How to treat ankylosing spondylitis and nonradiographic axial spondyloarthritis

Key practical messages from the 2015 American College of Rheumatology recommendations

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Introduction  Spondyloarthritis (SpA) is a group of heterogeneous but interrelated diseases that share many clinical manifestations and the association with the HLA-B27 antigen.¹ These diseases include ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, spondylitis associated with inflammatory bowel diseases, and undifferentiated SpA. The shared clinical manifestations consist of inflammatory back pain, sacroiliitis, asymmetric arthritis, dactylitis, and enthesitis, as well as extraarticular manifestations including uveitis, inflammatory bowel disease, and psoriasis.² SpA can be classified according to the dominant clinical features into axial SpA, which mainly involves the spine and sacroiliac joints, or peripheral SpA, which has features of peripheral arthritis, enthesitis, and dactylitis.³

There are no specific diagnostic criteria for SpA. The first step in the diagnosis remains a clinical examination coupled with an assessment of radiological and laboratory findings. Some studies have reported diagnostic algorithms and others have determined the likelihood ratios of disease associated with various clinical features in an attempt to calculate the probability of axial SpA.⁴,⁵ Diagnosing AS, the prototype disease in the spectrum of SpA, has mainly relied on the presence of clinical symptoms as well as plain radiographic evidence of sacroiliitis. However, radiographic findings of sacroiliitis can take several years to evolve, delaying the diagnosis of AS after symptom onset.⁴,⁸

Over the last few years, patients with classic AS symptoms but lacking the radiographic findings have been classified as having nonradiographic axial spondyloarthritis. These patients are characterized by the absence of sacroiliitis on plain radiography and are diagnosed based on magnetic resonance imaging findings of sacroiliac joint inflammation and/or the presence of other clinical and laboratory features.⁴ It is unclear whether it is an early stage of SpA or a distinct entity.

A number of disease activity scores have been proposed, mainly to assess the response of SpA to treatment. They also help clinicians in assessing the functional capacity of the patients. The most widely used are the Bath Ankylosing Spondylitis Functional Index and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),⁶ as well as the later proposed Ankylosing spondylitis assessment group improvement criteria.⁷,⁸

ABSTRACT  A panel of experts commissioned by the American College of Rheumatology have recently reviewed the literature related to the treatment of patients with ankylosing spondylitis and nonradiographic axial spondyloarthritis. They published a set of recommendations for the management of common clinical questions for both active and stable disease, including the appropriate use of nonsteroidal anti-inflammatory drugs, tumor necrosis factor inhibitors, rehabilitation, education, and preventive care. This article summarizes these recommendations and provides key practical messages for physicians taking care of these patients.

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The American College of Rheumatology (ACR) has recently published its clinical guidelines for the management of patients with AS and nonradiographic axial SpA. The guidelines’ development followed the GRADE methodology, and a panel of experts voted on the individual recommendations based on systematic reviews of the literature. In the present review, we summarize these recommendations and provide key practical messages for physicians taking care of these patients.

**TABLE 1** Implications for strong and conditional recommendations from the perspectives of patients, clinicians, and policy makers

<table>
<thead>
<tr>
<th></th>
<th>Strong recommendation</th>
<th>Conditional recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>patients</strong></td>
<td>Most people in your situation would want the recommended course of action and only a small proportion would not.</td>
<td>The majority of people in your situation would want the recommended course of action, but many would not.</td>
</tr>
<tr>
<td><strong>clinicians</strong></td>
<td>Most patients should receive the recommended course of action.</td>
<td>Be prepared to help patients to make a decision that is consistent with their own values.</td>
</tr>
<tr>
<td><strong>policy makers</strong></td>
<td>The recommendation can be adapted as a policy in most situations.</td>
<td>There is a need for substantial debate and involvement of stakeholders.</td>
</tr>
</tbody>
</table>

**Interpretation of recommendations** According to the GRADE methodology, a recommendation can be categorized as either strong or conditional. A strong recommendation means that the guideline panel was highly confident of the balance between the relative benefits and harms of the 2 management options under consideration. A conditional recommendation means that the guideline panel was less confident of the balance between the relative benefits and harms of the 2 management options under consideration.

A conditional recommendation typically reflects 1 of 2 situations:

1. The benefits and harms being closely balanced, that is, patients may choose either option depending on what they value more: experiencing the benefits or preventing the harms.
2. A low certainty in the effect estimates obtained from the available evidence (ie, lower quality of evidence), introducing uncertainty to the balance between benefits and harms.

Depending on whether benefits outweigh harms or vice versa, the recommendation, whether strong or conditional, may be either in favor or against.

**TABLE 1** explains the implications for strong and conditional recommendations from the perspectives of patients, clinicians, and policy makers.

**Key messages**

**A. Recommendations for the treatment of patients with active ankylosing spondylitis**

**A1. Pharmacologic treatment**

**a** The ACR panel strongly recommended treating patients with active AS with nonsteroidal anti-inflammatory drugs (NSAIDs) over not treating them with NSAIDs. The recommendation was based on low-quality evidence suggesting that treatment with NSAIDs may decrease pain in general, spinal pain, night pain, disease activity, and stiffness. Additionally, NSAID treatment may improve overall functional status. However, NSAID treatment increases the risk of serious adverse events, such as gastrointestinal (GI) bleeding. The decision should be strictly individualized to each patient, taking into consideration other comorbidities and the severity of symptoms. Giving the patient “drug-free holidays” should be considered in the course of treatment.

**b** The ACR panel provided a conditional recommendation in favor of continuous NSAID treatment over on-demand NSAID treatment in patients with active AS. The recommendation reflected the panel’s judgment in the face of very low-quality evidence, that is, not informing whether continuous use of NSAIDs decreases disease activity (BASDAI), and symptoms such as pain, fatigue, and stiffness, or improves functional status relative to on-demand NSAIDs. Potential harms identified for continuous use of NSAIDs include hypertension, dyspepsia, and depression. In view of this conditional recommendation probably a trial of a short course of continuous NSAID therapy, followed by a period of on-demand NSAID therapy, is to be considered with regular evaluation of the patient’s disease activity indices.

**c** The ACR did not recommend a particular NSAID as the preferred choice in adults with active AS. Indeed, the identified low-quality evidence suggested that indomethacin and celecoxib may make little or no difference in decreasing pain and stiffness or improving functional status quality compared with other NSAIDs. However, side effects, especially GI with indomethacin and GI and myocardial infarction with celecoxib, may occur more frequently. According to the evidence, naproxen probably makes little or no difference in decreasing pain and stiffness, but is possibly associated with GI side effects. Since no particular NSAID was recommended, the choice should be left to the clinician and patient to decide on the best drug. The alternate use of different NSAIDs might be considered to decrease cumulative side effects from a single drug.

**d** When considering adults with active AS despite NSAID treatment, the ACR panel provided a conditional recommendation against treatment with slow-acting antirheumatic drugs (SAARDs). Several drugs were assessed and the quality of supporting evidence was moderate for sulfasalazine, paminodronate, leflunomide, and apremilast, low for methotrexate, and very low for thalidomide. Sulfasalazine probably decreases pain, stiffness, joint swelling and tenderness, sleep disturbances, dactylitis, and enthesitis, and improves functional status slightly. Methotrexate may make little or no difference in decreasing disease activity, pain, stiffness, enthesitis, and spondylitis, or improving functional status. High-dose...
into account the patient's characteristics. Patients with contraindication to TNFi should take abatacept, rituximab, or tocilizumab decrease pain and disease activity or improve functional status. However, it is not known whether thalidomide decreases relapse rate. Potential harms for sulphasalazine, pamidronate, leflunomide, and apremilast include GI side effects, arthralgia/myalgia, deep vein thrombosis, and headache, respectively. In the absence of high-quality supportive evidence for the use of SAARDs, these drugs could be considered for therapeutic trials in a minority of patients.

e The ACR panel strongly recommended treating adult patients with active AS who do not respond to NSAID treatment trials, with tumor necrosis factor inhibitors (TNFi) over not treating them with TNFi. The recommendation was based on moderate quality of evidence suggesting that TNFi probably decrease pain, disease activity, and mortality, and improve functional status. However, treatment with TNFi might be associated with side effects such as myocardial infarction, serious infections, serious neurologic disease, and life-threatening cancer. In view of this strong recommendation, the early use of TNFi should be considered in patients with active AS who fail to respond to multiple continuous NSAID courses.

f When a TNFi is indicated in patients with active AS, the ACR panel did not prefer one over the others. The supporting moderate-quality evidence suggested that the choice of a specific TNFi probably makes little or no difference in terms of decreasing disease activity or improving functional status in patients with active AS. Only in patients with concomitant inflammatory bowel disease or recurrent iritis, the panel advocated for treatment with infliximab and adalimumab rather than etanercept. The choice of a particular TNFi should be based on a shared decision making with the patient, taking into consideration the associated extraarticular manifestations and the preferred mode of drug administration.

g When considering adult patients with active AS, in whom SAARDs were not effective and TNFi is contraindicated, the ACR panel suggested treatment with SAARD over treatment with non-TNFi biologic agents (conditional recommendation). The final judgment was based on indirect evidence due to the lack of direct comparisons in the population of interest. The quality of evidence was low for ustekinumab and very low for abatacept, rituximab, and tocilizumab. Ustekinumab may make little or no difference in terms of decreasing pain and disease activity or improving functional status. However, it is not known whether abatacept, rituximab, or tocilizumab decrease pain and disease activity or improve functional status. The choice of a particular SAARD in patients with contraindication to TNFi should take into account the patient’s characteristics.

h For adult patients with active AS despite treatment with the first TNFi, the ACR panel suggested treatment with a different TNFi over adding a SAARD or non-TNFi biologic agent (conditional recommendation). This recommendation was based on very low quality of evidence. Indirect comparison of outcomes from studies on patients who switched to a different TNFi after failure of the first TNFi and studies on patients treated with either SAARDs or non-TNFi biologic agents showed larger improvements in outcomes in those who switched to another TNFi and thus reflected the panel’s final judgment. In the absence of evidence of efficacy of non-TNFi biologic agents, the switch to another TNFi seems to be the most logical alternative in patients who fail to respond to the first TNFi.

i The ACR panel strongly recommended against treatment with systemic glucocorticoids in adult patients with active AS despite treatment with the first TNFi. This recommendation was based on very low quality of evidence, not clearly indicating whether treatment with systemic glucocorticoids is more effective than no such treatment in decreasing disease activity and pain or improving functional status. In view of this lack of evidence, for the efficacy of systemic glucocorticoids, these medications should not be considered in AS patients.

j For adult patients with AS who have isolated active sacroiliitis despite SAID treatment, the ACR panel suggested treatment with locally administered parenteral glucocorticoids over no such treatment (conditional recommendation). This recommendation was based on very low quality of evidence, not clearly indicating whether treatment with systemic glucocorticoids is more effective than no such treatment in decreasing disease activity and pain or improving functional status. In view of this lack of evidence, the panel favored the use of local corticosteroids in this case to avoid the use of systemic corticosteroids. The physician should consider performing the local steroid injection under ultrasound or computed tomography guidance.

k For adult patients with AS and stable axial disease but active enthesitis despite NSAID treatment, the ACR panel provided a conditional recommendation in favor of locally administered parenteral glucocorticoids over no such treatment. This recommendation was based on very low quality of evidence and reflected the panel’s judgment that was based on extrapolation of results from studies on other diseases. Given the risk of tendon rupture, the panel recommended against local injections around the Achilles, patellar, and quadriceps peritendons. In any case, the potential benefits of local steroid therapy should be carefully weighed against the risk of tendon rupture.

l For adult patients with AS and stable axial disease but active peripheral arthritis despite NSAID treatment, the ACR panel provided a conditional recommendation in favor of treatment with locally administered parenteral glucocorticoids over no such treatment. This recommendation was based on very low quality of evidence owing
FIGURE 1  Summary of the main recommendations for the treatment of patients with active ankylosing spondylitis (AS) (A) or stable AS (B) (continued on the next page)

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; IBD, inflammatory bowel disease; NSAIDs, nonsteroidal anti-inflammatory drugs; SSZ, sulfasalazine; TNFi, tumor necrosis factor inhibitors


<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>use continuously; no preferred drug</td>
</tr>
<tr>
<td>physical therapy</td>
<td>active over passive; land-based over aquatic</td>
</tr>
<tr>
<td>systemic glucocorticoids</td>
<td>consider if peripheral flare, pregnancy, IBD flare</td>
</tr>
</tbody>
</table>

A. Recommendations for the treatment of patients with active ankylosing spondylitis (AS) (A)

- TNFi
  - TNfi contraindication
  - non-TNFi biologic
  - remain active
  - use infliximab or adalimumab
  - IBD
  - use TNFi monoclonals

- alternative TNFi
  - isolated sacroiliitis
  - local GC
  - consider if ≤2 joints; use infrequently
  - peripheral arthritis
  - local GC
  - avoid Achilles, patellar, quadriceps
  - enthesis
  - local GC

Legend

- strongly recommend, □ conditionally recommend, □ conditionally recommend against, □ strongly recommend against, □ qualifier

A2. Rehabilitation

- The ACR panel strongly recommended physical therapy for adult patients with active AS. This recommendation was based on moderate-quality evidence suggesting that physical therapy probably decreases disease activity and improves functional status. In view of this strong recommendation, clinicians should urge their patients with active AS to perform regular physical therapy sessions to improve their physical function.

- The panel issued a conditional recommendation in favor of active physical therapy (eg, supervised exercise) over passive physical therapy (eg, massage, ultrasound, heat) in adult patients with active AS. While the quality of evidence was very low, the panel favored active physical therapy to encourage self-management. The panel suggested passive interventions as a supplement, but not a substitute for, active physical therapy interventions. Whenever possible, patients with active AS should be urged to perform active over passive physical therapy and given appropriate guidance and instructions.

B. Recommendations for the treatment of patients with stable ankylosing spondylitis

B1. Pharmacologic treatment

- For adults with stable AS, the ACR panel suggested on-demand over continuous NSAID treatment (conditional recommendation). This recommendation was based on very low quality of evidence suggesting that harms of continuous treatment with NSAIDs outweighed its benefits. The main harms include hypertension, dyspepsia, and depression.

- For adult patients with stable AS receiving both TNFi and NSAIDs, the ACR panel suggested a single drug treatment with TNFi over...
C. Recommendations for the treatment of patients with either active or stable ankylosing spondylitis

a The ACR panel provided a conditional recommendation for regular monitoring using a validated AS disease activity measure and using C-reactive protein or erythrocyte sedimentation rate levels, both in patients with active AS and in those with stable AS. This recommendation was based on very low quality of evidence (no relevant studies identified). The panel judged that regular monitoring would be helpful in following up on active symptoms, while clinically stable patients may not be monitored at every visit. In patients with stable disease, the frequency of monitoring is left to the judgment of the physician.

b The ACR panel voted in favor of advising unsupervised back exercises, without prior training by a therapist, in patients with either active or stable AS (conditional recommendation). The available moderate-quality evidence suggested that unsupervised back exercises probably makes little or no difference in decreasing disease activity and pain or improving functional status. While the panelists favored the general benefits of physical activity, they advised against unsupervised back exercises substituting back exercises supervised by a physical therapist. In the situation

b2. Rehabilitation

a The ACR strongly recommended physical therapy for adult patients with stable AS. This recommendation was based on low-quality evidence suggesting that physical therapy probably decreases disease activity, pain, stiffness, fatigue, and depression and slightly improves overall functional status.

Legend

- strongly recommend
- conditionally recommend
- conditionally recommend against
- strongly recommend against
- qualifier

continuing a combined TNFi/NSAID treatment (conditional recommendation). This recommendation was based on very low quality of evidence. The panel judged that the undesirable consequences of combined treatment might outweigh its desirable consequences, which warrants a trial of withdrawing NSAIDs. The clinician should be prepared to reintroduce NSAIDs in case their withdrawal reactivates AS symptoms.

c For adult patients with stable AS receiving both TNFi and SAARDs, the ACR panel suggested a single drug treatment with TNFi over continuing a combined TNFi/SAARD treatment (conditional recommendation). This recommendation was based on very low quality of evidence and had a rationale similar to that of the previous recommendation. The panel stressed that this recommendation does not apply to the use of low-dose methotrexate with TNFi therapy to decrease the chance of developing antidrug antibodies. The clinician should be prepared to reintroduce SAARDs in case their withdrawal reactivates AS symptoms.

AS and:

- advanced hip arthritis
- severe kyphosis
- acute iritis
- recurrent iritis
- IBD

if:

- use physical therapy
- monitor validated AS disease activity measure, and CRP or ESR regularly
- unsupervised back exercises, formal group or individual self-management education, fall evaluation / counseling

Legend

- strongly recommend
- conditionally recommend
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where supervised exercises are not accessible, patients with either active or stable AS should be encouraged to do unsupervised exercises.

c For adult patients with active or stable AS who progressed to spinal fusion or advanced spinal osteoporosis, the ACR panel strongly recommended total hip arthroplasty over no surgery. This recommendation was based on very low quality of evidence suggesting a positive impact of surgery on mobility and overall lower quality of life. The panel emphasized the importance of performing the surgery by surgeons and at hospitals highly experienced in joint replacement in patients with AS.

b For adult patients with AS who developed severe kyphosis, the ACR panel recommended against elective spinal osteotomy (conditional recommendation based on very low quality of evidence). The panel considered neurologic sequelae and mortality that are associated with surgery. Still, the panel suggested considering elective spinal osteotomy in patients with severe kyphosis who lack horizontal vision and those with major physical and psychological complications, after extensive discussion with the treating physician. Except in rare situations, elective spinal osteotomy in patients with AS and severe kyphosis is generally contraindicated.

c For patients with acute iritis, the ACR panel strongly recommended treatment by an ophthalmologist. Despite the very low quality of evidence, the panel endorsed a strong recommendation due to the expertise of ophthalmologists in diagnosing and managing iritis.

b For adult patients with AS and recurrent iritis, the ACR panel provided a conditional recommendation in favor of prescribing topical glucocorticoids for prompt at-home use in the event of eye symptoms to decrease the severity or duration of iritis symptoms. While the supporting evidence was very low-quality (due to unavailability of studies addressing this issue), the panel considered the importance of prompt treatment of iritis to decrease the severity of ocular complications.

e For adult patients with AS and recurrent iritis, the ACR panel provided a conditional recommendation in favor of infliximab or adalimumab treatment over etanercept treatment. This recommendation was based on very low quality of evidence suggesting lower flare rates of iritis with infliximab or adalimumab compared with etanercept.

f For adult patients with AS and IBD, the ACR panel did not suggest a preferred NSAID. This recommendation was based on very low quality of evidence with lack of studies of comparative harms and controversial findings from studies of comparative effectiveness than others in reducing the risk of worsening of IBD symptoms. The panel pointed to the fact that the short-term treatment course of celecoxib may decrease the risk of side effects.

g For adult patients with AS and IBD, the ACR panel strongly recommended treatment with TNFi monoclonal antibodies over etanercept. This recommendation was based on very low quality of evidence. Nevertheless, the panel extrapolated the results of trials on non-AS IBD patients that reported efficacy of TNFi monoclonal antibodies compared with nonefficacy of etanercept.

D. Recommendations for the treatment of patients with ankylosing spondylitis and specific impairments or comorbidities

a For adult patients with AS who developed advanced hip arthritis, the ACR panel strongly recommended total hip arthroplasty over no surgery. This recommendation was based on very low quality of evidence suggesting a positive impact of surgery on mobility and overall lower quality of life. The panel emphasized the importance of performing the surgery by surgeons and at hospitals highly experienced in joint replacement in patients with AS.

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E. Education and preventive care

a The ACR panel suggested that adult patients with AS should participate in a formal group or individual self-management education. This conditional recommendation was based on moderate quality of evidence suggesting that self-management education probably decreases disease activity, pain, stiffness, fatigue, and depression and improves functional status slightly. However, the panel advocated for involving patients only in programs with proven efficacy and stressed the importance of instructing patients about the disease, its management plan, and prognosis.

b The ACR panel suggested counseling and evaluating fall risk in adult patients with AS. This conditional recommendation was based on very low quality of evidence due to the unavailability of studies addressing this issue. However, the panel urged the clinicians to evaluate and counsel patients with AS about falls and its complications such as spinal fractures and neurologic deficits, especially in those with spinal fusion, osteoporosis, or neurologic/musculoskeletal diseases leading to balance problems and postural instability.

c The ACR panel suggested screening adult patients with AS for osteopenia and osteoporosis with dual-energy X-ray absorptiometry (DXA) scans over no screening. This conditional recommendation was based on very low-quality evidence. The panel suggested to subsequently scan the sites that are most informative on the initial screening.

d For adult patients with AS who developed syndesmophytes or spinal fusion, the ACR panel suggested screening for osteopenia/osteoarthritis with DXA scanning of both the spine and the hips compared with only scanning the hips or other nonspinal sites. This conditional recommendation was based on very low quality of evidence. The panel suggested to subsequently scan the sites that are most informative on the initial screening.

e The ACR panel strongly recommended against electrocardiograms screening for cardiac conduction defects in adult patients with AS. This recommendation was based on very low quality of evidence due to the unavailability of studies addressing this issue. The panel argued that treatment is not indicated for asymptomatic patients with
cardiac conduction defects, and thus detecting such defects will only lead to anxiety and additional medical tests. The panel, however, stressed the importance of investigations in patients with cardiac signs and symptoms such as palpitations, dizziness, syncope, fatigue, angina, and heart failure.

The ACR panel provided a strong recommendation against screening adult patients with AS with echocardiograms for valvular heart disease. This recommendation was based on very low quality of evidence due to the unavailability of studies addressing this issue, but considered the anxiety associated with detecting minor abnormalities as well as the cost of these procedures.

F. Recommendations for the treatment of patients with nonradiographic axial spondyloarthritis

The ACR panel provided a conditional recommendation in favor of TNFi treatment in adult patients with nonradiographic axial SpA despite NSAID treatment over no treatment with TNFi. This recommendation was based on moderate quality of evidence suggesting that TNFi treatment in this category of patients probably decreases disease activity, pain, and stiffness and improves overall functional and mental status slightly. Potential harms include serious infections. The use of TNFi should be considered and discussed with patients with active nonradiographic axial SpA who are poorly responding to NSAIDs.

Summary

We summarized the recent ACR recommendations for the treatment of AS and nonradiographic axial SpA. We reviewed the recommendations for the use of different therapeutic modalities such as NSAIDs, TNFi, glucocorticoids, physical therapy, and the role of joint replacement surgery in the different stages of these 2 diseases. Proper and timely management of these inflammatory conditions by the different medical specialists taking care of these patients will help decrease the burden and long-term complications of these chronic and disabling diseases.

REFERENCES


ARTYKUŁ POGLĄDOWY

Jak leczyć zesztywniające zapalenie stawów kręgosłupa i nieradiograficzną postać spondyloartropatii osiowej?

Najważniejsze wskazówki praktyczne wynikające z zaleceń American College of Rheumatology 2015

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STRESZCZENIE

Grupa ekspertów na zlecenie American College of Rheumatology dokonała niedawno przeglądu piśmiennictwa dotyczącego leczenia chorych na zesztywniające zapalenie stawów kręgosłupa i nieradiograficzną postać spondyloartropatii osiowej. Na jego podstawie opublikowano zalecenia dotyczące postępowania w częstych sytuacjach klinicznych związanych zarówno z aktywną, jak i ze stabilną postacią choroby, w tym właściwego stosowania niesteroidowych leków przeciwapalnych, czynnika martwicy nowotworów (tumor necrosis factor-TNF), rehabilitacji, edukacji i profilaktyki. Poniższy artykuł podsumowuje te zalecenia i dostarcza najważniejszych praktycznych wskazaówek lekarzom sprawującym opiekę nad pacjentami.