Ankylosing Spondylitis

Joachim Sieper
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CLINICIAN'S MANUAL

Springer Healthcare

Clinician's Manual on Ankylosing Spondylitis

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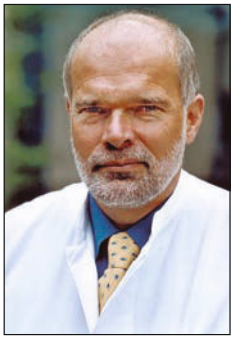
Joachim Sieper, MD, is a Consultant and Head of Rheumatology at the Charité University Hospital, Campus Benjamin Franklin in Berlin, Germany. After receiving his medical degree in 1978 from Free University, in Berlin, Germany, he underwent his training in internal medicine in the Department of Cardiology at the Rudolf–Virchow clinic in Berlin, Germany. He continued his training in internal medicine and rheumatology at the University Hospital Benjamin Franklin, in Berlin, Germany. During this time he had a number of fellowships abroad including 8 weeks at The London Lupus Clinic, Hammersmith Hospital, in London, UK, led by Professor Graham Hughes. He also spent over a year at the Rheumatology Unit of Guy's Hospital, in London, UK, led by Professor G Panayi. In 1998 he became Professor of Medicine at Free University and that same year he was also appointed Deputy Head of the Department of Internal Medicine at the same institution. In 2000 he became Head of Rheumatology at Free University.

Professor Sieper is also a prolific researcher and writer. He has been an investigator since 1989, and a principal investigator since 1993 on several placebo-controlled randomised trials, which have been published internationally. He has authored and contributed to over 300 journal papers.

He is a member of numerous societies including the German Society of Rheumatology and the American College of Rheumatology.

He has also been the recipient of many awards and honours for excellence in rheumatology, including the Carol–Nachman award for rheumatology in 2000 and the European League Against Rheumatism (EULAR) award in 2003.



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Jürgen Braun, MD, is Medical Director of the Rheumatology Medical Centre, Ruhrgebiet in Herne, Germany, and is a lecturer at the Ruhr University in Bochum, Germany. He is also an honorary Professor in Rheumatology at the Charité Medical School in Berlin, Germany.

He received his doctor of medicine degree in 1987 at the Free University, Berlin, Germany, and went on to become certified as a specialist in rheumatology, internal medicine, laboratory medicine, physical therapy and sports medicine. In 2000, he became Professor of Rheumatology at the Free University, Berlin. The following year he became Medical Director of the Rheumatology Medical Centre, Ruhrgebiet in Herne, one of the major hospitals in Germany specialised in the management of patients with rheumatic diseases, a position he still holds.

Professor Braun has been an invited speaker at a number of universities and institutions including the National Institutes of Health, the American College of Rheumatology, the European League Against Rheumatism (EULAR), and the Asia Pacific League of Associations for Rheumatology. He has also been invited to speak about his research at the national meetings of the British, Irish, Indian, Scandinavian, Danish, Dutch, Belgian, Italian, Spanish, Greek, Turkish, Moroccan, Russian, Chinese, and German Society of Rheumatology. In 2004, he was appointed as the inaugural Robert Inman lecturer at the University of Toronto, Canada.

Professor Braun has been the recipient of several prestigious awards, including the Ankylosing Spondylitis Patients Association Award in 1996, the Tosse-Research Award in Pediatric Rheumatology in 1998, the Carol Nachman Research Award in 2000, and the EULAR prize in 2003.

As one of the leading specialists in the field of the spondyloarthritides, Professor Braun has published more than 300 papers on different aspects of this subject. He is a member of the Steering Committee of the Assessments in Ankylosing Spondylitis Working group and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis.

Acknowledgements

Our thanks go to our colleagues in the Assessment in SpondyloArthritis international Society (ASAS) for their permission to reproduce Figures 3.8, 4.3, 4.4, 4.5, 6.8 and 6.18 in this manual.

Abbreviations

AS	ankylosing spondylitis
ASAS	Assessment in SpondyloArthritis international Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASSERT	Ankylosing Spondylitis Study for the Evaluation of Recombinant infliximab Therapy study
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BASFI	Bath Ankylosing Spondylitis Functional Index
COX-2	cyclooxygenase 2
CRP	C-reactive protein
CT	computed tomography
CV	cardiovascular
DISH	diffuse idiopathic skeletal hyperostosis
DMARD	disease-modifying anti-rheumatic drug
ESR	erythrocyte sedimentation rate
ESSG	European Spondylarthropathy Study Group
EULAR	European League Against Rheumatism
GI	gastrointestinal
HLA	human leukocyte antigen
IBD	inflammatory bowel disease
IBP	inflammatory back pain
IL	interleukin
JIA	juvenile idiopathic arthritis
LR	likelihood ratio
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MRI	magnetic resonance imaging
NRS	numerical rating scale
NSAID	nonsteroidal anti-inflammatory drug
PsA	psoriatic arthtitis
SI	sacroiliac
SpA	spondyloarthritis
STIR	short tau inversion recovery
TB	tuberculosis
Th-17	T-helper cell 17
TNF	tumour necrosis factor
TNF-α	tumour necrosis factor alpha
VAS	visual analogue scale

Chapter 1

Introduction

Only slightly more common in men than in women, ankylosing spondylitis (AS) is a chronic inflammatory disease which, probably as a result of an autoimmune response, causes inflammation in the sacroiliac joints, vertebrae and adjacent joints. Patients also frequently have inflammation of an enthesis (insertion of a tendon or ligament into the bone), the peripheral joints and the eye; the lungs, heart valves and kidneys are only rarely affected. The onset of symptoms – notably back pain and stiffness – is normally already noticeable in adolescence or early adulthood. Eventually, AS can cause the vertebrae to fuse together, with obvious adverse impact on patient mobility and function. To date, the disease has no cure, but drug and physical therapy can improve pain, inflammation and other symptoms considerably; indeed, even remission is now a realistic goal. A major breakthrough in the treatment of this disease was the demonstration of the high efficacy of the tumour necrosis factor (TNF)-blocking agents [1].

The diagnosis of AS is often delayed as symptoms can be confused with other more common, but normally less serious, disorders because chronic low back pain is such a common complaint. Furthermore, typical radiological changes of the sacroiliac joint become visible only after some time, often years, of ongoing inflammation. Therefore, it is proposed that the term 'axial spondyloarthritis' be used, which covers both patients with ankylosing spondylitis and those with non-radiographic sacroiliitis. Early accurate diagnosis and intervention can, however, minimize or even prevent years of pain and disability. In the face of these challenges, the *Clinician's Manual on Ankylosing Spondylitis* provides a concise, clinically focused overview of the manifestations, diagnosis and management of this potentially debilitating condition.

A historical perspective

Studies of Egyptian mummies indicate that the disease now known as AS has afflicted humankind since antiquity. The first historical description of

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AS appeared in the literature in 1559, when Realdo Colombo provided an anatomical description of two skeletons with abnormalities typical of AS. More than 100 years later, the Irish doctor Bernard Connor described a bony fusion of spine and sacroiliac joints of a human skeleton. Despite several descriptions of conditions resembling AS later on, the reports of Bechterew in Russia (1893), Strümpell in Germany (1897) and Marie in France (1898) are often cited as the first descriptions of AS. Around 1900 the terms 'Bechterew's disease', used preferentially in German-speaking countries and Russia, and 'ankylosing spondylitis' were introduced.

At this time a diagnosis could be made only when an AS patient had already developed the typical posture (see Figure 1.1a) that results from an advanced ankylosis of the spine or *post mortem*. It was not until the 1930s that roentgenology was applied to AS, and it became evident from these studies that, in about 95% of cases, the sacroiliac joint is affected in AS (Figure 1.1b). These findings are the basis for the prominent role of radiographic sacroiliitis in the currently used diagnostic and classification criteria for AS, such as the 1984 modified New York criteria [2]. However, there was already some evidence, both clinically and from scintigraphy, that patients may have symptoms caused by inflammation many years before structural damage becomes visible on radiographs. The presence of an inflammatory non(pre)-radiographic stage early in the course of the disease became much clearer when magnetic resonance imaging (MRI) was used in AS in the 1990s (Figure 1.1c) [3]. Consequently, acute inflammatory sacroiliitis shown by MRI has become part of the new classification criteria for axial spondyloarthritis.

Starting in the 1920s radiation treatment was used for AS patients to treat spinal pain and had good results such as improvement of the symptoms. However, this therapy was abandoned because of the serious long-term side effects of such treatment, such as leukaemia and other malignancies. Although treatment with salicylates has been used for the treatment of inflammatory rheumatic diseases since about 1900, this drug was not effective in AS. Phenylbutazone was introduced into clinical practice in 1949 and became the first drug to which the term 'non-steroidal anti-inflammatory drug' (NSAID) was applied. It has been highly effective for the treatment of AS with control of pain and inflammation. However, its use has been restricted to only short-term treatment of AS because of potentially serious side effects, notably aplastic anaemia and hepatic injury. Subsequently, since around 1965 a second generation of NSAIDs, led by indometacin, has been successfully used in the treatment of AS up to the present. Finally, the high efficacy of TNF-blocker treatment was demonstrated in AS patients in the first years of the new century.

Historical aspects of AS

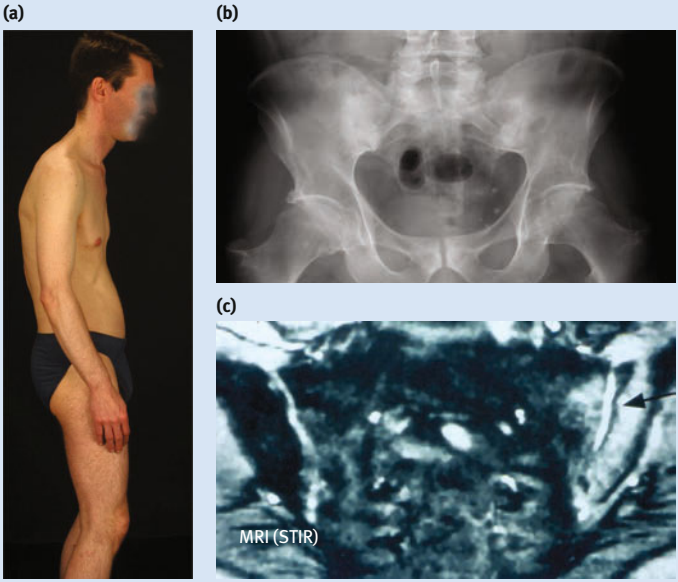

Figure 1.1. Historical aspects of AS. AS, ankylosing spondylitis; MRI, magnetic resonance imaging; STIR, short tau inversion recovery. **(a)** in the 1900s a diagnosis could only be made when the patient exhibited the typical posture associated with AS; **(b)** a radiograph showing bilateral sacroilitis - roentgenology began to be applied to AS in the 1930s; **(c)** a magnetic resonance image showing a patient with acute sacroiliitis – the use of MRI in the early 1990s helped to identify the presence of an inflammatory non-radiographic stage early in the course of AS.

Chapter 2

Overview of ankylosing spondylitis

The concept and classification of spondyloarthritis

The term 'spondyloarthritis' (SpA) comprises AS, reactive arthritis, arthritis/spondylitis associated with psoriasis, and arthritis/spondylitis associated with inflammatory bowel disease (IBD). There is considerable overlap between the single subsets (Figure 2.1). The main link between each is the association with the human leukocyte antigen (HLA)-B27, the same pattern of peripheral joint involvement with an asymmetrical, often pauciarticular, arthritis, predominantly of the lower limbs, and the possible occurrence of sacroiliitis, spondylitis, enthesitis, dactylitis and uveitis. All SpA subsets can evolve into AS, especially in those patients who are positive for HLA-B27. The SpA subsets can also be split into patients with predominantly axial and predominantly peripheral SpA (Figure 2.2), with an overlap between the two parts in about 20–40% of cases. Through use of such a classification the presence or absence of evidence for a preceding gastrointestinal or urogenital infection, psoriasis or IBD is recorded but does not result in a different classification. The term 'predominant axial SpA' covers patients with classic AS and those with non-radiographic axial SpA [4]. The latter group of patients would not have radiographic sacroiliitis according to the modified New York criteria, but would normally have evidence of active inflammation as shown by magnetic resonance imaging (MRI) or other means (discussed in more detail in Chapter 5).

The concept of 'seronegative spondarthritides', now known as 'spondyloarthritides', was first introduced in 1974 by Moll and Wright from Leeds. 'Seronegative' stands here for rheumatoid factor negative. Subsequently, both the European Spondyloarthropathy Study Group (ESSG) classification criteria and the Amor criteria (from the French rheumatologist Bernard Amor) tried to define the whole spectrum of SpA [5, 6]. It was thanks to the ESSG criteria that in 1991 the SpA group was first split into predominantly axial and peripheral subsets. Figure 2.3 shows the current ESSG classification criteria for spondyloarthritis. Most recently the Assessment in SpondyloArthritis international Society (ASAS) has proposed new classification criteria on axial spondyloarthritis, a term that is used throughout this book [7].

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Epidemiology of ankylosing spondylitis

AS is a disease that starts normally in the third decade of life, with about 80% of patients developing the first symptoms before the age of 30 and less than 5% of patients being older than 45 at the start of the disease. Up to 20% of patients are even younger than 20 years when they experience their first symptoms (Figure 2.4) [8]. Patients who are positive for HLA-B27 are about 10 years younger than HLA-B27-negative patients when the disease starts [9].

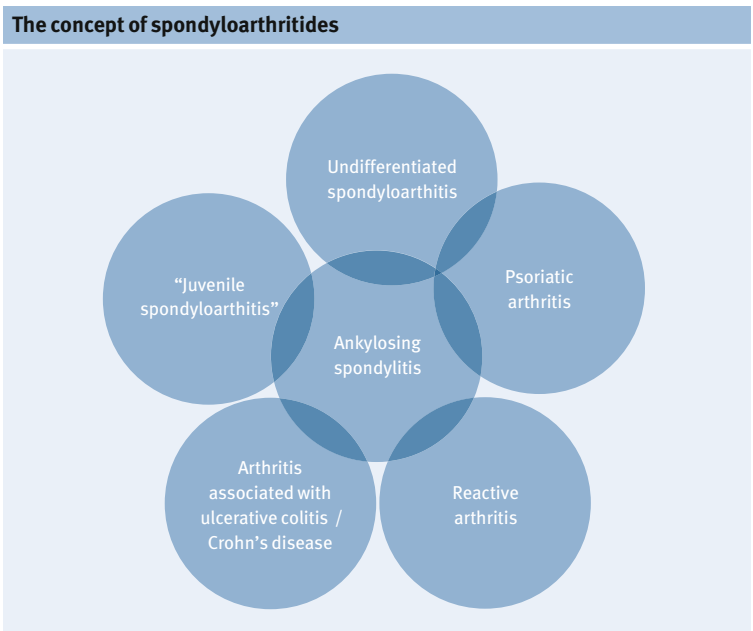

Figure 2.1 The concept of spondyloarthritides.

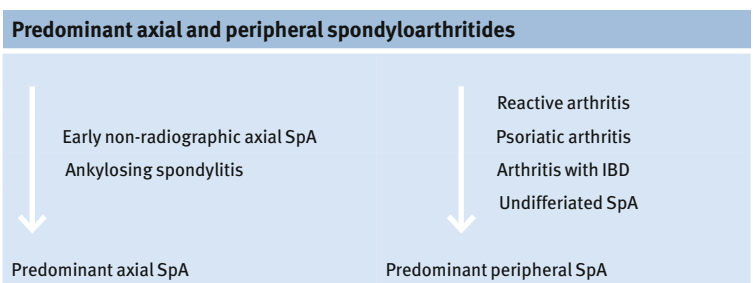

Figure 2.2 Axial and peripheral spondyloarthritides. IBD, inflammatory bowel disease; SpA, spondyloarthritis. Data from Rudwaleit et al. [4].

ESSG classification criteria for spondyloarthropathy

Inflammatory back pain	or	**Synovitis**
		• asymmetrical or
		• predominantly in the lower limbs
plus one of the following:		
• alternating buttock pain		
• sacroiliitis		
• heel pain (enthesitis)		
• positive family history		
• psoriasis		
• Crohn's disease, ulcerative colitis		
• urethritis / acute diarrhea in the preceding 4 weeks		

Figure 2.3 ESSG classification criteria for spondyloarthropathy. ESSG, European Spondyloarthropathy Study Group. Data from Dougados et al. [5].

Age at first symptoms and at first diagnosis in patients with AS

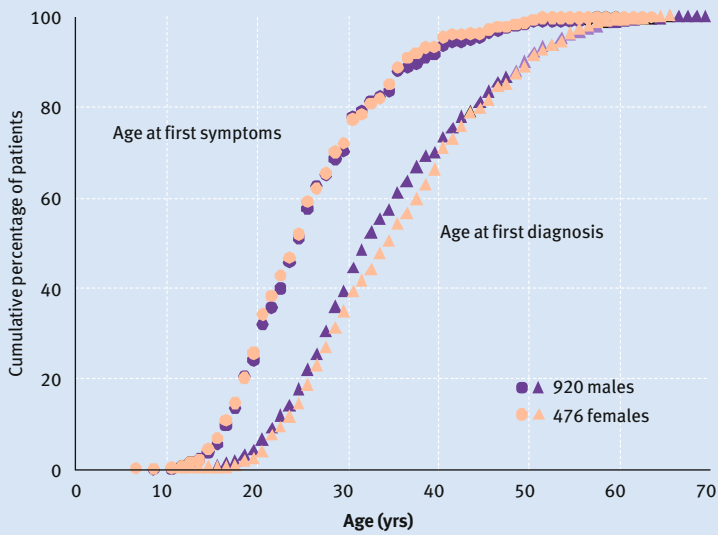

Figure 2.4 Age at first symptoms and at first diagnosis in patients with AS. AS, ankylosing spondylitis. Reproduced with permission from Feldtkeller et al [8].

Men are slightly more affected than are women, with a ratio of about 2:1. However, women develop chronic radiographic changes of the sacroiliac joints and the spine later than men, a possible explanation for the frequent underdiagnosis of AS in women in the past, resulting in a much higher male:female ratio than currently accepted [9].

There is a clear correlation between the prevalence of HLA-B27 and the prevalence of AS in a given population: the higher the HLA-B27 prevalence the higher the AS prevalence. HLA-B27 is present throughout the world with a wide ethnic and geographical variation. It is most prevalent in northern countries and some tribes (Figure 2.5). Overall, estimations about the prevalence of AS

Prevalence of AS

Country	AS prevalence	HLA-B27 prevalence
US*	1.0–1.5%	8%
The Netherlands†	0.1%	8%
Germany‡	0.55%	9%
Norway§	1.1–1.4%	14%
Haida Indians¶	6.1%	50%

Figure 2.5 Prevalence of AS. AS, ankylosing spondylitis; HLA, human leukocyte antigen. *Data from Calin et al. [10]; †Data from van der Linden et al. [11]; ‡Data from Braun et al. [12]; §Data from Gran et al. [13]; ¶Data from Gofton et al. [14].

Prevalence of spondyloarthritides and rheumatoid arthritis

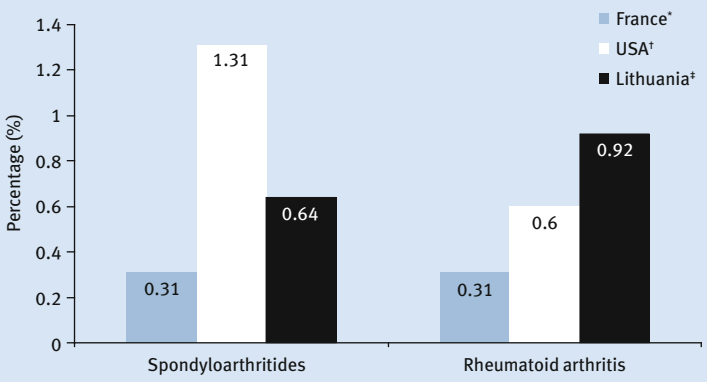

Figure 2.6 Prevalence of spondyloarthritides and rheumatoid arthritis.
*Data from Saraux et al. [15] and Guillemin et al. [16]; †Data from Adomaviciute et al. [17]; ‡Helmick et al. [18].

are between 0.1% and 1.4%, with most of these data coming from Europe. In western and mid-Europe a prevalence of 0.3–0.5% for AS and of 1–2% for the whole SpA group is likely. Recent studies from France, the USA and Lithuania indicate that SpA is at least as common as rheumatoid arthritis (Figure 2.6), which makes AS and SpA one of the most important chronic inflammatory rheumatic diseases [15–19].

HLA-B27 is positive in 90–95% of AS patients and in about 80–90% of patients with non-radiographic axial SpA. This percentage goes down to about 60% in AS patients who also have psoriasis or IBD. In predominant peripheral SpA, less than 50% of patients are positive for HLA-B27.

Aetiopathogenesis of ankylosing spondylitis

A major breakthrough in the research on the pathogenesis of AS and related SpA was the reported strong association of the disease with HLA-B27 in 1973 [20]. However, intensive research over more than three decades has not clarified the functional role of the HLA-B27 molecule in the pathogenic process. In the centre of the discussion about pathogenesis of SpA is the interaction between bacteria and HLA-B27, as a result of known triggering bacteria in reactive arthritis (after preceding bacterial infections of the urogenital or gastrointestinal tract) and the association with IBD; in the latter the immune system can interact with local gut bacteria because of a damaged mucosa [21]. Between 10% and 50% of HLA-B27-positive patients with reactive arthritis or IBD develop AS over the years, supporting a central role for such an interaction between bacteria and HLA-B27 in its pathogenesis. Although in most AS patients no bacterial exposure can be detected, subclinical bacterial infection or gut inflammation would be a possibility in these patients.

Many recent MRI studies and older pathological investigations suggest that the primary target of the immune response is at the cartilage/bone interface, including the insertion of tendon and ligaments at the bone (enthesis) [22]. Such an immunopathology would most probably differ from rheumatoid arthritis, in which inflammation occurs primarily in the synovium. We have recently provided further evidence for this hypothesis, showing that the presence of mononuclear cell infiltrates and osteoclasts depends on the presence of cartilage on the joint surface in AS patients (Figure 2.7) [23]. However, there is currently no evidence that bacteria or bacterial antigens persist in the cartilage or close to the cartilage of spine and joints. Thus, there have been speculations that bacteria might trigger an autoimmune response against cartilage-derived antigens such as proteoglycan or collagen, possibly mediated somehow through HLA-B27, although this hypothesis has not yet been proved. A third