

# Ankylosing spondylitis

## New insights into an old disease

LAURA J. ROSS MB BS

RUSSELL R.C. BUCHANAN MB BS(Hons), MD, FRACP

**Early recognition and treatment of patients with ankylosing spondylitis (AS) improves prognosis but is challenging. Suggestive symptoms include chronic back pain that worsens with rest and early morning axial pain and stiffness. NSAIDs and stretching exercises remain the mainstays of treatment. Tumour necrosis factor inhibitors improve quality of life for patients with refractory AS.**

**A**nkylosing spondylitis (AS) is the prototypic form of spondyloarthritis (SpA). Historically, the term SpA has referred to a group of chronic systemic, inflammatory diseases that include AS, psoriatic arthritis, arthritis related to inflammatory bowel disease, reactive arthritis, undifferentiated SpA and a subgroup of juvenile idiopathic arthritis.<sup>1</sup> These diseases share overlapping features, such as sacroiliitis, extra-articular manifestations (e.g. acute anterior uveitis, psoriasis and inflammatory bowel disease), human leucocyte antigen (HLA)-B27

positivity and familial aggregation.<sup>2</sup>

In the past decade, major progress has been made in the understanding, recognition and treatment of SpA. As a result, the Assessment of SpondyloArthritis International Society (ASAS) has developed new classification criteria for SpA.<sup>3</sup> The ASAS system characterises SpA as either axial (affecting the spine and sacroiliac joints) or peripheral (affecting mainly peripheral joints), according to the predominant articular features at presentation, although these groups overlap and one may progress to the other. Axial SpA



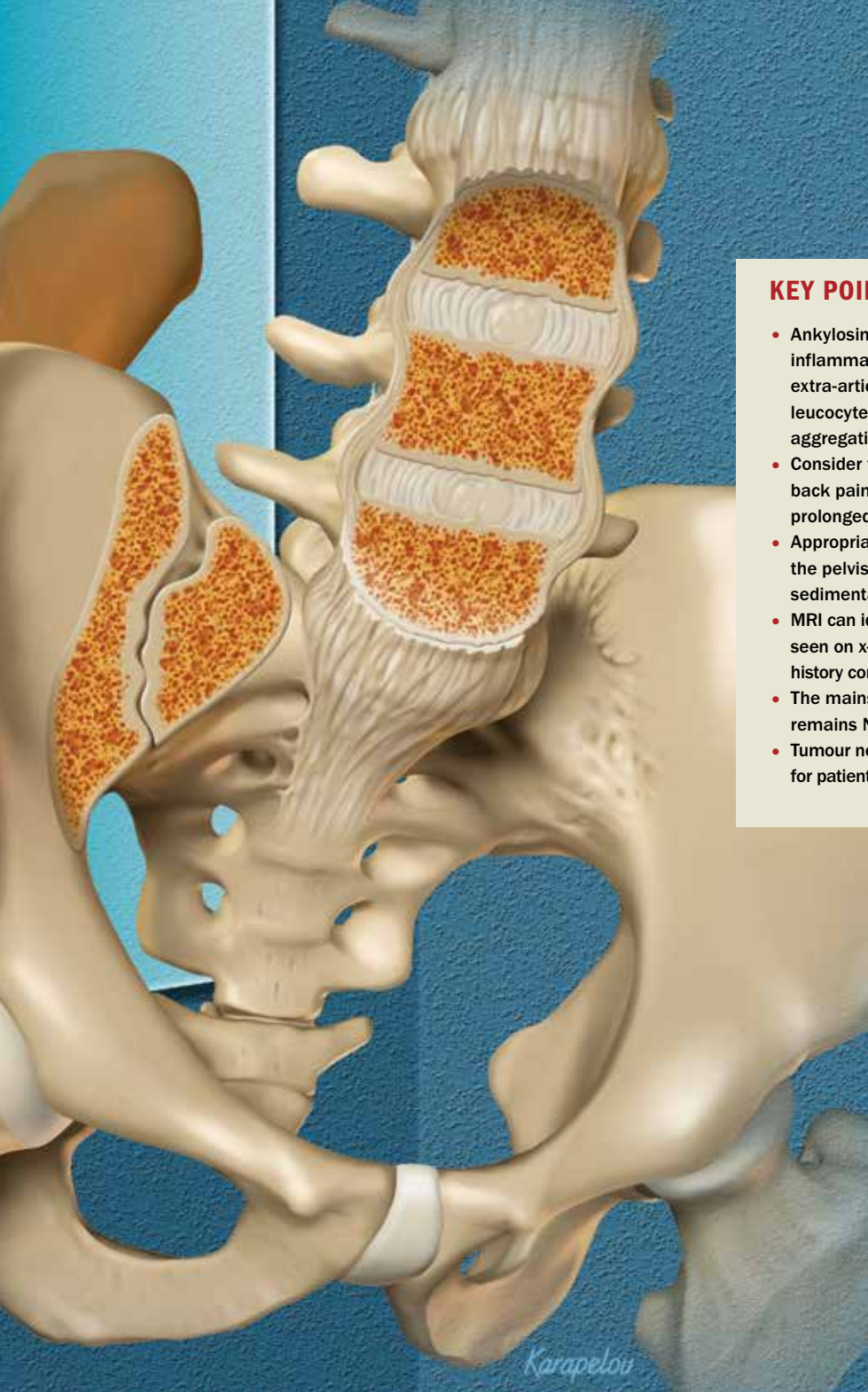
includes AS and nonradiographic axial SpA (Box 1).<sup>4</sup>

A characteristic feature of SpA is enthesitis, defined as inflammation at the site of attachment of tendons, ligaments, joint capsule or fascia to bone.<sup>2</sup> The enthesis is thought to be the major target of the immune response in SpA and thus the primary site for its immunopathology.<sup>2</sup> The different forms of SpA are associated

MedicineToday 2016; 17(1-2): 16-24

Dr Ross is a Registrar in the Department of Rheumatology, Austin Health, Melbourne.

Professor Buchanan is Director of the Department of Rheumatology, Austin Health, Melbourne; and Associate Professor in the Department of Medicine, University of Melbourne, Melbourne, Vic.



## KEY POINTS

- Ankylosing spondylitis (AS) is a chronic systemic inflammatory disease characterised by sacroiliitis, extra-articular manifestations such as uveitis, human leucocyte antigen (HLA)-B27 positivity and familial aggregation.
- Consider the diagnosis of AS in young patients with back pain and stiffness early in the morning and after prolonged sitting.
- Appropriate initial investigations are a plain x-ray of the pelvis and blood tests for HLA-B27, erythrocyte sedimentation rate and C-reactive protein level.
- MRI can identify early inflammatory bony changes not seen on x-ray and is prudent in patients with a clinical history consistent with AS but a normal x-ray appearance.
- The mainstay of treatment for patients with AS remains NSAIDs and stretching exercises.
- Tumour necrosis factor inhibitors are effective therapy for patients who fail to respond to first-line treatments.

bridging and fusion of joints and ankylosis of the spine. Characteristic extra-articular manifestations in AS include acute anterior uveitis (prevalence of 26%), psoriasis (9%) and inflammatory bowel disease (7%).<sup>5</sup> The prevalence of acute anterior uveitis increases with longer disease duration.<sup>5</sup>

AS is a slowly progressive disease, and x-ray changes often do not appear until a decade after onset of symptoms.<sup>6</sup> In some people who have a clinical history consistent with AS but lack the characteristic x-ray changes, MRI can identify early inflammatory bony changes not seen on plain x-ray.<sup>7</sup> Patients may be diagnosed with nonradiographic SpA when they have a history of inflammatory back pain and MRI changes of sacroiliitis with a normal appearance on plain x-rays.

Clinical experience and limited data suggest a sizeable proportion of patients with inflammation of sacroiliac joints on MRI will go on to develop x-ray changes.<sup>6</sup> A review of the MRI changes associated with axial SpA suggests that there is a window of six months to two years during which inflammatory changes seen on MRI evolve into early structural changes associated with AS.<sup>8</sup> Clinical symptoms among patients with nonradiographic SpA are

with characteristic extra-articular manifestations, which can be useful to distinguish SpA from other types of inflammatory arthritis and assist with prognostication.<sup>5</sup>

This article will address the contemporary definition of AS, early recognition in general practice of patients with AS and recent advances in diagnosis and management.

## Definition of ankylosing spondylitis

AS is characterised by inflammatory back pain that is typically subacute in onset and starts before the age of 45 years. Radiographic changes characteristically affect the sacroiliac joints and may involve variable levels of the spine. Inflammation at these sites results in new bone formation leading to the typical AS features of

### 1. CLASSIFICATION OF THE SPONDYLOARTHROPATHIES\*

#### Predominantly axial SpA

- Ankylosing spondylitis
- Nonradiographic axial SpA

#### Predominantly peripheral SpA

- Arthritis with inflammatory bowel disease
- Psoriatic arthritis
- Reactive arthritis
- Undifferentiated SpA

Abbreviation: SpA=spondyloarthritis.

\* Adapted from ASAS (Assessment of SpondyloArthritis International Society). Slide-educational kit. Available online at: <http://www.asas-group.org> (accessed February 2016).<sup>4</sup>

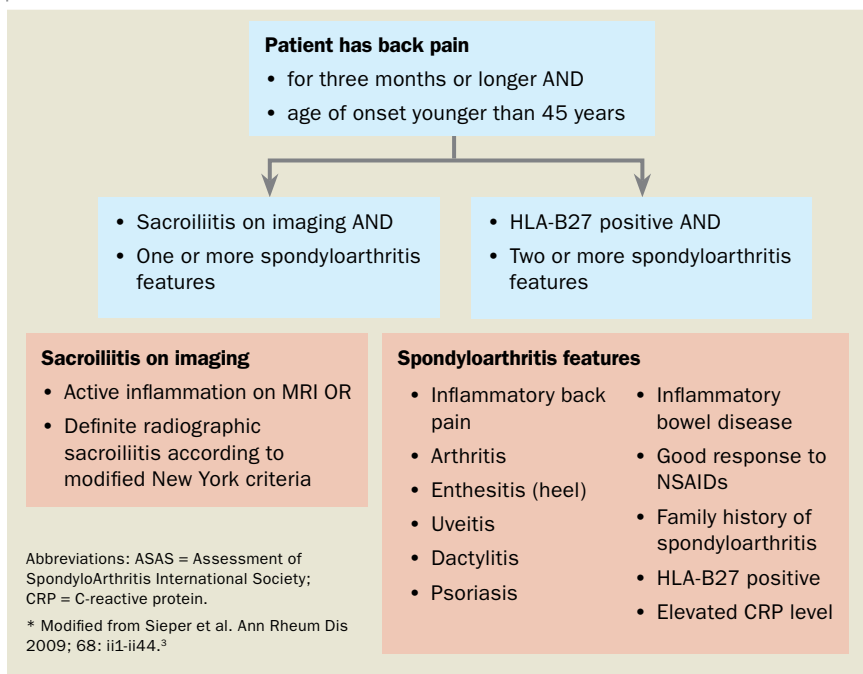
comparable with those among patients with x-ray-proven AS.<sup>1</sup>

ASAS has validated classification criteria for axial SpA, including AS and non-radiographic axial SpA (Box 2).<sup>3</sup> Criteria include the presence of inflammatory back pain, extra-articular manifestations of SpA and HLA-B27 positivity, with or without x-ray changes of sacroiliitis.

### Diagnosis

Early diagnosis of AS remains a challenge and is typically delayed up to eight to 10 years after symptom onset.<sup>9</sup> AS remains a clinical diagnosis based on symptoms and signs. Treatment response is generally better in patients with short disease duration and good functional status.

### 2. ASAS CLASSIFICATION CRITERIA FOR AXIAL SPONDYLOARTHRITIS\*



### History

Patients with AS account for 5% of patients with chronic low back pain.<sup>10</sup> Identifying patients with inflammatory back pain is the key to diagnosing AS and requires a targeted history.<sup>7</sup> Useful questions to ask patients are listed in Box 3.<sup>11</sup> Important features of inflammatory back pain include significant morning stiffness, gel phenomenon (stiffness following sitting or other inactivity) and awakening in the second half of the night with spinal stiffness. In

contrast, mechanical back pain is often intermittent, exacerbated by activity and better with rest (Table).

Important additional clues to identifying patients with inflammatory back pain include a history of peripheral inflammatory arthritis, a family history of AS and a good response of the pain to NSAIDs. The presence of alternating buttock pain, commonly radiating into the posterior thighs, is highly suggestive of sacroiliac joint pain.

### 3. QUESTIONS TO HELP IDENTIFY PATIENTS WITH INFLAMMATORY BACK PAIN\*

In patients with back pain of three months' duration or longer:

- Did your back pain start when you were younger than 40 years?
- Did your back pain develop gradually?
- Does your back pain improve with movement?
- Do you find your back pain worsens when you rest?
- Do you have back pain that worsens overnight and then improves when you get up?
- Do you ever have back pain that radiates into your buttocks?

A 'yes' answer to four or more of these questions usually indicates inflammatory back pain requiring further investigation.

\* Adapted from Sieper et al. Ann Rheum Dis 2009; 68: 784-788.<sup>11</sup>

### Examination

The characteristic examination finding in patients with AS is a reduced range of spinal movement. Lateral spinal flexion is often the first movement to be affected. Important objective measures of spinal mobility are described in Box 4 and Figure 1.

### Extra-articular manifestations

Extra-articular manifestations that support the diagnosis of AS or other forms of SpA include anterior uveitis, psoriasis and inflammatory bowel disease. Around



**TABLE. COMPARISON OF INFLAMMATORY AND MECHANICAL BACK PAIN**

Inflammatory back pain	Mechanical back pain
Morning stiffness for longer than 30 minutes	Minimal morning stiffness
Back pain improves with exercise	Back pain improves with rest
Awakening with back pain during the night	Back pain exacerbated by activity
Alternating buttock pain	Intermittent in nature

9 to 11% of patients diagnosed with psoriasis and 1.8 to 2.6% of those diagnosed with inflammatory bowel disease have SpA at diagnosis.<sup>6</sup>

The presence of dactylitis or enthesitis supports a diagnosis of SpA. It has been reported that 39% patients with AS have enthesitis and 6% have dactylitis at diagnosis.<sup>6</sup> Enthesitis often manifests as recurrent heel pain, indicating inflammation of the plantar fascia ligament or swelling of the Achilles tendon near its insertion.

AS can be associated with aortic regurgitation, caused by thickening of the aortic valvular cusps and dilation of the aortic root.<sup>12</sup> Aortic regurgitation occurs in approximately 10% of patients with AS, an incidence slightly higher than the general population. Patients with long-standing AS have also been found to have a higher rate of left ventricular systolic dysfunction, but it is unclear whether this is the result of underlying inflammatory disease or comorbidities such as hypertension and advancing age.<sup>13</sup>

Pulmonary dysfunction may occur as the result of interstitial lung disease or restriction caused by diminished chest wall and spinal mobility. Upper lobe fibrosis occurs in 1 to 2% of patients with AS and is typically asymptomatic and associated with long disease duration.<sup>14</sup> High resolution CT of the chest has shown that AS can also cause a range of other lung pathologies, including interstitial lung disease, bronchiectasis, emphysema, septal thickening and pleural thickening. Of these changes, septal and pleural thickening can be seen early in the disease course.

## Investigations

### Radiography

Plain x-ray remains the best investigation to diagnose AS and then to monitor for disease progression. Plain x-ray films are more sensitive than MRI for detecting new bone formation, including ankylosis and syndesmophytes.<sup>15</sup>

All patients with possible SpA should undergo a single anteroposterior x-ray of the pelvis with the sacroiliac joints centred

## 4. OBJECTIVE MEASURES OF SPINAL MOBILITY

### Modified Schober's test (Figure 1)

- Place a mark on the patient's back in the midline between the lumbosacral junctions (dimples of Venus)
- Mark a point 10 cm above
- Ask the patient to bend forward to try to touch the floor
- Measure the distance between the marks at full forward flexion
- Normal increase in distance between the two marks  $\geq 5$  cm

### Lateral spinal flexion

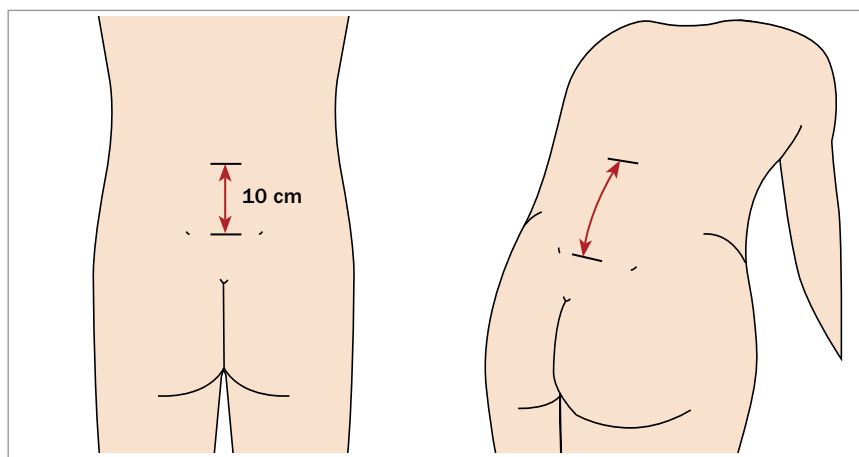
- Have the patient stand with their back against a wall and feet 30 cm apart
- Measure fingertip to floor distance on each side
- Ask the patient to bend laterally as far as possible
- Measure fingertip to floor distance in full lateral flexion on each side
- Normal change in fingertip to floor distance between standing upright and laterally flexed  $\geq 10$  cm

### Occiput to wall distance

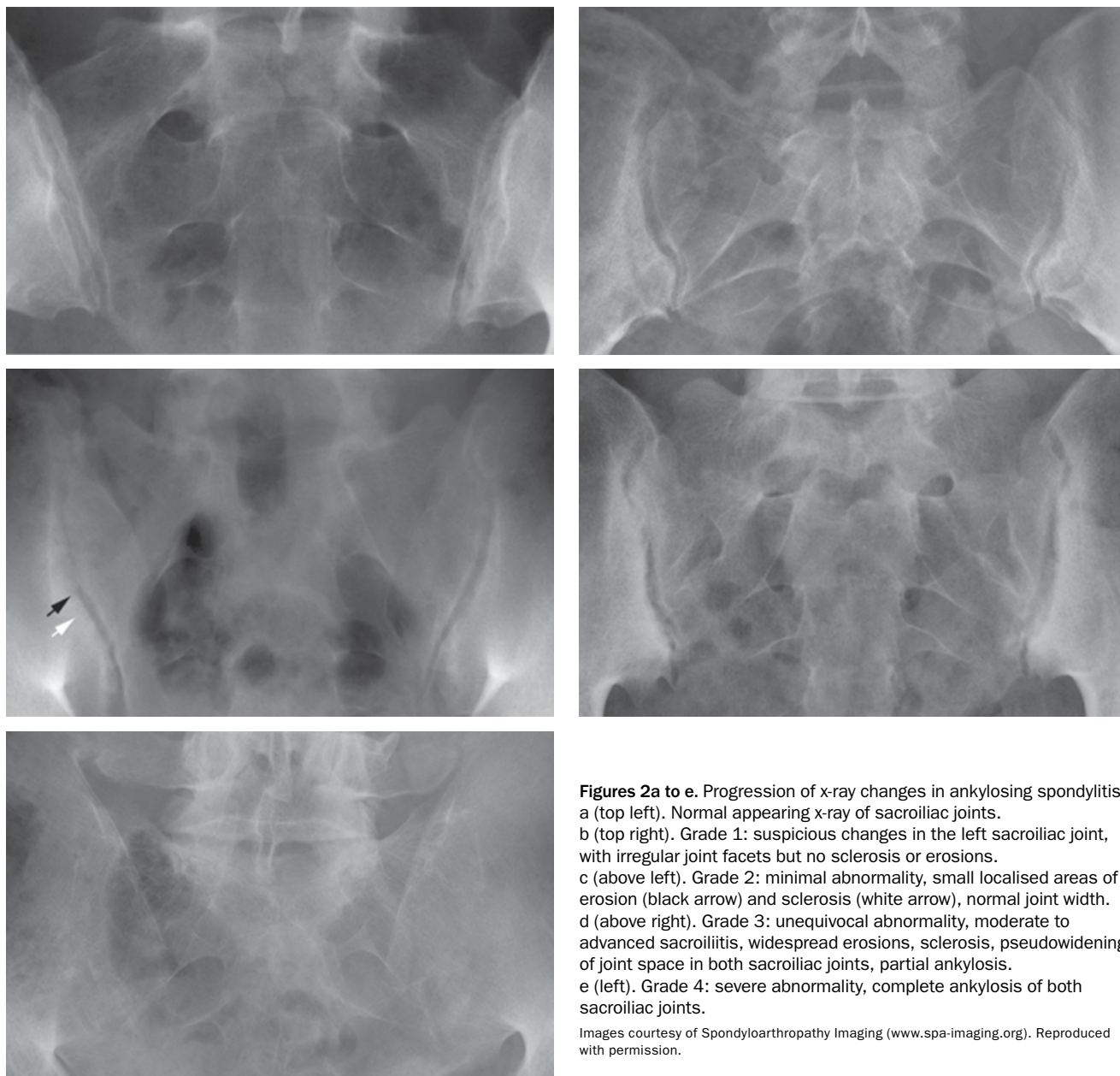
- Have the patient stand with heels and buttocks against a wall
- Ask the patient to extend their head back as far as possible in the horizontal plane
- Measure the distance between the wall and occiput
- Normal occiput to wall distance, 0 cm

### Chest expansion (a late sign)

- Normal chest expansion  $> 4$  cm



**Figure 1.** Modified Schober's test. a (far left). With the patient standing upright, two marks are placed over the spine, one midway between the lumbosacral junctions and the other 10 cm above. b (left). The patient is asked to bend forward to try to touch the floor and the distance between the marks is remeasured. A normal value is  $\geq 15$  cm.



**Figures 2a to e.** Progression of x-ray changes in ankylosing spondylitis. a (top left). Normal appearing x-ray of sacroiliac joints. b (top right). Grade 1: suspicious changes in the left sacroiliac joint, with irregular joint facets but no sclerosis or erosions. c (above left). Grade 2: minimal abnormality, small localised areas of erosion (black arrow) and sclerosis (white arrow), normal joint width. d (above right). Grade 3: unequivocal abnormality, moderate to advanced sacroiliitis, widespread erosions, sclerosis, pseudowidening of joint space in both sacroiliac joints, partial ankylosis. e (left). Grade 4: severe abnormality, complete ankylosis of both sacroiliac joints.

Images courtesy of Spondyloarthropathy Imaging ([www.spa-imaging.org](http://www.spa-imaging.org)). Reproduced with permission.

in the field of view. This x-ray may show structural changes, including subchondral bone sclerosis, erosions and ankylosis in later stages of disease.<sup>1</sup>

A progression of radiographic changes is seen at the various stages of axial SpA (Figures 2a to e). In longer standing disease, spinal x-rays may also show changes such as squaring of vertebrae, reactive sclerosis (shiny corners), syndesmophyte formation and bony bridging (Figure 3).

### Magnetic resonance imaging

MRI can identify early inflammatory bony changes not seen on plain x-ray.<sup>7</sup> In patients with a history of inflammatory back pain and/or HLA-B27 positivity who have signs consistent with AS but a normal x-ray appearance, it is prudent to undertake MRI of the pelvis and lumbar spine to investigate for evidence of sacroiliitis. T1-weighted and short tau inversion recovery (STIR) imaging sequences best demonstrate the

features of axial SpA.<sup>8</sup> The presence of specific MRI findings consistent with sacroiliitis in these patients confirms the diagnosis of nonradiographic SpA.

However, MRI changes in the sacroiliac joints can be caused by other conditions. Noninflammatory causes of sacroiliitis include the following.

- Osteitis condensans ilii. Sclerosis is classically seen on the iliac side of the sacroiliac joint, which retains



**Figure 3.** Typical x-ray changes of ankylosing spondylitis in the spine: shiny corners, squaring of the vertebral bodies and bridging syndesmophytes between vertebral bodies (arrows). (Frontal and lateral views.)

Images courtesy of Spondyloarthropathy Imaging (www.spa-imaging.org). Reproduced with permission.

well-defined joint margins with no erosions and normal width.

- Diffuse idiopathic skeletal hyperostosis (DISH). This is classically diagnosed in older men; imaging reveals irregularly shaped joints and significant bony bridging.
- Septic arthritis. This should be considered in patients with acute-onset back pain with associated constitutional symptoms. Unilateral sacroiliitis is rarely caused by an inflammatory condition. When there is evidence of inflammation in surrounding soft tissue, septic arthritis should be excluded by either a joint aspirate or bone biopsy.

### Blood tests

The inflammatory markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) should be measured in patients with possible AS. However, normal levels of these markers do not preclude a diagnosis of AS. Disease activity, particularly of spinal disease, does not always correlate with changes in inflammatory markers.<sup>2</sup>

HLA typing for HLA-B27 is also recommended for all people with suspected AS (see below).

### Genetic associations of ankylosing spondylitis

The main genetic risk factor for AS is HLA-B27, a major histocompatibility complex (MHC) class I molecule. Genetic risk factors are thought to account for 80 to 90% of susceptibility to AS.<sup>1</sup> Approximately 80 to 90% of patients with AS are HLA-B27 positive, but only about 10% of people who are HLA-B27 positive have AS.<sup>15</sup> Not surprisingly, there is strong concordance between monozygotic twins.<sup>16</sup> HLA-B27 is postulated to have a pathogenic role in the development of AS by triggering the innate immune system, causing an autoinflammatory response.<sup>7</sup>

Recently, genome-wide association studies have identified genes other than the HLA-B27 gene that are potentially involved in the development of AS. In particular, the gene encoding endoplasmic reticulum aminopeptidase 1 (*ERAP1*) has been shown to interact with HLA-B27.<sup>7</sup> Interleukin-23 has also been shown to have a pivotal role in the pathogenesis of SpA, suggesting potential future treatment targets.<sup>7</sup>

### Management NSAIDs

NSAIDs remain first-line treatment for AS. Symptom relief is typically seen within 48 to 72 hours of initiation of full-dose

NSAIDs.<sup>1</sup> There is also evidence suggesting that continuous NSAID use (compared with on-demand use) can delay radiographic disease progression over a two-year period.<sup>1</sup> NSAIDs can also be effective for treating extra-axial symptoms such as peripheral inflammatory arthritis and enthesitis. Adjusting the dose to the lowest effective dose is advised. Patients taking NSAIDs long term should be monitored for potential gastrointestinal and cardiovascular side effects.

### Corticosteroids

Local corticosteroid therapy to affected joints or entheses can be considered if there are ongoing symptoms despite full-dose NSAIDs.<sup>17,18</sup> However injections into the Achilles, patellar and quadriceps tendons should be avoided because of the risk of tendon rupture.

For patients with ongoing isolated active sacroiliitis despite treatment with NSAIDs, the use of guided corticosteroid injections into the sacroiliac joint can be helpful.<sup>17</sup> There is no role for the regular use of systemic glucocorticoids in the management of AS.

### Physical treatments

Physiotherapy is effective at improving pain, physical function, spinal mobility and patient global assessment scores.<sup>19</sup> Arthritis self-help groups recommend daily stretching exercises to manage the symptoms of AS and potentially improve the long-term outcome. Some useful websites with suggested exercises and information for patients with AS are listed in Box 5. GPs have a pivotal role in encouraging patients to perform recommended exercises regularly.

### Disease-modifying antirheumatic drugs

Synthetic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and sulfasalazine have no effect on axial disease symptom management or disease progression.<sup>20</sup> However, synthetic DMARDs have a role in the



## 5. USEFUL WEBSITES FOR PATIENTS WITH ANKYLOSING SPONDYLITIS

### Arthritis Australia

<http://www.arthritisaustralia.com.au>

### Arthritis and Osteoporosis New South Wales

<http://arthritisnsw.org.au>

### Arthritis Victoria

<http://www.arthritisvic.org.au>

### Arthritis Research UK

<http://www.arthritisresearchuk.org>

### Exercises for patients with ankylosing spondylitis

- [http://www.arthritisaustralia.com.au/images/stories/Michael\\_Slater/MS\\_exercisesheet\\_V4%20FINAL-red.pdf](http://www.arthritisaustralia.com.au/images/stories/Michael_Slater/MS_exercisesheet_V4%20FINAL-red.pdf)
- <http://www.arthritisresearchuk.org/arthritis-information/conditions/ankylosing-spondylitis/self-help-and-daily-living/exercise.aspx>

management of patients with coexisting peripheral joint inflammatory arthritis.

## Tumour necrosis factor inhibitors

Tumour necrosis factor alpha (TNF $\alpha$ ) inhibitors such as etanercept, infliximab, golimumab and adalimumab have revolutionised treatment of AS. These biological DMARDs have improved the quality of life for more than two-thirds of patients with AS who do not respond to first-line therapy.<sup>21</sup>

PBS criteria stipulate a three-month trial of exercise and daily use of two different NSAIDs before TNF inhibitor therapy may be considered. Currently patients qualify for PBS-subsidised TNF inhibitor therapy only when there is radiographic evidence of sacroiliitis (bilateral grade 2 or unilateral grade 3 sacroiliitis changes on x-ray). However, there is evidence to suggest that early treatment can reduce radiographic progression.<sup>7</sup> Current ASAS guidelines support the use of TNF inhibitor therapy in clinically active nonradiographic SpA.<sup>17</sup>

## Specialist referral

Delay to diagnosis remains a key challenge in the management of patients with AS.

Patients should be referred to a rheumatologist for assessment if the clinical history is consistent with inflammatory back pain or there is evidence of sacroiliitis on x-ray or MRI. These patients can be commenced on NSAIDs and given physical exercises while they await assessment by a rheumatologist.

## Complications

All-cause mortality is increased in patients with AS. A Swedish nationwide cohort study found that predictors of death include lower socioeconomic status, increased general medical comorbidities and previous hip replacement.<sup>22</sup> Cardiovascular disease was the most common medical comorbidity, and patients had a higher baseline comorbidity than matched healthy control subjects. Common causes of death of AS patients were infection and cardiovascular disease.

Patients with AS are considered to have an increased risk of cardiovascular disease compared with healthy control subjects, with epidemiological data suggesting that ischaemic heart disease is a greater problem in young patients.<sup>23</sup> This higher risk may be due to inflammatory disease, traditional cardiovascular risk factors or NSAID use. It highlights the importance of long-term optimisation of modifiable cardiovascular risk factors.

Patients with AS have an increased prevalence of both osteopenia and osteoporosis. High disease activity, generally detected by increased ESR and CRP level, predicts increased bone loss.<sup>24</sup> Patient screening with dual emission x-ray absorptiometry (DXA) scanning of both the spine and hip is recommended.<sup>17</sup> It is important to consider spine bone mineral density results carefully, as patients with AS have an increased rate of spinal fracture and spinal cord injury.

## Conclusion

Early recognition of signs and symptoms of AS and prompt referral to a rheumatologist remain a challenge in this condition. AS should be considered if symptoms

consistent with inflammatory back pain are noted. These include waking in the second half of the night with back pain, axial early morning stiffness and alternating buttock pain.

The mainstay of treatment remains NSAIDs and stretching exercises. The quality of life for patients with refractory axial SpA has improved significantly with the introduction of anti-TNF $\alpha$  therapy.

Ongoing research into the genetics and pathophysiology of this condition has improved our understanding of this disease, leading to better classification and diagnostic testing. This also leads to much optimism for future management of patients with AS.

MT

## Acknowledgement

The authors are grateful for the helpful comments from Dr Lionel Schachna, Austin Spondylitis Clinic, Austin Health, Melbourne, Vic, in the preparation of this article.

## References

A list of references is included in the website version ([www.medicinetoday.com.au](http://www.medicinetoday.com.au)) of this article.

COMPETING INTERESTS: None.

## ONLINE CPD JOURNAL PROGRAM

**What is the characteristic physical examination finding in patients with ankylosing spondylitis?**



Review your knowledge of this topic and earn CPD points by taking part in **MedicineToday's** Online CPD Journal Program. **Log in to** [www.medicinetoday.com.au/cpd](http://www.medicinetoday.com.au/cpd)

© STOCKDEVIL/ISTOCKPHOTO

# Ankylosing spondylitis

## New insights into an old disease

**LAURA J. ROSS** MB BS; **RUSSELL R.C. BUCHANAN** MB BS(Hons), MD, FRACP

### References

1. Dougados M, Baeten D. Spondyloarthritis. *Lancet* 2011; 177: 2127-2137.
2. Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A. Ankylosing spondylitis: an overview. *Ann Rheum Dis* 2002; 61 Suppl III: iii8-iii18.
3. Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009; 68: ii1-ii44.
4. ASAS (Assessment of SpondyloArthritis International Society). Slide-educational kit. Available online at: <http://www.asas-group.org> (accessed January 2016).
5. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015; 74: 65-73.
6. Rudwaleit M, Haibel H, Baraliakos X, et al. The early disease stage in axial spondylarthritis: results from the German spondyloarthritis inception cohort. *Arthritis Rheum* 2009; 60: 717-727.
7. Rudwaleit M, Metter A, Listing J, Sieper J, Braun J. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. *Arthritis Rheum* 2006; 54: 569-578.
8. Hermann KG, Baraliakos X, van der Heijde D, et al. Descriptions of spinal MRI lesions and definition of a positive MRI of the spine in axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI study group. *Ann Rheum Dis* 2012; 71: 1278-1288.
9. Feldtkeller E, Khan M, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int* 2003; 23: 61-66.
10. Poddubnyy D, Rudwaleit M. Early spondyloarthritis. *Rheum Dis Clin N Am* 2012; 38: 387-403.
11. Sieper J, van der Heijde D, Landewé R, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis International Society (ASAS). *Ann Rheum Dis* 2009; 68: 784-788.
12. Vinsonneau U, Brondex A, Mansourati J, et al. Cardiovascular disease in patient with spondyloarthritis. *Joint Bone Spine* 2008; 75: 18-21.
13. Brunner F, Kunz A, Weber U, Kissling R. Ankylosing spondylitis and heart abnormalities: do cardiac conduction disorders, valve regurgitation and diastolic dysfunction occur more often in male patients diagnosed with ankylosing spondylitis for over 15 years than in the normal population? *Clin Rheumatol* 2006; 25: 24-29.
14. Quismorio F Jr. Pulmonary involvement in ankylosing spondylitis. *Curr Opin Pulm Med* 2006; 12: 342-345.
15. Robinson P, Benham H. Advances in classification, basic mechanisms and clinical science in ankylosing spondylitis and axial spondyloarthritis. *Intern Med J* 2015; 45: 127-133.
16. Dougados M, Baeten D. Spondyloarthritis. *Lancet* 2011; 177: 2127-2137.
17. Ward M, Deodhar A, Akl E, et al. American College of Rheumatology/ Spondylitis Association of America/ Spondyloarthritis Research and Treatment Network 2015 recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 2015 Sep 24; epub ahead of print (doi: 10.1002/art.39298).
18. Braun J, van den Berg R, Baraliakos X, et al. 2010 update of the ASAS/ EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2011; 70: 896-904.
19. Dagfinrud H, Kvien TK, Hagen KB. Physiotherapy interventions for ankylosing spondylitis. *Cochrane Database Syst Rev* 2008; (1): CD002822.
20. van den Berg R, Baraliakos X, Braun J, van der Heijde D. First update of the current evidence for the management of ankylosing spondylitis with non-pharmacological treatment and non-biologic drugs: a systematic literature review for the ASAS/EULAR management recommendations in ankylosing spondylitis. *Rheumatology (Oxford)* 2012; 51: 1388-1396.
21. van der Heijde D, Sieper J, Maksymowych W, et al. 2010 update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann Rheum Dis* 2011; 70: 905-908.
22. Exarchou S, Lie E, Lindstrom U, et al. Mortality in ankylosing spondylitis: results from a nation-wide population-based study. *Ann Rheum Dis* 2015 Sep 2; pii: epub ahead of print (annrheumdis-2015-207688).
23. Huang YP, Wang YH, Pan SL. Increased risk of ischaemic heart disease in young patients with newly diagnosed ankylosing spondylitis – a population-based longitudinal follow-up study. *PLoS One* 2013; 8: e64155.
24. Wang DM, Zeng QY, Chen SB, Gong Y, Hou ZD, Zhao ZY. Prevalence and risk factors of osteoporosis in patients with ankylosing spondylitis: a 5-year follow up study of 504 cases. *Clin Exp Rheumatol* 2015; 33: 465-470.