# Evidence-based recommendations for the management of ankylosing spondylitis: results of the Hellenic working group of the 3E Initiative in Rheumatology

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## Abstract

### Objective

*The 3E (Evidence, Experts and Exchange) Initiative is a multi-national effort that involves a large number of experts and practicing rheumatologists addressing specific questions relevant to everyday clinical practice, concerning the management of Ankylosing Spondylitis. Within this multinational group, the Hellenic working group, addressed specific issues complementary to the international ones, and formulated evidence-based recommendations, in order to improve everyday clinical practice for patients with Ankylosing Spondylitis.*

### Methods

*A scientific committee of rheumatologists specializing in AS formulated a set of 7 questions in three domains: diagnosis, monitoring and treatment. Literature search in MedLine for papers published up to August 2006 was conducted. The evidence to support each proposition was evaluated and scored. To avoid any conflict of interest with the sponsor issues related to the use of biologics were not discussed. After extensive discussion among 50 rheumatologists and one Delphi round of votes, the final recommendations were formulated.*

### Results

*A literature search resulted in a total of 320 relevant papers of which 29 were evaluated. A total of seven recommendations were formulated: two concerning diagnosis (role of HLA-B27 and MRI) and prognosis, one concerning monitoring for extra-articular manifestations and four concerning treatment (analgesics, disease modifying agents and physical therapy) were made. The level of evidence and the strength of recommendation were reported. The compiled agreement among experts ranged from 90% up to 100%.*

### Conclusion

*Recommendations for the management of AS were developed using an evidence-based approach followed by physicians' consensus with high level of agreement. These are complementary to existing ones, and address specific domains of everyday clinical practice.*

**Key words**

Ankylosing spondylitis, recommendations, monitoring, diagnosis, treatment.

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## Introduction

Ankylosing spondylitis (AS) is a chronic rheumatic disease with reported prevalence ranging from 0.2-1.1% (1-4). Chronic inflammation, bone destruction and aberrant bone repair result in significant disability (5).

Although diagnosis in established disease is rather easy, in the majority of the cases diagnosis is delayed by 5-10 years, mainly because of delayed referral from general practitioners or non-specialists (6). Restriction of spinal mobility and sacroiliitis by imaging studies, the two main characteristics of AS, may be absent in early stages of the disease and thus contribute to delay diagnosis. AS is a rather heterogeneous disease; patients may have only axial involvement, but they may also have peripheral joint inflammation, extra-spinal manifestations or extra-skeletal inflammation (*i.e.*, uveitis) (7). This heterogeneity poses problems in every day clinical practice to define disease activity and severity. Pharmacological treatment modalities for AS are limited. Non-steroidal anti-inflammatory drugs (NSAIDs) are the cornerstone of pharmaceutical treatment, disease modifying antirheumatic drugs (DMARDS) have been used mainly to treat extraarticular disease, while anti-TNFα agents have been proven effective for patients refractory to NSAIDs (8-11).

Evidence-based recommendations have been increasingly applied in every day clinical life, to aid practicing physicians in clinical decision making. They will hopefully help to improve clinical practice and reduce unjustified health-related costs. The 3E (Evidence, Experts, Exchange) Initiative in Rheumatology is a multinational effort of rheumatologists with a special interest in clinical research. The aim of the initiative is to improve everyday clinical practice for patients with rheumatic diseases by formulating evidence-based recommendations for practical problems (12). Within this multinational group, the Hellenic working group addressed specific issues independently and complementary to the international ones in the domains of diagnosis, monitoring and treatment.

## Methods

*The "3E Initiative" and formulation of national questions by the Hellenic committee*

In the "3E Initiative", 10 countries were represented by national scientific committees. A subgroup committee of seven Greek rheumatologists which consisted of 1 principal investigator (PI) and a scientific committee of 6 members with special interest in AS, participated in 3 rounds of discussions and votes. A set of 7 questions relevant to the management of AS in every day clinical practice was finally formulated, in the domains of diagnosis, monitoring and treatment (Table I).

*Systematic literature search and formulation of the recommendations*

One research fellow (AR) was appointed to perform the literature search. The literature search in MedLine and PubMed was conducted for papers published up to August 2006. The search strategy included all relevant terms for AS combined with different set of keywords specific for each question. The outcome parameters to be assessed in the literature relevant for each domain were predefined by the scientific committee. These were, for the domain of diagnosis sensitivity, specificity and likelihood ratio, whereas for treatment, effect size (ES), number needed to treat (NNT) and number needed to harm (NNH) were assessed. Evidence was categorized according to study design using a hierarchy of evidence in descending order according to study qualities (13) (Table II), and the highest level of available evidence for each question was reviewed in detail.

The evidence from the literature search was then presented by the research fellow to a broad panel of 50 Greek rheumatologists. Data concerning each national question was extensively discussed and a final set of propositions was presented. In one final Delphi round of votes the final national recommendations were formulated (Tables III and IV).

## Results

### *Diagnosis*

*Diagnostic value of HLA-B7 testing versus imaging methods (MRI)*

Chronic low back pain (LBP) is a

**Table I.** Questions selected for literature search by the Hellenic scientific committee*.

*Diagnosis*
- What is the relative contribution of HLA-B27 (compared to MRI) in the diagnosis of AS?
- Are there any predictive factors for evolution into AS in patients with reactive arthritis?

*Monitoring*
- How and how frequently to monitor for extrarticular manifestations of AS?

*Treatment*
- What is the efficacy of analgesics, including muscle relaxants and antidepressants, in the management of AS?
- What is the role of conventional DMARDS for the treatment of peripheral arthritis /enthesitis in AS?
- Should life-style factors (employment) affect therapeutic decisions in AS?
- What are the indications, cost-effectiveness and predictors of response to physical therapy modalities?

*MRI: magnetic resonance imaging; AS: ankylosing spondylitis; DMARDS: disease modifying antirrheumatic drugs.

**Table II.** Category of evidence and strength of recommendation rating scale.

| Category of evidence | Strength of recommendation |
|---|---|
| Ia: Meta-analysis of randomized controlled trials<br>Ib: Randomized controlled trial | A: Category I evidence |
| IIa: Controlled study without randomization<br>IIb: Quasi-experimental study | B: Category II evidence or extrapolated from category I evidence |
| III: Non-experimental descriptive studies, such as comparative, correlation, and case-control studies | C: Category III evidence or extrapolated from category I or II evidence |
| IV: Expert committee reports or opinion or clinical experience of respected authorities, or both | D: Category IV evidence or extrapolated from category II or III evidence |

**Table III.** Summary of recommendations/statements and compiled agreement*.

| *Diagnosis* | Compiled agreement (%) |
|---|---|
| Imaging studies – especially MRI- have better diagnostic performance than HLA-B27 testing. Nevertheless, HLA-B27 could be used as a screening test for patients with inflammatory chronic LBP* that need to be referred. | 100 |
| In patients with reactive arthritis there are no reliable prognostic factors in order to predict the development of AS. | 100 |
| *Monitoring*<br>In the absence of clinical symptoms and signs, no further monitoring of extra-articular manifestations should be performed. | 94.8 |
| *Treatment*<br>Common analgesics may be used in addition to conventional treatment for pain relief. There is no evidence supporting the use of muscle relaxants in AS treatment. Antidepressants could be of benefit in selected cases, particularly for improvement of sleep and possibly of BASDAI. | 94.4 |
| Sulfasalazine and Methotrexate have no effect on enthesitis but may have limited efficacy in selected patients with peripheral arthritis. | 91.5 |
| Functional limitations are greater among AS patients with more physically demanding jobs and therefore these patients might benefit from more aggressive treatment strategies. | 82.9 |
| Physical therapy may contribute to improvement of symptoms and function of AS patients; preferably the program should be individualized and performed in groups or in specialized centers. There is inadequate evidence to support physical therapy cost-effectiveness. | 96 |

*LBP: low back pain; AS: ankylosing spondylitis.

common problem in general practice and the identification of treatable cases such as AS and undifferentiated spondyloarthritis (SpA) is of clinical relevance. Chronic LBP is the leading symptom of AS and undifferentiated axial SpA, and precedes the development of radiographic sacroiliitis, sometimes by many years. There has been controversy about the diagnostic value of HLA-B27 determination in AS. On the other hand, the sacroiliac joints (SI) are involved almost invariably in the disease. Several studies have emphasized the value of computed tomography (CT) and magnetic resonance imaging (MRI) in the diagnosis of AS (14, 15) due to their ability to visualize sacroiliitis earlier than plain radiography (16-22). In addition, MRI can detect inflammatory changes of the sacroiliac joints before any changes are visible by CT (23).

*HLA-B27*: In one uncontrolled study that prospectively followed 88 patients with possible AS for 10 years, HLA-B27 had a moderate sensitivity for AS (68.8%) (24). Studies with patients with established AS were analyzed; in some of them mechanical LBP patients were used as controls, whereas in others the control population included a broader group of patients with other rheumatic diseases, healthy individuals, and mechanical LBP. A very high likelihood ratio (LR) was found for HLA-B27 positivity (11.9 for Caucasians and 14.1 for all ethnic groups). Comparable results were found when data were analyzed with a broader control group (LR: 12.6) (3, 21, 25-44). In a recent analysis of published studies of patients with axial spondylarthropathies without radiographic sacroiliitis – a group that can be described as early spondylarthropathy – Rudwaleit *et al*. found a high likelihood ratio (approaching 9) for HLA-B27 (45).

*MRI*: Concerning MRI in established AS, combined sensitivity from different studies for active lesions was 79.6% (14, 17, 18, 22, 46-52), while specificity ranged from 94.6% to 100% (17) and the LR was 14.7 (14; 48). Comparable high sensitivity (85.5%) was found for chronic lesions of SI joints. (22, 46, 51, 53).

There is also data for the diagnostic properties of MRI in patients with

**Table IV.** Category of evidence and level of recommendations*.

| | Number of studies | Level of evidence | Strength of recommendation |
|---|---|---|---|
| *Diagnosis* | | | |
| Relative contribution of HLA-B27 | 25 | Ia | A |
| Prediction of evolution of ReA into AS | 3 | IV | D |
| *Monitoring* | | | |
| Extra-articular disease | 0 | IV | D |
| *Treatment* | | | |
| Use of analgesics and DMARDs | | | |
| Muscle relaxants | 0 | IV | D |
| Antidepressants and analgesics | 1 | IIa | B |
| MTX for peripheral arthritis | 1 | Ia | A |
| SSA for peripheral arthritis | 6 | Ia | A |
| MTX for enthesitis | 1 | Ia | A |
| SSA for enthesitis | 6 | Ia | A |
| Employment and therapy | 0 | IV | D |
| *Physiotherpy* | | | |
| Symptom improvement | 8 | Ia | A |
| Cost effectiveness | 1 | Ib | B |

*ReA: reactive arthritis; AS: ankylosing spondylitis; DMARDs: disease modifying antirheumatic drugs; MTX: methotrexate; SSZ: sulphasalazine.

suspected sacroiliitis (16, 21, 22, 54-59). Sensitivity for active inflammation was 40.1% as compared to 27% for chronic changes. A high and comparable specificity (93%-100%) for both active and chronic lesions was found.

In early AS diagnosis, the analysis of different studies of patients with early axial spondylarthropathies without radiographic sacroiliitis, showed a high likelihood ratio (LR=9) for MRI, comparable to that of HLA-B27 (45). Additionally, Heuft-Dorenbosch L *et al*., in a cohort of 68 patients with low back pain of less than 2 years duration, showed that inflammation in the SI joints on MRI could be detected early in the course of disease but concluded that contribution of both MRI and HLA-B27 to purely clinical criteria was rather limited in making a diagnosis (60). This conclusion however lacks specificity, since, from patients analysed, only 1/3 had positive MRI at baseline.

*Statement 1*

Imaging studies, especially MRI, have better diagnostic performance than HLA-B27 testing. Nevertheless, HLA-B27 could be used as a screening test for patients with inflammatory chronic LBP that need to be referred.

*Evaluation of the predictive value of clinical, laboratory, imaging or other tests/findings for evolution to AS in patients with reactive arthritis*

The duration of acute reactive arthritis varies with most patients recovering within the first three to five months. Studies on the long term prognosis have shown that within the subsequent 10 years, many of those patients present with radiological sacroiliitis (61). However, it is still uncertain which parameters may predict this evolution (62).

We evaluated studies assessing genetic parameters (HLA-B27), triggering infection, demographics, clinical, laboratory (ESR, CRP) and imaging test results. A 10-year follow-up study (61) suggested that HLA-B27 contributes to the severity of acute disease and to the possibility of AS development (20% of HLA-B27+ reactive arthritis patients developed AS) while a literature review paper (62) also implicated triggering infections for late AS development (reactive arthritis patients developing AS: Yersinia 15%, Salmonella 12%, Shigella 14%, Chlamydia trachomatis 26%). Nevertheless, number of patients included in the above studies was small and both studies were uncontrolled.

*Statement 2*

In patients with reactive arthritis there are no reliable prognostic factors in order to predict the development of AS.

***Monitoring***

*Performance (sensitivity/specificity) of methods to monitor for extra-articular AS manifestations*

Concerning monitoring of AS extra-articular manifestations, we focused on uveitis, enthesitis, aortic root dilatation, lung and intestine involvement. We reviewed parameters (laboratory and imaging) used to assess the activity and severity of the above-mentioned extra-articular manifestations. We found no studies addressing monitoring issues of extrarticular manifestations. The panel agreed that monitoring for extraarticular involvement should be individualized according to symptoms.

*Statement 3*

In the absence of clinical symptoms and signs, no further monitoring for extra-articular manifestations should be performed.

***Treatment***

*Evaluation of the relative benefits and harm of analgesics (including muscle relaxants and antidepressants) for the treatment of AS*

Symptomatic treatment for AS may include – apart from NSAIDs – analgesics, muscle relaxants and antidepressants. Paracetamol and other simple analgesics have not been prospectively studied for pain control in AS. Studies in musculoskeletal diseases other than AS assessing paracetamol induced toxicity have shown no major differences from placebo (63-64). The EULAR recommendations for AS management, propose that analgesics might be considered for pain control in patients in whom NSAIDs are insufficient, contraindicated, and/or poorly tolerated (65). Muscle relaxant and antidepressant use was addressed by one placebo-controlled short-term prospective study (88 AS patients, 2 weeks duration) that showed superiority of amitriptyline over placebo (66) for sleep and BASDAI improvement.

*Statement 4*
Common analgesics may be used in addition to conventional treatment for pain relief. There is no evidence supporting the use of muscle relaxants in the treatment of AS. Antidepressants could be beneficial in selected cases, particularly for improvement of sleep and possibly of BASDAI (Bath Ankylosing Spondylitis Disease Activity Index).

*Evaluation of the relative benefits and harms of MTX/SSA use in the management of peripheral arthritis – enthesitis in AS*
Methotrexate (MTX) is currently one of the most widely used DMARDs in rheumatoid arthritis (RA), but controlled studies in AS are few. Sulfasalazine (SSA) on the other hand, is the best studied DMARD in AS, but its efficacy in specific indications remains unclear. We found two systematic reviews addressing SSA and MTX respectively, for AS treatment (67-69) and 6 randomized control studies that assessed enthesitis as an outcome parameter. In 11 studies included in the systematic review (469 patients on sulfasalazine, 426 on placebo, treatment duration 12 weeks up to 3 years) the effect size for enthesopathy was mild (0.11) and the NNH (withdrawals because of toxicity) was 23 (70-72). Authors concluded that patients with peripheral arthritis might benefit from SSA while there was no evidence of benefit for enthesitis. In two small studies included in the systematic review (81 patients, 12 months duration), MTX had contradictory results compared to naproxen (73). The panel concluded that the included trials did not show any statistically significant benefit of MTX for AS patients.

*Statement 5*
Sulfasalazine and methotrexate have no effect on enthesitis but may have limited efficacy in selected AS patients with peripheral arthritis.

*Evaluation of the impact of employment on disease prognosis and therapeutical decisions*
Functional ability, determined by AS activity and severity, is a major component of health related quality of life and employment restrictions. Studies assessing the impact of employment on disease prognosis have contradictory results. Two studies, a retrospective cohort study of 234 patients and a cross-sectional 326 patients study, indicated that functional limitations correlated with employment and were greater among AS patients with a history of more physically demanding jobs (74, 75). On the other hand, in one prospective 5-year follow-up longitudinal study of 212 patients, no correlation was found between employment and functional disability progression rate (76). Nevertheless, these studies were not designed to address the question of whether aggressive treatment affects employment outcome and thus statement 6 is experts' opinion.

*Statement 6*
Functional limitations are greater among AS patients with more physically demanding jobs, therefore, those patients might benefit from more aggressive treatment strategies.

*Assessment of physiotherapy in AS treatment*
A growing body of research reveals that exercise is a crucial and necessary adjunct to pharmacotherapy in the management of AS as it increases the functional capacity and quality of life in those patients. We evaluated data for the relative benefits and harms, cost effectiveness and predictors of good response of physical therapy in the management of AS. Literature search revealed 13 randomized controlled prospective studies, one systematic review (77) and one retrospective study (78). Physiotherapy lasted from 3 weeks to 9 months, and follow-up period varied from 10 months up to three years (Table V).
*Assessment of physiotherapy*: Home exercise, educational programs and intensive multimodal physiotherapy showed superiority over no physiotherapeutic

**Table V.** Assessment of physiotherapy in AS treatment*.

| Comparisons | Treatment groups | Reference | Patients | SG | CG | Beneficial outcomes |
|---|---|---|---|---|---|---|
| Physiotherapy *vs*. other treatment | • Home exercise, educational programs and intensive multimodal physiotherapy<br>• No physiotherapeutic intervention | 78-82 | 339 | 171 | 168 | Intensive multimodal physiotherapy |
| Various modalities or applications of physiotherapy | • Supervised group physiotherapy (including hydrotherapy)<br>• Home exercise regimes | 83-85 | 233 | 117 | 116 | |
| | • Short and long term effect of global posture reeducation method<br>• Conventional physiotherapy | 86-87 | 40 | 20 | 20 | Supervised group physiotherapy |
| | • Spa therapy | 88 | 120 | 80 | 40 | |
| | • Weekly group physiotherapy<br>• Combined spa exercise | | | | | Combined spa exercise |
| Cost-effectiveness evaluation | • Group physical therapy<br>• Group therapy | 89 | 120 | 80 | 40 | Combined spa exercise |
| | • Therapy at home | 90 | 111 | 34 | 37 | Combined spa exercise |

*SG: study group; CG: control group.

intervention (79-83). Although evidence from studies was not very strong, patients experienced beneficial effects from both individualized home exercise and supervised group physiotherapy programs while short duration combined spa exercise intervention seemed to have even better outcomes when compared to weekly group physiotherapy (84-89).

*Cost-effectiveness evaluation*: Spa therapy seemed to show favorable cost effectiveness and cost-utility ratios compared with standard treatment alone. Sample size for reviewed studies was however very small and thus, results should be interpreted with caution (90, 91).

*Statement 7*

Physical therapy may contribute to improvement of symptoms and function of AS patients; preferably the program should be individualized and performed in groups or in specialized centers. There is inadequate evidence to support physical therapy cost-effectiveness.

**Discussion**

These are the first national recommendations for the management of AS focusing on practical issues of everyday clinical practice. In contrast to guidelines developed by a limited panel of experts in the field, like the ASAS/EULAR recommendations, the 3E involves both experts and a large number of practicing rheumatologists addressing specific questions relevant to clinical practice. Therefore, 3E national recommendations should be considered supplementary to the ASAS/EULAR general guidelines for the management of AS (65, 92) and to the more specific ones formulated by the 3E International Initiative (12). They should facilitate physicians in clinical decisions and optimize the care of AS patients. To this end, efficient dissemination and implementation of the recommendations are of paramount importance.

AS is a rather common chronic inflammatory disease with reported prevalence ranging 0.2-1.1% (1-3). In this project we reviewed a total of 326 papers and selected 140 for detailed analysis. The final set of recommendations was formulated following extensive discussions and votes over a national meeting (Table III). This approach has led to a reduction of personal bias, good external validity, and clear identification of areas of clinical practice where more research data are required. The final level of agreement between members of the initiative was excellent (mean 94.3%, range 82.9 - 100%) (Table IV). Nonetheless, these recommendations do not lack limitations, especially regarding the selection of circumstantial evidence, in the absence of direct evidence, and the incorporation of expert's opinion where data was absent or inadequate.

The diagnosis of AS is based on a combination of clinical, laboratory and radiological findings. Several epidemiologic surveys (studies of hospital records, blood donors, or population prevalence) have been performed to estimate HLA-B27 prevalence in AS patient population. On the other hand, radiological sacroiliitis, the hallmark of the disease, develops after a variable period from the onset of symptoms. MRI represents a significant advance in the diagnosis of AS during the pre-radiographic stage. Active inflammation in sacroiliac joints is depicted by MRI years prior to plain radiography (17, 22, 54). Literature search revealed very high likelihood ratio (LR) for HLA-B27 positivity. In line with this, it has been suggested that HLA-B27 is of value in patients with spondyloarthritis and no radiographic evidence of sacroiliitis (45). The same group supports the value of MRI in diagnosing early spondyloarthritis. They state that if the probability of axial spondyloarthritis in a given patient with normal or equivocal radiograph of the SI joints does not exceed 50–70%, a positive MRI enables one to make the diagnosis of axial spondyloarthritis (probability of >90%), whereas normal MRI may help to render the diagnosis as unlikely (probability 10-20%).

One could support the use of HLA-B27 testing in the setting of general practitioners for screening patients with a history compatible with spondyloarthritis, for further referral to rheumatologists. On the other hand MRI may be used in selected, atypical cases to rule out or establish the diagnosis by rheumatologists. High cost and limited availability are however major disadvantages of MRI routine use at present.

Studies on the long term prognosis of reactive arthritis have shown that within the subsequent 10 years, many patients present with radiological sacroiliitis. Depending on the triggering infection, patient collection, number of patients, and follow-up time, ankylosing spondylitis is observed in 12% to 26% of reactive arthritis patients (61, 93, 94). Although transition rates correlate better with triggering infection and HLA-B27 positivity, their predictive value for AS development is not very strong. We thus conclude that there are no reliable prognostic factors to predict those patients with reactive arthritis who will eventually develop AS.

Simple analgesics, such as paracetamol and opioids, seem to be of value for pain control, especially in patients in whom NSAIDs cannot be used. Although muscle relaxants and antidepressants are often used in everyday practice for symptomatic AS management, no published data exist to support their use. Additionally, only one small short-term study correlates antidepressant drugs with AS patients' quality of life amelioration. We conclude that both simple analgesics and antidepressants could be used in AS patients mainly to improve quality of life.

For many years treatment of AS had been limited to the alleviation of symptoms, mainly using non-steroidal anti-inflammatory drugs. Although disease modifying antirheumatic drugs, especially SSA and MTX, have proven very valuable in other inflammatory arthritides treatment (*e.g.*, RA), their use for AS treatment is of limited (if any) value.

Functional disability predicts future work loss and is the main determinant of medical costs in AS (74, 76, 95-98); thus it is crucial to identify those patients at greater risk for future disability. Functional limitations seem to increase among AS patients with a history of more physically demanding jobs. We conclude that employment of AS patients may affect in some cases treatment strategy and determine requirements for more aggressive treatment.

The long-term goal for AS patients that undergo physical therapy is to try to maintain normal posture, aiming to avoid stiffening in a flexed position. Several trials have analyzed the therapeutic effects of different modalities of physical therapy, demonstrating that physiotherapeutic exercise improves spinal mobility and also reduces functional impairment, at least in the short term. Those studies share however certain limitations, mainly due to patient selection, heterogeneous interventions, different outcome measures and varying methodological quality. Cost effectiveness analysis of various physiotherapeutic modalities is helpful in setting priorities for funding of health care programs. Data however on that field is very limited and should be interpreted cautiously.

In summary, our analysis has confirmed previous findings, demonstrating even stronger that important aspects of disease management, including diagnosis, monitoring and treatment, are based on suboptimal evidence. This study combined systemic literature review together with expert opinion; to this has brought up the daily practice perspective with the inclusion of a large number of practicing rheumatologists. These recommendations should facilitate the care of AS patients without restricting the autonomy of treating physicians. Increasing the familiarity of practicing rheumatologists with available evidence, together with a critical overview of their strength and weakness, may facilitate their implementation in clinical practice. Longitudinal studies are needed to document the effect of these recommendations in curving unjustified variation in clinical practice and in reducing of health related costs.

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