

* Sacroiliitis on imaging:

- Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- or
- Definite radiographic sacroiliitis according to mod. New York criteria

Sensitivity 82.9%, specificity 84.4%; n = 649 patients with chronic back pain and age at onset < 45 years. Imaging arm (sacroiliitis) alone has a sensitivity of 66.2% and a specificity of 97.3%.

** Note: Elevated CRP is considered a SpA feature in the context of chronic back pain

In this criterion, imaging includes the use of MRI scanning, which is able to demonstrate inflammation at the affected joints. The advantage of this approach is that patients can be identified early, prior to the onset of any structural damage, such that treatment can be commenced with the aim of retarding or ideally preventing the long-term sequel of the disorder. This is further emphasized by the fact that a large proportion of disease progression and functional loss occurs in the first ten years of the disease.

There are a number of other investigations that are useful for the Rheumatologist in the assessment of Ankylosing Spondylitis and the related disorders, even though these may not be necessary or useful in the diagnosis. Of these, the inflammatory markers are worthy of mention. The markers of inflammation that are most commonly measured are the C-Reactive Protein (CRP) and the Erythrocyte Sedimentation Rate (ESR). These measures are elevated at some time in the course of the disease in 50-70% of patients, which may but not always correlate with disease activity. As such, these tests may have a limited role in the



diagnosis and monitoring of the disease. It seems that these tests are most useful in those patients who have an arthritis affecting joints other than the spine. In addition, ultrasound evaluation, especially with Power Doppler, has proven useful when assessing for inflammation at the sites where tendons join onto bone, called entheses, especially when that inflammation is not clinically apparent. However, ultrasound has not been of much use in the evaluation of spinal symptoms.



MRI of the sacroiliac joints showing bone marrow oedema and irregularity of the joint margins, due to sacroiliitis. Image courtesy of Anatomate-Apps

What are the signs and symptoms of Ankylosing Spondylitis?

Ankylosing Spondylitis usually presents with inflammatory spinal pain and stiffness. The most common site of spinal involvement is the sacroiliac joints, with the thoracic spine (midback), lumbar (low back) and cervical spine (neck) becoming affected as the

disease progresses. What defines inflammatory back pain has been debated for many years. Most recently the Assessment of SpondyloArthritis international Society (ASAS) suggested that the following features of back pain are most suggestive of an inflammatory spinal disease, such as AS;

1. Age at onset <40 years
2. Insidious onset
3. Improvement with exercise
4. No improvement with rest
5. Pain at night with improvement upon getting out of bed

When at least 4 of these 5 features are present, the back pain is essentially related to inflammation of the spine. A number of other features have also been considered suggestive of inflammation at the spine and sacroiliac joints, such as;

1. Duration of back pain extending beyond 3 months
2. Morning stiffness lasting more than 30 minutes
3. Alternating buttock pain
4. Waking during the second half of the night only



Overtime the spine progressively stiffens as inflammation settles and extra bone formation develops. This results in a loss of motion and often deformity, especially in the spine where the patient develops a stooped flexed hip posture. This can make it difficult to perform usual daily activities such as walking. Loss of movement and deformity is usually a late manifestation of the disease.

AS Patient with Disappearance of the Lordosis of the Lumbar Spine



ASAS Educational Slide Kit (<http://www.asas-group.org/education.php?id=04>)

In addition to inflammation at the spine, those affected with AS and the related condition also develop inflammation at the entheses, which is the site where tendons or ligaments join onto bone. This is termed enthesitis. The most common sites of involvement include the insertion of the Achilles tendon and the Plantar fascia on the calcaneus (heel bone). A special type of enthesitis, where tendons and ligaments of the fingers or toes are involved is termed Dactylitis. This can also be referred to as 'sausage' fingers or toes because of the appearance.

Arthritis of joints not involving the spine can also occur, termed peripheral arthritis. This can occur in up to 20-50% of patients. This is less commonly the case in AS compared to the other SpondyloArthritides, which when present often affects a small number of joints in an asymmetrical pattern, with the most commonly affected joints being the hips and knees.

AS can also be associated with inflammation affecting other body organs in addition to joints. The most common extra-articular manifestation of the disease is acute anterior uveitis, which occurs in up to 20-30% of patients. This usually presents with a sudden onset of eye pain that is often accompanied by visual changes, sensitivity to light, and increased lacrimation (tears). The development of such symptoms should prompt an urgent referral to the ophthalmologist.

Less common extra-articular problems in AS include insufficiency of the aortic valve due to aortitis, disturbance in the conduction of electrical signal in the heart, inflammation of the lung termed pneumonitis, and rarely secondary amyloidosis where abnormal insoluble proteins are deposited in various bodily tissues.

Finally, AS is a systemic disease and as such fatigue is often reported. Less commonly fever and weight loss can occur, especially during periods of very active disease.

How do we treat Ankylosing Spondylitis?

There have been recent significant advances in the management of Ankylosing Spondylitis, predominantly with regards to the pharmacological treatments available. However, the most important aspect of management is commencing treatment as



early as possible in the course of the disease, with the aim being to retard or prevent the natural history of the disease. This generally follows a chronic relapsing and remitting course, resulting in joint damage or fusion leading to an impairment of function. Early treatment is particularly important, since the large proportion of damage related to the disease occurs in the first ten years following the onset of the condition.

Enthesitis (Insertion of Achilles Tendon at Calcaneus) Right Heel



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(<http://www.asas-group.org/education.php?id=04>)

Treatment of AS is essentially divided into two groups, which are not mutually exclusive but rather are often used in conjunction with each other. These include non-pharmacological modalities, which is predominantly in the form of exercise, and pharmacological treatments, that traditionally has included anti-inflammatory with the recent addition of biological agents that specifically target the drivers of inflammation.

The major component of non-pharmacological therapy is exercise, which is a cornerstone of treatment of AS. This has been shown to reduce pain and stiffness, increase mobility and

function, and have a positive effect on mood, attitude, health, and quality of life. In addition, a major aim of exercise is to slow the progression to ankylosis. The evidence in the scientific literature supports the use of exercise that is based on strengthening, stretching, and aerobic fitness. This can be performed either individually or as part of a group exercise session. A physiotherapist/physical therapist with experience in the management of AS is best placed to prescribe an exercise program that is most appropriate for each individual, which may include water based activity such as hydrotherapy or swimming. Land based exercises that include high impact, such as jumping and contact sport should probably be avoided in the initial stages of treatment.

The pharmacological approach to managing the disease has predominantly focused on symptom control, and the first line therapy to achieve this aim in patients with AS has been the non-steroidal anti-inflammatory medications, termed NSAIDs. There are a large number of NSAIDs available, some of which can be purchased without prescription from the local pharmacy or supermarket. However, discussing the medication with your doctor is important prior to their use as there are a number of potential complications/harms that need to be considered.

Nevertheless, these medications have been shown to be quite effective in reducing the pain associated with the disease, allowing those affected to participate in the exercise program as described above. In fact, the response to NSAID therapy can in itself be a further clue to the diagnosis of an inflammatory spinal disease and can predict to some degree the likely course of the disease. Patients with AS have generally found that taking NSAIDs in the evening is most helpful in managing their nocturnal



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and early morning symptoms, which is usually the time of day that is most troublesome. Interestingly, there is a suggestion that NSAIDs, when used continuously rather than on-demand, may have an effect in reducing the radiological progression of the disease independent of its effect on the symptoms of the disease.

Oral corticosteroids have not demonstrated a significant long-term benefit in the management of AS and therefore has little role in management, particularly given the number of potential side effects associated with long-term use of the medication. However, corticosteroid injections can be useful in managing inflammation in the short term, especially for enthesitis, peripheral arthritis, and sacroiliitis. Steroids, though, do play a major role in treating the potentially serious extra-articular manifestations, such as acute anterior uveitis where they are often given as topical therapy in the form of eye drops.

Disease Modifying Anti-Rheumatic Drugs (DMARDs) have been disappointing in the treatment of spinal inflammation. However, they do have a role in the treatment of peripheral arthritis that can occur with the disease and in other rheumatic diseases such as Rheumatoid arthritis. The most commonly used DMARDs in AS have been Salazopyrin and Methotrexate.

The most exciting recent advance in the treatment of AS and the related Spondyloarthritides has been the emergence of the TNF α inhibitors. TNF α is a chemical messenger (cytokine) that has been shown to be an important factor in driving the inflammation seen in these conditions. Medications have been developed that are able to specifically inhibit the action of this cytokine, which are termed biological Disease Modifying Anti-Rheumatic Drugs (bDMARDs). Those currently licensed in Australia for use in AS

include Infliximab (Remicade), Etanercept (Enbrel), Adalimumab (Humira), and Golimumab (Simponi). These are delivered via either an intravenous infusion or sub-cutaneous injection every 1, 2, 4, or 6 weeks depending on which medication is chosen.

These medications have proven very effective in managing most aspects of the disease, including many of the extra-articular manifestations of the disease such as uveitis. They have shown a positive effect on disease activity and function, with 50% of patients reporting a 50% improvement in a composite outcome measure. These are expensive medications and as such subsidised therapy is only available for those with severe AS that has not responded to NSAID therapy and exercise, where radiological evidence of sacroiliitis is present and the inflammatory markers are raised.

There are potential complications associated with the use of these medications, particularly infection, and as such prior to treatment patients are tested for the presence of past or current Tuberculosis and both Hepatitis B and C as well as HIV. Therefore, at present, Rheumatologists alone are permitted to prescribe these medications for the treatment of AS.