

Early diagnosis of spondyloarthritis

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SUMMARY

The term 'spondyloarthritis', which is preferred to 'spondyloarthropathy', refers to a group of similar diseases with distinct clinical features and a common genetic predisposition, rather than one disease with different clinical presentations. Mainly for clinical purposes, five disease subtypes are recognized: ankylosing spondylitis (AS), psoriatic spondyloarthritis, reactive spondyloarthritis, spondyloarthritis associated with inflammatory bowel disease, and undifferentiated spondyloarthritis. Irrespective of the disease subtype, the main clinical manifestations of spondyloarthritides are inflammatory back pain, peripheral arthritis, enthesitis and anterior uveitis, while other organ manifestations are rare. The need for a standardized, evidence-based approach to disease classification led to the development of the European Spondyloarthropathy Study Group preliminary criteria for spondyloarthritis in 1991, which confirmed the unifying concept of this group of diseases. In the past 10 years, the work of the European Spondyloarthropathy Study Group has been taken over by the Assessments in AS working group. There is still a considerable delay in diagnosis of AS and, because of the well-documented efficacy of anti-tumor-necrosis-factor therapy for all spondyloarthritis subtypes, diagnostic criteria (especially for early forms of spondyloarthritis) are needed. Diagnosis can be achieved by determination of the predominant clinical manifestation, and by the inclusion of sensitive diagnostic tools for early disease (such as HLA-B27 genotype and MRI) in the criteria set. In addition, because of the high incidence of back pain in affected individuals, the development of practical screening parameters that facilitate referral to the rheumatologist is important.

KEYWORDS ankylosing spondylitis, diagnostic criteria, HLA-B27, inflammatory back pain, spondyloarthritis

REVIEW CRITERIA

Published articles for inclusion in this review were identified from the authors' extensive records of papers on spondyloarthritis dating from 1990 to date. All papers identified were English-language full-text papers. We also searched the reference lists of identified articles for further papers.

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INTRODUCTION

In 2002, an international workshop on ankylosing spondylitis (AS) reached a consensus view that the term spondyloarthritis is preferable to spondyloarthropathy, to emphasize the inflammatory nature of these diseases.¹ This terminology is consistent with recommendations from the European League against Rheumatism (EULAR).² The term spondyloarthritis is often quoted in the plural form, spondyloarthritides, which accentuates the view that spondyloarthritis is a group of similar diseases with distinct clinical features and a common genetic predisposition, rather than one disease with different clinical presentations. Irrespective of the spondyloarthritis subtype (see below), the main clinical manifestations of spondyloarthritides are inflammatory back pain (IBP) due to sacroiliitis, inflammation at other locations in the axial skeleton, peripheral arthritis, enthesitis³ and anterior uveitis,⁴ while manifestations in other organs such as the heart are rare.⁵

Predisposition to spondyloarthritis, especially AS, is determined largely by genetic factors. Indeed, more than 90% of patients with AS carry the MHC class I molecule HLA-B27, and at least one-third of the total heritability of AS is explained by this trait. The genetic factors involved in the remaining cases are, as yet, incompletely defined.⁶ The risk of developing AS is as high as 5–7% in HLA-B27-positive individuals. Psoriatic skin lesions and colitis due to inflammatory bowel disease (IBD) have been considered as both basic, subtype-defining entities with their own genetic background (distinct from HLA-B27 genotype), and as manifestations of spondyloarthritis.⁷

Mainly for clinical purposes, five subtypes of spondyloarthritis are currently recognized. In 2005,⁸ it was proposed to define the subgroups as AS, psoriatic spondyloarthritis, reactive spondyloarthritis, spondyloarthritis associated with inflammatory bowel disease, and undifferentiated spondyloarthritis. This terminology makes sense because, for example, not all patients with arthritis

associated with psoriasis have spondyloarthritis. There is no clear agreement over whether the SAPHO syndrome (i.e. synovitis, acne, pustulosis, hyperostosis and osteitis) should be included in the spectrum of the spondyloarthritis.⁹ Although SAPHO syndrome has clinical features that overlap with spondyloarthritis, it is usually not included in the classification system for practical reasons (for simplicity) and because SAPHO syndrome is relatively rare.

AS is the most frequent and most severe subtype,¹⁰ but patients with psoriatic spondyloarthritis could also experience a severe course of disease. The prevalence of AS is about 0.3–0.5%,¹¹ and the overall prevalence of spondyloarthritis is similar to that of rheumatoid arthritis.¹²

There is a strong need to diagnose patients with AS earlier; currently there is a delay of 5–10 years between onset of the first symptoms and diagnosis, which is unacceptably long.¹³ An earlier diagnosis is important for several reasons: effective treatments for patients with active AS, such as tumor necrosis factor (TNF)-blockers, are now available;^{14,15} the value of established treatments such as NSAIDs is currently being redefined;¹⁶ and early diagnosis might help to avoid unnecessary diagnostic and therapeutic procedures.

In this article, we will discuss how an early diagnosis of spondyloarthritis can be achieved for patients with predominantly axial or predominantly peripheral symptoms, on the basis of the available data. We will also elaborate on the differences between diagnosis and classification, and how these differences might influence clinical practice. Three major features will be identified as being important for early diagnosis: IBP, HLA-B27 genotype, and imaging of the sacroiliac joints by X-ray and MRI.

CLASSIFICATION CRITERIA FOR SPONDYLOARTHRITIS

The need for a standardized, evidence-based approach to spondyloarthritis classification led to the development of the European Spondyloarthropathy Study Group (ESSG) preliminary classification criteria for spondyloarthritis in 1991,¹⁷ an initiative of the EULAR working group for spondyloarthritis. This consensus report confirmed the unifying concept of spondyloarthritis as a group of related diseases with common features, including IBP and peripheral arthritis as the leading clinical symptoms (Box 1). The rather characteristic feature of enthesitis is often not clinically predominant,

Box 1 European Spondyloarthropathy Study Group classification criteria for spondyloarthritis.

The presence of inflammatory back pain or asymmetric synovitis (predominantly in the lower limbs), plus any one of the following features:

- Enthesopathy
- Alternating buttock pain
- Positive family history
- Psoriasis
- Inflammatory bowel disease
- Preceding infection in the urogenital or enteral tract

Reprinted with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. © Dougados M *et al.* (1991) The European Spondyloarthropathy Study Group preliminary criteria for the classification of spondyloarthropathy. *Arthritis Rheum* 34: 1218–1227.

but might be of major pathogenetic significance.¹⁸ In the past 10 years, the work of ESSG has been taken over by the Assessments in AS (ASAS) working group, who have proposed a core set of criteria for the assessment of AS.¹⁹ In 2005, ASAS also published recommendations for the performance of clinical trials in AS²⁰ and for the management of AS²¹ that included the use of anti-TNF therapies.²² There is work in progress on a novel set of criteria based on recent statistical calculations, and on a probability model²³ that has defined the value of MRI^{24,25} and redefined the value of association with HLA-B27 genotype in the diagnosis and classification of spondyloarthritis.^{26,27}

DIAGNOSTIC CRITERIA FOR SPONDYLOARTHRITIS

There is a long history of developing criteria for spondyloarthritis. The Rome criteria for AS were published in 1963²⁸ and revised in 1968.²⁹ The most recent modifications to these criteria were made in New York in 1984; the latest version is still used in current clinical trials (Box 2).^{30–32} The New York criteria concentrate on back pain and AS, whereas the ESSG criteria have substantially broadened the spectrum of spondyloarthritis.¹⁷ The ESSG criteria for spondyloarthritis have been well studied and validated as classification criteria in population studies; for example, a study in Eskimos³³ showed these criteria to have a sensitivity of 75% and a specificity of 87%. An alternative classification

Box 2 Modified New York criteria for ankylosing spondylitis from 1984.

Clinical criteria

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

Radiologic criterion

- Bilateral sacroiliitis of grade ≥ 2 , or unilateral sacroiliitis of grade 3–4

Definite ankylosing spondylitis is present if the radiologic criterion is associated with at least one of these clinical criteria. Reprinted with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. © van der Linden S *et al.* (1984) Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 27: 361–368.

scheme proposed by Amor *et al.*³⁴ is more complicated, but has a better sensitivity (85%) and specificity (90%) than the ESSG criteria. These improvements result from the incorporation of common extra-articular disease manifestations such as enthesopathy, dactylitis, anterior uveitis and HLA-B27 positivity and, even more importantly, from the requirement for more parameters to be fulfilled (in comparison with the ESSG criteria requirements) before a classification can be made. Another set of criteria proposed by Mau and Zeidler³⁵ have not been commonly used. The basic concepts underlying the classification sets for AS and spondyloarthritis are similar.

All criteria developed so far (including the ESSG and Amor criteria) were developed as classification criteria, although they are often used as diagnostic criteria. The general differences between classification and diagnostic criteria have recently been discussed in detail elsewhere.²⁶ The main problem is that the use of classification criteria to diagnose individual patients leads to an overestimation of the probability of a diagnosis, because this approach does not take into account the pretest probability of the disease (see below). Although the ESSG and the Amor criteria are useful for epidemiologic studies, they are not ideal tools for use in daily clinical practice, where the spectrum of disease is broad and where it is especially important to identify patients with very early stages of

disease. The New York and the ESSG criteria have been shown to have both reduced sensitivity and reduced specificity when disease has been present for less than 12 months.³⁶ Nevertheless, it has been suggested that these classifications might also be a useful guide in a clinical setting.³⁷ These criteria have been commonly used until now because of the lack of useful alternatives.

In discussion of the early diagnosis of spondyloarthritis it is first important to state that, at present, there is no classification scheme or diagnostic criteria for early stages of disease. The next question to ask is, to which subtype of spondyloarthritis, or to which predominant symptom or stage of disease should such criteria apply? This article focuses mainly on early axial and peripheral spondyloarthritis that presents without disease-defining features such as psoriasis and IBD. The clinical problem of early diagnosis of psoriatic skin lesions and Crohn-like gut lesions is not discussed here. Diagnosis of axial spondyloarthritis has to take into account the observation that 40% of patients with undifferentiated spondyloarthritis have both IBP and peripheral arthritis.³ This observation is the reason why a diagnosis of 'predominant axial spondyloarthritis' might be preferable for patients whose spondyloarthritis is characterized by IBP and/or inflammation of the sacroiliac joints and the spine.

There is no formal agreement on the definition of 'early' diagnosis of spondyloarthritis. On the basis of the diagnostic delay mentioned above, 2 years and 5 years duration, respectively, of spondyloarthritis-related symptoms have been used to define early diagnosis in Dutch³⁸ and German³⁹ cohort studies.

HOW CAN AN EARLY DIAGNOSIS BE ACHIEVED?

The first important clinical question when examining a patient with possible spondyloarthritis is whether the back pain reported by the patient can be diagnosed as IBP. The original guidelines developed by Calin 30 years ago⁴⁰ have been re-evaluated.⁴¹ The main features of an early diagnosis of any rheumatic disease, including spondyloarthritis, are clinical history, clinical symptoms, clinical examination, laboratory parameters and imaging (Box 3). On the basis of a recent study from Berlin,⁴¹ new criteria for IBP have been proposed (Box 4), which have been developed in patients with established AS.

Clinical symptoms

The main clinical symptoms of spondyloarthritis are IBP, joint and/or enthesal pain, and swelling. Other symptoms suggest organ involvement, such as eye inflammation due to anterior uveitis. Since anterior uveitis is often not present at the time of presentation, patients should be routinely asked for past symptoms when spondyloarthritis is a possible diagnosis. Cardiac involvement at first presentation is rare, and does not usually have a role in early diagnosis.

Clinical history

A family history of spondyloarthritis or of a related disease such as psoriasis or IBD is of importance. A history of definite anterior uveitis or enthesitis might also contribute to a diagnosis. In patients who present with suspicious skin or gut findings, these need to be assessed properly with the involvement of appropriate specialists.

Clinical examination

In early disease, clinical examination is of limited value for assessing the cause of IBP, because sacroiliitis and spondylitis cannot be diagnosed solely by clinical means. If there is axial involvement, the earliest clinical signs are thought to be reduced lateral spinal flexion, decreased chest expansion and limitations in cervical rotation. Restriction of spinal mobility is a feature of rather more advanced disease. The clinical assessment of peripheral arthritis and enthesitis is assisted if swelling is present. In the case of pain only, imaging is needed to detect inflammatory changes. Patients who have possible eye and skin involvement might, again, require the judgment of a specialist.

Laboratory parameters

There are two main laboratory parameters that are relevant for diagnosis: HLA-B27 genotype and C-reactive protein levels. The role of erythrocyte sedimentation rate measurement is less clear. HLA-B27 is the most important factor, especially in early disease. The correlation of disease activity with laboratory parameters of inflammation is limited, and only half of the patients who present with AS have elevated serum levels of C-reactive protein.⁴²

Imaging

Imaging has been crucial to the diagnosis of spondyloarthritis, especially AS, for decades. The principal reason for its importance is because

Box 3 Parameters considered in the early diagnosis of spondyloarthritis.

Clinical symptoms

- Inflammatory back pain
- Arthritis (swelling, joint effusion, or detected by imaging)
- Enthesitis (swelling, or detected by imaging)
- Accompanying features, including psoriasis (clinical examination, dermatologist), Crohn-like colitis (detected by ileocolonoscopy) and anterior uveitis (clinical examination, ophthalmologist)

Clinical history

- Family
- Rheumatic symptoms
- Accompanying features

Clinical examination

- Lateral flexion of the lumbar spine (<10 cm)
- Chest expansion (<4 cm)
- Cervical rotation (<70°)

Laboratory parameters

- HLA-B27
- C-reactive protein
- Erythrocyte sedimentation rate

Imaging

- Radiography
- MRI
- Ultrasonography

conventional imaging modalities, such as radiography, are both sensitive and specific means for diagnosis of established disease and because more than 95% of AS patients have structural changes in the sacroiliac joints that can be detected using this approach (consequently the 1984 New York criteria require such changes to be present for a diagnosis of AS to be made). Up to about 30% of patients with early disease, however, already have radiographic changes in their sacroiliac joints at first presentation.³⁸ It seems possible (but remains to be proven) that patients with early structural damage might experience a more severe course of disease than those without early damage.

The detection of typical syndesmophytes might be useful to establish a diagnosis of AS by experienced rheumatologists (because of the

Box 4 Proposed new criteria to define inflammatory back pain.

The individual criteria that follow can be used to define the presence of inflammatory back pain (IBP) in adults aged <50 years with chronic back pain and ankylosing spondylitis. The classification criteria for IBP are considered to be fulfilled if two or more out of the following four parameters are present (sensitivity 70.3%, specificity 81.2%^a):

- Morning stiffness of duration >30 min
- Improvement with exercise but not with rest
- Awakening during the second half of the night
- Alternating buttock pain

Use of new criteria for IBP in diagnosis

| Number of parameters present | Sensitivity % (95% CI) | Specificity % (95% CI) | LR ⁺ (95% CI) | Post-test probability (%) ^b |
|------------------------------|------------------------|------------------------|--------------------------|--|
| ≥3 | 33.6 (25.1–43.3) | 97.3 (92.4–99.1) | 12.4 (4.0–39.7) | 39.4 |
| 2 | 36.6 (27.9–46.4) | 83.9 (76.0–89.6) | 2.3 (1.4–3.7) | 10.8 |
| 1 | 18.8 (12.4–27.5) | 61.6 (52.4–70.1) | 0.5 (0.3–0.8) | 2.6 |
| 0 | 10.9 (6.2–18.5) | 57.1 (47.9–65.9) | 0.25 (0.14–0.46) | 1.3 |

^aThese values represent the best trade-off between sensitivity and specificity. ^bThe post-test probability that a patient has ankylosing spondylitis or axial spondyloarthritis relies on the assumption that the prevalence (pretest probability) of these conditions is 5% among patients with chronic back pain.⁵¹ Reprinted with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. © Rudwaleit M *et al.* (2006) Inflammatory back pain in ankylosing spondylitis—a reassessment of the clinical history for classification and diagnosis. *Arthritis Rheum* 54: 569–578. Abbreviations: IBP, inflammatory back pain; LR⁺, positive likelihood ratio.

similarities of syndesmophytes to the spondylophytes that are characteristic of diffuse idiopathic skeletal hyperostosis). Structural changes in the spine caused by new bone formation, however, do not tend to occur early in the course of spondyloarthritis.

MRI has provided much additional diagnostic benefit in early disease. A field strength of 2 T is used for fat-saturated and short tau inversion recovery MRI sequences, and/or a field strength of 1 T, used after application of contrast agents (such as gadolinium diethylenetriamine pentaacetic acid). These techniques increase the sensitivity of detection of inflammation because they produce additive effects on signal intensity and suppress the signal from fat.

MRI has been shown to be particularly useful in the identification of early sacroiliitis,^{24,43} and can predict the development of radiographic changes that are associated with significant sacroiliitis at least 3 years before they occur,⁴⁴ with a positive predictive value of 60%. A new, sensitive, MRI-based scoring system⁴⁵ can be used to measure the changes that occur in AS

patients with IBP on anti-TNF therapy.^{46,47} MRI is regarded as a valuable tool in the assessment of spondyloarthritis patients with early disease,²³ including those with undifferentiated spondyloarthritis.⁶ MRI is useful for detecting enthesitis and synovitis, not only in the axial skeleton, but also in peripheral joints and entheses;⁴⁷ the latter can also be adequately assessed by ultrasonography.^{48–50} The cost effectiveness of these imaging techniques in early disease has not yet been assessed. Nevertheless, from a clinical point of view, MRI findings should be included in future classification and diagnostic criteria for early spondyloarthritis.

Screening

In order to shorten the time interval between onset of first symptoms and diagnosis of spondyloarthritis, it is important not only to improve the diagnostic criteria but also to develop screening strategies that enable primary care physicians to identify patients with spondyloarthritis from the pool of their patients with chronic back pain. According to our proposal,²⁷ patients with chronic back pain that has been present for more than 3 months should be screened for the presence of IBP, the presence of HLA-B27, or for evidence of sacroiliitis by any imaging method.²⁷ If one or more of these parameters are confirmed, patients should be referred to a rheumatologist for a detailed diagnostic work-up. In about 95% of patients, the first onset of spondyloarthritis symptoms occurs before the age of 45 years¹¹ and, therefore, screening should focus on this age-group.

DIAGNOSTIC CHALLENGES AND USE OF A SYSTEMIC APPROACH

It can be a challenge to diagnose early spondyloarthritis, which is why a systematic approach to diagnosis is useful. The predominant symptoms of spondyloarthritis (IBP, asymmetrical arthritis [often gonarthritis] predominantly of the lower limbs, or enthesitis) have to be differentiated from similar symptoms with other causes, such as mechanical disorders and those that result from other rheumatic diseases. Clearly, mechanical pain syndromes are common and, as recently estimated, only about 5% of patients with chronic low back pain who are seen in a primary-care setting can be diagnosed with spondyloarthritis.⁵¹ Furthermore, a painful and swollen knee joint is a frequent complaint,

which can have several causes other than spondyloarthritis⁵² such as meniscal tear, gout or Lyme disease. Similarly, painful swelling of entheses, tendons or ligaments, can frequently occur as a consequence of mechanical stress.⁵³ In a primary-care setting, therefore, the pretest probability that a patient has spondyloarthritis is relatively low in those who present only with the main clinical symptoms of spondyloarthritis. By contrast, if the patient has peripheral arthritis and a clear presence of psoriasis or an established diagnosis of IBD, it is quite likely that spondyloarthritis is present,⁶ especially if other diagnoses are excluded by appropriate clinical, laboratory and imaging investigations. In our opinion, only the aspects of psoriatic arthritis that are associated with an asymmetrical arthritis of the lower limbs should be seen as a spondyloarthritis (i.e. psoriatic spondyloarthritis); other symptoms of psoriatic arthritis, such as arthritis predominantly of the hand and finger joints, could be distinct from spondyloarthritis.⁶ There is, however, no international agreement on this topic so far.⁵⁴

Interestingly, in patients with established AS, macroscopic or microscopic Crohn-like gut lesions (or both) have been detected by colonoscopy even in patients without gut-related symptoms and with no previous diagnosis of IBD.⁵⁵ A substantial proportion of these patients might develop overt IBD later on. Until now, however, screening for IBD by colonoscopy has not been included as part of the diagnostic procedure in patients with rheumatic symptoms compatible with a diagnosis of spondyloarthritis and, therefore, no recommendations in relation to these lesions can be made.

In the past 5 years, a systematic approach has been taken to the diagnosis of reactive arthritis in patients who present with peripheral arthritis,⁵² and to the (predominantly early) diagnosis of axial spondyloarthritis before the presence of radiologically visible sacroiliitis in patients who present with low back pain.^{23,26} The first step in these calculations is always an accurate estimation of the probability that the disease is present in an individual patient before any test is ordered, and before the presence or absence of any specific clinical parameter is taken into account. If the pretest probability that a patient has the disease is low, it can usually be expected that several parameters have to be combined to increase the probability of reaching a diagnosis to 80–90%.

The situation is only different if a single parameter has an extremely high diagnostic value (e.g. an elevated blood glucose level for the diagnosis of diabetes mellitus); however, this situation is uncommon in most rheumatic diseases, including the spondyloarthritides.

Diagnostic values and likelihood ratios

The diagnostic value of a single parameter is determined by its specificity and sensitivity, which can be combined in the calculation of a likelihood ratio (LR) that is equivalent to the percent sensitivity divided by (100 minus the percent specificity). The LR represents the percentage of sick patients with a given test result, divided by the percentage of well individuals with the same result.⁵⁶ Ideally, abnormal test results should be much more typical of ill individuals than of those who are well (high LR) and normal test results should be more frequent in well people than in sick people (low LR). LRs have broad clinical applications, and the LRs of parameters such as symptoms, physical examinations, medical history, laboratory tests, and imaging procedures can be used for a diagnostic work-up. When combined with an accurate clinical diagnosis, LRs from ancillary tests improve diagnostic accuracy in a synergistic manner. Although LRs of 2–5 and 5–10 yield only small or moderate increases, respectively, in the post-test probability that a patient has a particular condition, LRs above 10 lead to a considerable increase in the probability that the patient has the disease.⁵⁶

LRs for the parameters that are used to diagnose (predominantly early) axial spondyloarthritis (i.e. without radiologically evident sacroiliitis) are shown in Table 1. The term axial spondyloarthritis is generally used to refer to all spondyloarthritis patients who have clinical evidence of involvement of the axial skeleton. The main intention, in diagnosis of axial spondyloarthritis, is the early identification of the population of spondyloarthritis patients who are likely to develop AS (i.e. about 50–60% of all patient with undifferentiated spondyloarthritis patients; less than 20% of patients with other spondyloarthritis subtypes). The highest LR values were obtained in young patients with back pain for more than 3 months, with positive MRI findings, and a positive HLA-B27 result. In patients who present with predominant symptoms of back pain, combinations of parameters are necessary to reach a diagnosis with good

Table 1 Sensitivities and specificities for single parameters that can be used for the diagnosis of early, predominantly axial spondyloarthritis, in patients with chronic back pain of >3 months' duration.

| Parameter | Sensitivity (%) | Specificity (%) | LR ^a |
|---|-----------------|-----------------|-----------------|
| Inflammatory back pain | 75 | 76 | 3.1 |
| Alternate buttock pain | 20.4 | 97.3 | 6.5 |
| Enthesitis (especially heel pain) | 36.5 | 88.9 | 3.4 |
| Anterior uveitis | 21.7 | 97.2 | 7.4 |
| Family history of spondyloarthritis | 32.2 | 94.5 | 6.4 |
| Asymmetrical synovitis | 41.3 | 87.3 | 4.0 |
| Psoriasis | 22.7 | 95.2 | 4.0 |
| Inflammatory bowel disease | 9.6 | 97.3 | 4.0 |
| Good response to NSAIDs | 77 | 85 | 5.1 |
| HLA-B27-positive (with axial involvement) | 88 | 90 | 9.0 |
| Elevated erythrocyte sedimentation rate | 50 | 80 | 2.5 |
| Positive MRI findings | 90 | 90 | 9.0 |

These parameters were developed in patients with established AS. ^aThe likelihood ratio is calculated from the percent values for sensitivity and specificity, as follows: $LR = \text{sensitivity} / (100 - \text{specificity})$. Reprinted with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. © Sieper J *et al.* (2002) Diagnosing reactive arthritis: role of clinical setting in the value of serologic and microbiologic assays. *Arthritis Rheum* 46: 319–327. Abbreviation: LR, likelihood ratio.

certainty. Single LRs can be multiplied together to provide LRs for combinations of parameters, which results in an LR product. As calculated in 2004,²³ a post-test probability of accurate diagnosis of axial spondyloarthritis of about 50%, 80%, and greater than 90% is reached if the LR product is approximately 20, 80, and greater than 200, respectively. The basis for this calculation is an assumption that the pretest probability is 5% that a patient who presents with chronic low back pain in the primary-care setting has spondyloarthritis.⁵¹

In the past 30 years, the clinical symptom of IBP have been used as an important parameter both for diagnosis (including early and late diagnosis), and for classification of spondyloarthritis and AS.^{15,30,40} On the basis of our review of the literature, we have calculated a LR of only 3.1 for IBP alone as a diagnostic parameter²¹ (Table 1). All these LR calculations were based on data obtained from patients with established AS. It seems unlikely that IBP-related symptoms differ much between early and late disease, or in other spondyloarthritis subtypes; clearly, however, these potential differences remain to be studied. We have tested the different parameters used to define IBP in AS, and have reported that a new set of IBP criteria (Box 4) has a higher LR than the historical IBP criteria⁴⁰ if two of these four parameters were

present (specificity of 81.2% and sensitivity of 70.3%).⁴¹ With these new IBP criteria, the LR is increased to 12.4 (owing to an increased specificity of 97.3% and a reduced sensitivity of 33.6%) if three or more of the parameters are present. This finding suggests that a combination of the major symptom of IBP with other important parameters, such as HLA-B27 and imaging results, is also relevant in the diagnosis of axial spondyloarthritis and AS.

Similar reasoning has been used to improve the classification and diagnosis of reactive arthritis. On the basis of a review of the published literature on sensitivity and specificity of the tests used to detect a preceding bacterial infection, LRs have been calculated that provide a diagnostic algorithm for the diagnosis of reactive arthritis induced by *Chlamydia trachomatis*, *Salmonella* spp or *Yersinia* spp (Table 2).⁴⁵ A similar approach could also be used to diagnose reactive arthritis induced by *Campylobacter* spp and *Shigella* spp, but this condition has been less well studied. Most of the tests that are used to detect bacterial infections of relevance for spondyloarthritis have limited LRs, especially if a serologic test is used. In the case of reactive arthritis preceded by enteritis, stool cultures are normally negative at the time of onset of the arthritis. Routine use of stool cultures, therefore, is not recommended as a diagnostic

Table 2 Sensitivities and specificities for single parameters that can be used for the diagnosis of reactive arthritis.

| Test | Sensitivity (%) | Specificity (%) | LR ^a |
|--|-----------------|-----------------|-----------------|
| Tests for the detection of infection with <i>Chlamydia trachomatis</i> | | | |
| Antibodies against <i>Chlamydia</i> spp | 73 | 78 | 3.3 |
| Anti- <i>Chlamydia</i> peptide antibodies | 76 | 85 | 5.0 |
| Microimmunofluorescence assay (for <i>Chlamydia</i>) | 70 | 90 | 7.0 |
| <i>Chlamydia</i> in urine sample | 50 | 96 | 12.5 |
| <i>Chlamydia</i> in synovial fluid (on PCR) | 80 | 96 | 20.0 |
| Antibodies against <i>Salmonella</i> spp | 90 | 90 | 9.0 |
| Antibodies against <i>Yersinia</i> spp | 90 | 90 | 9.0 |
| HLA-B27 | 50 | 90 | 5.0 |

^aThe likelihood ratio is calculated from the percent values for sensitivity and specificity, as follows: LR = sensitivity / (100 – specificity). Reprinted with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. © Sieper J *et al.* (2002) Diagnosing reactive arthritis: role of clinical setting in the value of serologic and microbiologic assays. *Arthritis Rheum* **46**: 319–327. Abbreviations: LR, likelihood ratio; PCR, polymerase chain reaction assay.

strategy for reactive arthritis; however, a test such as ligase chain reaction (which can detect *C. trachomatis* in a first morning urine sample) should be performed, because *C. trachomatis* can persist for a long time in the urogenital tract if not treated with appropriate antibiotics. If the infection that precedes reactive arthritis is symptomatic, only one of the bacteria-specific tests need be positive to obtain a diagnosis of reactive arthritis. Since preceding infections are often asymptomatic, however—especially those that involve *C. trachomatis* and *Yersinia* spp—more than one diagnostic parameter must be present to enable a diagnosis of reactive arthritis in patients who present with a clinical picture of undifferentiated oligoarthritis. In this case, HLA-B27 might also be useful in the diagnosis of reactive arthritis.⁴⁷

CONCLUSIONS

In summary, new and improved criteria, both for the diagnosis and classification of predominantly axial or peripheral spondyloarthritis, need to be established and validated by the international scientific community. ASAS is currently working to develop such criteria. These new criteria should be applicable in early stages of disease (i.e. before the occurrence of chronic changes detectable by radiography). Good criteria for early diagnosis will allow for early treatment, which might be essential to prevent progressive structural damage in patients with spondyloarthritis. It remains to be seen whether the presentations of spondyloarthritis can be covered by one set of diagnostic criteria, or whether

these criteria should be chosen according to the predominant clinical manifestations of the main spondyloarthritis subtypes. Either way, the three main clinical presentations—IBP, arthritis and enthesitis—remain, together, as the leading symptoms of spondyloarthritis.

KEY POINTS

- The most frequent, predominant symptoms of spondyloarthritis are inflammatory back pain and asymmetric peripheral arthritis
- Currently, the mean delay between onset of first symptoms and making a diagnosis of ankylosing spondylitis is over 5 years
- The availability of effective therapies makes an early diagnosis mandatory
- The clinical symptoms of inflammatory back pain, structural changes in the sacroiliac joints as seen on X-ray, active inflammation as seen by MRI, and positivity for HLA-B27 are the most important parameters for an early diagnosis of spondyloarthritis, especially in combination
- A combination of clinical and laboratory parameters is necessary for the early diagnosis of both predominantly peripheral and predominantly axial spondyloarthritis

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Competing interests

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