The introduction of TNF inhibitor biologic drugs has dramatically changed the treatment of ankylosing spondylitis (AS). In spite of this, many patients still fail to achieve optimal outcomes, largely because of delayed or failed diagnosis. Estimates of the prevalence of AS vary but it is likely that the prevalence in the UK adult population is approximately 0.2%.\(^1\) Men predominate, but with a sex ratio of 3:1, it is not the much higher ratio that was once thought to apply. Thus a Trust serving 500,000 adults should expect that 1000 people with AS live within the area. To this must be added others with related forms of spondyloarthritis and an unknown number of undiagnosed cases.

## Diagnosis

AS is conventionally diagnosed using the modified New York Criteria\(^1\) (Van der Linden 1984), which include radiographic evidence of sacroiliitis.

It is now clear that in some patients, especially early in the course of AS, radiographic changes are not apparent. In reality, there is a spectrum of disease ranging from inflammatory symptoms in the absence of radiographic changes to end-stage disease with extreme, irreversible X-ray changes and complications.

Since the diagnostic criteria for AS require radiographic changes, the whole spectrum has been named “Axial Spondyloarthritis (SpA)”.\(^2\) Diagnostic criteria for Axial SpA have not yet been agreed but classification criteria have been established by the Assessments of Ankylosing Spondylitis (ASAS) International Society and are included in Box 1 and 2.

### Recognition of Axial SpA and AS

#### Key symptoms

Onset of AS is usually in the late teens and twenties with buttock or back pain, which may be episodic and associated with sacroiliitis, morning stiffness and fatigue. Since back pain is such a prominent early feature of Axial SpA, the critical step in early diagnosis is recognition of characteristic inflammatory features. These characteristics are referred to as inflammatory back pain (IBP) and are outlined in Box 3 along with the key contrasting features of mechanical back pain. Differentiation of IBP from mechanical back pain (MBP) is critical. Up to 50% of younger adults (age <40 years) with pain for more than three months will have IBP though the proportion in older adults is much less. Most IBP sufferers will not turn out to have AS but this is an effective filter to apply to patients with back pain.

A few patients develop AS in mid-adult life and in others the diagnosis is only made in old age as a result of a fortuitous X-ray or a spinal fracture due to rigidity and fragility of the spondylitic spine.

Approximately 50% of AS sufferers have involvement of peripheral joints, particularly the hip and knee or entheses. The Achilles’ tendon and plantar fascia calcaneal insertion are typical sites. In younger teenagers with juvenile spondyloarthritis spinal involvement is rare; instead, presentation with knee swelling or comorbidity is usual. Both axial and peripheral symptoms are often associated with marked fatigue.

Up to 40% of people with SpA/AS experience at least one episode of acute anterior uveitis (AAU) and a smaller proportion have psoriasis.
Box 1: Modified New York Criteria1 for the diagnosis of AS

1. Clinical
- Low back pain and stiffness >3 months, which improves with exercise and not relieved by rest
- Limitation of lumbar spine in both sagittal and frontal planes
- Limitation of chest expansion relative to normal for age and sex

2. Radiological
- Bilateral sacroiliitis >grade 2
- Unilateral sacroiliitis >grade 3 or 4

Grade 0 = normal
Grade 1 = suspicious
Grade 2 = sclerosis, some erosions
Grade 3 = severe erosions, widening of the joint space, some ankylosis
Grade 4 = complete ankylosis

AS is present if the radiological criterion is associated with at least one clinical criterion.

Box 2: ASAS classification criteria for Axial SpA3,4

ASAS criteria of diagnosis
1. Sacroiliitis on imaging plus one SpA feature
   OR
2. HLA B27 positive plus 2 SpA features

SpA features
- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn’s/collitis
- Good response NSAIDs
- Family history of SpA
- Raised CRP
- HLA B27

Sacroiliitis on imaging
- Active inflammation on MRI suggestive of sacroiliitis associated with SpA
   OR
- Definite radiographic sacroilitis according to modified NY criteria.

Diagnostic investigations
In most but not all patients, active disease is reflected by an increased acute phase response. The HLA B27 gene is present in 95% of patients with typical AS but in a lower proportion of Axial SpA patients. The detection of this gene in people with IBP has diagnostic and prognostic value. Recognition of spinal inflammation requires appropriate spinal imaging. Plain radiographs may remain normal up to 7–10 years after the onset of axial SpA6 so that radiography is of limited value in early diagnosis. In suspected early disease, magnetic resonance imaging (MRI) is therefore the investigation of choice. At minimum, views of the SI joints with T1, T2 and STIR (fat-suppressed) sequences are desirable.7 The more extensive the spinal scan the greater the likelihood of detecting diagnostic inflammatory lesions

or inflammatory bowel disease. A personal or family history of these may be valuable clues to the diagnosis. Thus a careful history is essential both to identify IBP as a first step to diagnosis and to detect characteristic axial SpA comorbidities, which may greatly enhance the diagnostic likelihood.

Physical findings
Physical examination may reveal restricted spinal segments although in early disease mobility may be normal. Tenderness on pressure over the sacrum may indicate sacroilitis though clinical assessment is insensitive. Peripheral enthesitis, commonly affecting the Achilles’ tendon and plantar fascia insertions at the calcaneum, the patella, tendon insertion on the tibial tubercle and around the pelvis, affects 50% of patients at some point. Costovertebral and sternal tenderness is common and may cause both pain and anxiety. Reduced chest expansion (<2.5cm) may cause breathlessness on exertion. Aortic regurgitation affects 1% of patients with AS, though electrocardiographic and echocardiographic anomalies are more common.5

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but individual spinal lesions may be indistinguishable from degenerative or malignant change. Subsequent structural changes detectable by plain radiography include sacroiliitis, vertebral squaring, syndesmophytes and obliteration of facet joints. The lesions underpinning the radiological appearances are principally enthesitis and osteitis. Doppler ultrasound may be helpful for assessment of enthesitis. The investigation of AS is well described in the ASAS Handbook. Genetics and aetiology

AS appears to result from a combination of genetic and environmental factors. Twin studies show that monozygotic twins have a 63% concordance rate whereas that in dizygotic twins is only 24%, indicating a polygenic background. HLA-B27 remains the strongest genetic association, almost all allotypes of HLAB27, (there are more than 40) predisposing to AS but ongoing genetic studies have revealed likely links within genes in the IL-1, IL-17, IL-12, IL-23R and ARTS-1/ERAP-1 regions. Potential mechanisms by which genetic factors lead to AS are discussed elsewhere. A role for gut bacteria has been suggested by both animal and human studies but no clear pathogenic mechanism has been demonstrated.

Measurement of disease characteristics

A number of compound indices have been devised for the measurement of aspects of AS. Of these, the most commonly used are listed below.

Management

Good management of AS involves timely and appropriate treatment of each element of the disease present in the individual. Thus, treatment should be targeted specifically at spinal disease, peripheral disease, enthesitis, comorbidities and associated features, always bearing in mind the need to maintain quality of life, capacity for work and well-being. The management of comorbidities, especially acute anterior uveitis, psoriasis and inflammatory bowel disease is critically important but is outwith the scope of this article.

Exercise

Regular spinal exercise, whether in the form of sport, approved gym exercises or a regime of stretches each morning, is vital both for the antagonism of ankylosis and for maintaining well-being. Physiotherapy is crucial to the planning of regular exercise and in sustaining what is often a demanding and irksome routine; breathing exercises and spinal stretching should be incorporated into a daily routine lifelong.

The National Ankylosing Spondylitis Society (NASS) provides regular exercise or hydrotherapy sessions at locations throughout the country and also has recently published a new handbook and iphone app of gym exercises (www.nass.co.uk/exercise). Swimming and pilates are often helpful.

NSAIDs

Non-steroidal anti-inflammatory drugs remain the first-line medical treatment. Commonly used agents include naproxen, ibuprofen and diclofenac and the cox-2 selective anti-inflammatories such as celecoxib and etoricoxib. Long acting preparations have significant advantages in terms of providing overnight comfort and reduced morning stiffness. Patients vary in responsiveness to individual NSAIDs, so finding the right NSAID and prescribing it at an adequate dosage is important. Experience with rofecoxib (Vioxx) has given appropriate prominence to potential dose-related cardiovascular toxicity of all NSAIDs and has been
Box 4: Measurement tools of AS

<table>
<thead>
<tr>
<th>Measurement tool</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASDAI</td>
<td>Disease activity</td>
</tr>
<tr>
<td>BASMI</td>
<td>Measurement of spinal</td>
</tr>
<tr>
<td></td>
<td>movements</td>
</tr>
<tr>
<td>BASFI</td>
<td>Function</td>
</tr>
</tbody>
</table>

Biologic (TNF-inhibitor) therapy

The introduction of TNF inhibitor therapy has revolutionised the management of AS. Several anti-TNF agents are licensed in the UK for treatment of ankylosing spondylitis but only etanercept, adalimumab and golimumab are approved for usage by NICE (NICE technology appraisal guidance 143 and TA233).

Treatment of patients with AS with TNF inhibitor drugs in the UK should be in accordance with NICE guidelines (Box 5).

Adalimumab and golimumab are human monoclonal antibodies binding to TNF alpha and etanercept is a fusion protein, which binds to the TNF receptor.

Although not NICE-approved for AS treatment in the UK, due to cost, infliximab is widely used throughout Europe and has been investigated in many clinical trials. TNF blocking drugs appear to share class effect with regard to both efficacy and toxicity though possible variations in toxicity and drug survival have become apparent.

Remission is unusual but 30% of patients develop partial remission after three to six months of treatment. On stopping treatment, however, most patients relapse. Approximately 10% of patients per year fail treatment due to loss of efficacy or toxicity. Switching to a second anti-TNF agent may be beneficial but costly and is not currently recommended by NICE.

The key side effects of anti-TNF drugs concern immunosuppression. Screening for TB (as per British Thoracic Society guidelines) prior to initiating treatment is mandatory, as latent TB may be activated once the patient is immunosuppressed; exclusion of viral hepatitis and HIV infection in at risk individuals is also necessary. In AS there is thus far no evidence of increased tumour risk. TNF blockers should be used cautiously in patients with NYHC stage 3 and 4 heart failure as preliminary evidence suggested that treatment may be linked to higher mortality.

Spinal surgery

Up to a third of patients with AS have hip involvement and many of these come to hip replacement, often later requiring revision surgery. Other large joints, especially the knee may also fail and require surgical treatment.

DMARDs and corticosteroids

DMARDs are not effective in spinal disease and are not indicated for its treatment.

Oral corticosteroids may provide symptomatic relief for active spondylitis but may aggravate osteoporosis in AS. Intramuscular corticosteroid injections may also be considered when spinal or peripheral symptoms are severe especially before a rehabilitation programme and CT guided injections into the sacro-iliac joints may be valuable when other treatment modalities cannot be used or are ineffective.
Box 5: Nice guidelines for anti-TNF therapy

1. Patient’s disease must satisfy modified New York criteria for the diagnosis of ankylosing spondylitis
2. There is confirmation of sustained active spinal disease as evidenced by:
   - Score of at least 4 units on BASDAI index
   - At least 4cm on visual analogue scale (0–10cm)
   - These should be demonstrated on two occasions 12 weeks apart without any change in treatment
3. Conventional treatment with two or more NSAIDS has failed to control the symptoms.

Surgery to the spine may be immensely valuable for a small minority of patients but should only be undertaken by a specialist team with appropriate anaesthetic and post-operative care and high patient care throughout. Spinal surgery should be considered in patients with severe spinal flexion deformity who are unable to make eye contact or find difficulty with balance or field of vision. Correction of hip flexion deformities may also improve posture. With careful selection of both patients and technique \(^1\) the risks of surgery have reduced in recent years and patient satisfaction is high.\(^2\)

Treatment of peripheral spondyloarthritis

In addition to the symptomatic benefit of NSAIDs, sulfasalazine may be helpful in the treatment of peripheral spondyloarthritis.\(^17,23\) Methotrexate is often used as in rheumatoid arthritis but without the convincing supportive data. Oral corticosteroids may provide symptomatic relief for active peripheral spondyloarthritis but may aggravate osteoporosis in AS.\(^17\) Intra-articular steroid injections may be helpful and local injection treatment is often the treatment of choice for peripheral monoarthritis. TNF blockade treatment is also effective and appropriate for peripheral arthritis though most trial data have focused on axial disease. Persistent painful enthesitis may be a challenging clinical problem. For heel enthesitis conservative measures such as corrective insoles and stretching exercises may be used but in non weight-bearing sites local steroid injections may be helpful. NSAIDs may provide some relief and TNF blockade has been shown to be effective in severe refractory cases.\(^24\) The potential benefits and risks of the various treatment modalities are summarised in box 6.

Adjunct medical treatment

**Bisphophonates**

In addition to their value in treatment of post-menopausal osteoporosis, oral and intravenous bisphophonates have been used in the treatment of AS.\(^25\) Evidence of benefit is slight and their place in the treatment of AS and associated osteoporosis is not clear currently.

**Tricyclics**

Low dose tricyclics such as amitriptyline and nortriptyline may be valuable adjuncts in the reduction of sleep disturbance and associated fibromyalgic symptoms.

Assessing prognosis

Assessment of the prognosis is an important part of treatment planning. The presence of peripheral joint involvement, young age of onset, elevated acute phase response, hip involvement, smoking and poor response to NSAIDs predict poor outcome.\(^27,28\) Presently there is a dearth of prognostic biomarkers though degree of intensity of sacroiliitis on initial MRI scan may predict the subsequent fulfilment of modified New York Criteria for AS.\(^29\)

Referral

All adult patients under 40 years with back pain of more than three months should be assessed for IBP. Those with IBP should be asked about linked factors, including family history or history of SpA comorbidities. In these individuals consideration should be given to the possibility of a spondyloarthritis and referral to a rheumatologist.
### Box 6: Overview of treatment modalities in spinal disease of AS

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Exercise</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintain spinal mobility</td>
<td>Maintain spinal mobility</td>
<td>Time management</td>
</tr>
<tr>
<td>Maintain good posture</td>
<td>Maintain good posture</td>
<td>Lack of motivation</td>
</tr>
<tr>
<td>Delay disease progression</td>
<td>Delay disease progression</td>
<td>Injury</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Quality of life</td>
<td></td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td><strong>Exercise</strong></td>
<td><strong>Time management</strong></td>
</tr>
<tr>
<td>Readily available first-line agent</td>
<td>Readily available first-line agent</td>
<td>Lack of motivation</td>
</tr>
<tr>
<td>Effectively reduce joint pain and stiffness by at least 20%[^26]</td>
<td>Effectively reduce joint pain and stiffness by at least 20%[^26]</td>
<td>Injury</td>
</tr>
<tr>
<td>Promote sleep efficacy</td>
<td>Promote sleep efficacy</td>
<td></td>
</tr>
<tr>
<td>Ability to maintain exercise regime</td>
<td>Ability to maintain exercise regime</td>
<td></td>
</tr>
<tr>
<td>Improve quality of life</td>
<td>Improve quality of life</td>
<td></td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td><strong>Corticosteroids</strong></td>
<td><strong>Gastrointestinal side effects</strong></td>
</tr>
<tr>
<td>Suppression of inflammation</td>
<td>Suppression of inflammation</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Symptom relief</td>
<td>Symptom relief</td>
<td>May cause wheezing or worsen asthma symptoms</td>
</tr>
<tr>
<td>Allows full benefit of rehabilitation programmes</td>
<td>Allows full benefit of rehabilitation programmes</td>
<td>Skin reactions</td>
</tr>
<tr>
<td><strong>TNF blockade</strong></td>
<td><strong>TNF blockade</strong></td>
<td>Interaction with warfarin</td>
</tr>
<tr>
<td>Reduce inflammation and symptoms</td>
<td>Reduce inflammation and symptoms</td>
<td>Antagonism/synergism with aspirin</td>
</tr>
<tr>
<td>Improve quality of life</td>
<td>Improve quality of life</td>
<td></td>
</tr>
<tr>
<td>Maintain/improve work capacity</td>
<td>Maintain/improve work capacity</td>
<td></td>
</tr>
<tr>
<td>Generally well-tolerated</td>
<td>Generally well-tolerated</td>
<td></td>
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<tr>
<td><strong>Surgery</strong></td>
<td><strong>Surgery</strong></td>
<td><strong>Short term side effects include</strong></td>
</tr>
<tr>
<td>Correct deformities</td>
<td>Correct deformities</td>
<td>headache, insomnia, mood changes</td>
</tr>
<tr>
<td>Increase functional ability (regain use of joints)</td>
<td>Increase functional ability (regain use of joints)</td>
<td>Long-term use results in osteoporosis, acne, water retention, hypertension, diabetes mellitus,</td>
</tr>
<tr>
<td>Relieve pain</td>
<td>Relieve pain</td>
<td>adrenal suppression</td>
</tr>
<tr>
<td>Improve quality of life</td>
<td>Improve quality of life</td>
<td></td>
</tr>
<tr>
<td>Improved self-confidence</td>
<td>Improved self-confidence</td>
<td></td>
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<tr>
<td><strong>Side effects:</strong></td>
<td><strong>Side effects:</strong></td>
<td><strong>Side effects:</strong></td>
</tr>
<tr>
<td><strong>TNF blockade</strong></td>
<td><strong>TNF blockade</strong></td>
<td>Skin irritation, allergic reaction, nausea</td>
</tr>
<tr>
<td>Side effects: skin irritation, allergic reaction, nausea</td>
<td>Side effects: skin irritation, allergic reaction, nausea</td>
<td>Lymphoma</td>
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<tr>
<td>Lymphoma</td>
<td>Lymphoma</td>
<td>Systemic and local infections, especially TB</td>
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<td>Systemic and local infections, especially TB</td>
<td>Systemic and local infections, especially TB</td>
<td>Heart failure (contraindication)</td>
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<td>Heart failure (contraindication)</td>
<td>Heart failure (contraindication)</td>
<td>Induction of auto antibodies</td>
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<tr>
<td>Induction of auto antibodies</td>
<td>Induction of auto antibodies</td>
<td>Possible demyelinating disease</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td><strong>Surgery</strong></td>
<td><strong>Anaesthetic risk</strong></td>
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<tr>
<td>Anaesthetic risk</td>
<td>Anaesthetic risk</td>
<td>Post-op complications such as pain, infection, technical failure</td>
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<tr>
<td>Post-op complications such as pain, infection, technical failure</td>
<td>Post-op complications such as pain, infection, technical failure</td>
<td>Paralysis in spinal surgery</td>
</tr>
<tr>
<td>Improved self-confidence</td>
<td>Improved self-confidence</td>
<td></td>
</tr>
</tbody>
</table>
Conflict of interest: none

References