



Clinical Practice Guideline

Axial Spondyloarthritis (axSpA)

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Table of Contents

Introduction	5
Diagnosis	6
Classification	6
Inflammatory Back Pain	9
Initial Laboratory Testing	10
Imaging for the Diagnosis of axSpA.....	10
Treatment	10
Goals of Therapy	10
Nonpharmacologic Management of Radiographic and Nonradiographic axSpA	13
Pharmacologic Treatment.....	13
Monitoring	18
Women’s Reproductive Health and axSpA	19
Contraception	20
Pregnancy	21
Lactation	23
Medications Used to Treat axSpA and Their Potential Effects on Pregnancy and Lactation	23
Anxiety and Depression	27
Glossary	28
References	30
Document Updates	34

List of Tables

Table 1. Clarification of the additional findings required to establish the diagnosis of axSpA	7
Table 2. Treatment goals in patients with axSpA	11
Table 3. Pharmacologic management of axSpA	17
Table 4. Medications used in the treatment of patients with AS or axSpA	26

List of Figures

Figure 1. Prevalence of SpA, AS, and RA in France and the US	6
Figure 2. Chart demonstrating the ASAS classification system for axial SpA.....	8
Figure 3A. Management of patients with axSpA.....	15
Figure 3B Management of patients with axSpA and poor response to NSAIDs	16

Abbreviations

ACR	American College of Rheumatology
AS	Ankylosing spondylitis
ASAS	Assessment of Spondyloarthritis international Society
axSpA	Axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD(s)	Biologic disease-modifying antirheumatic drug(s)
BHPR	British Health Professionals in Rheumatology
boDMARD	Biologic originator disease-modifying antirheumatic drug
bsDMARD	Biosimilar disease-modifying antirheumatic drug
BSR	British Society for Rheumatology
COX-2	Cyclooxygenase-2
CRP	C-reactive protein
csDMARD(s)	Conventional synthetic disease-modifying antirheumatic drug(s)
CVD	Cardiovascular disease
DMARD(s)	Disease-modifying antirheumatic drug(s)
DMPA	Depot medroxyprogesterone acetate
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GI	Gastrointestinal
HIV	Human immunodeficiency virus
HLA-B27	Human leukocyte antigen B27
IBD	Inflammatory bowel disease
IBP	Inflammatory back pain
IL-17i	Interleukin-17 inhibitor
IL-12/23	Interleukin 12/23
IUDs	Intrauterine devices
IVF	In-vitro fertilization
MDA	Minimal disease activity
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NSAID(s)	Nonsteroidal anti-inflammatory drug(s)
PDE4	Phosphodiesterase 4
PsA	Psoriatic arthritis
QoL	Quality of life
RA	Rheumatoid arthritis
SI	Sacroiliac
SLE	Systemic lupus erythematosus
SpA	Spondyloarthritis
SSA	Anti-Sjögren's syndrome-related antigen A
SSB	Anti-Sjögren's syndrome-related antigen B
STIR	Short tau inversion recovery
T2T	Treat to target
TNFi	Tumor necrosis factor inhibitor
UC	Ulcerative colitis
US	United States

Introduction

Spondyloarthritis (SpA) is a life-long, immune-mediated, inflammatory arthritis of the spine and sacroiliac (SI) joints and, less commonly, peripheral joints. One common complaint in many but not all patients with SpA is back pain. Patients may also present with extraspinal symptoms such as peripheral arthritis, enthesitis, dactylitis, uveitis, inflammatory bowel disease (IBD), and psoriasis.

There is no known single etiology for SpA. It is likely caused by a combination of genetic, environmental, and immunologic factors. Spondyloarthritis tends to cluster in families, affect young adults (under 45 years of age), and require costly lifelong management. The disease negatively impacts the quality of life (QoL) of those affected. The most common problems are stiffness, back pain, fatigue, poor sleep, side effects of medications, negative body image, and concerns about the future; especially the ability to maintain full-time employment. The latter problem also contributes to the high costs associated with caring for these patients.¹

There are very few estimates of the actual cost of caring for patients with SpA in the United States (US). A 2011 study estimated the mean annual medical cost of caring for a patient with radiographic axial SpA (axSpA; see Classification below) to be approximately \$17 728; this did not include costs for those with nonradiographic axSpA (see Classification below).² The implications of these high medical expenditures become more urgent when they are considered in the context of prevalence rates. Ankylosing spondylitis (AS) is one of the most common rheumatologic diseases in the US, almost equal to rheumatoid arthritis (RA; Figure 1).^{3,4} Helmick et al.⁵ estimated the prevalence of SpA (axial and peripheral) in the population to be as high as 1.31%, that of AS to be 0.52%, and that of RA to be 0.60%.

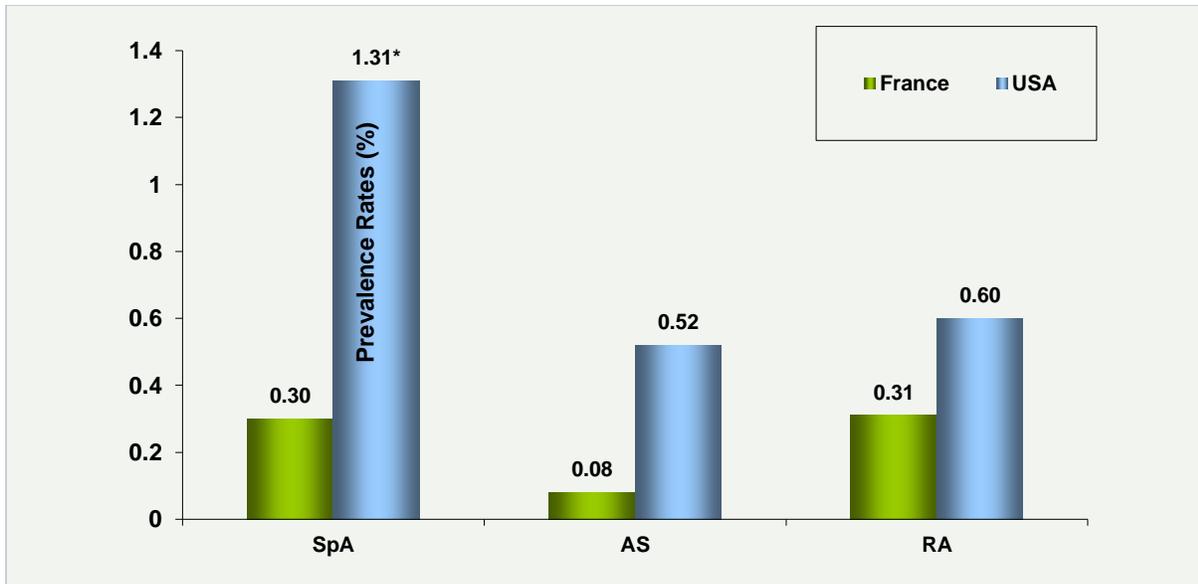


Figure 1. Prevalence of SpA, AS, and RA in France and the USA

*Prevalence estimate ranged from 0.345 to 1.310%.

AS, ankylosing spondylitis; RA, rheumatoid arthritis; SpA, spondyloarthritis

Guillemin F, et al. *Ann Rheum Dis* 2005;64:1427-1430.³ Saraux A, et al. *Ann Rheum Dis* 2005;64:1431-1435.⁴ Helmick CG, et al. *Arthritis Rheum* 2008;58:15-25.⁵

Diagnosis

The diagnosis of SpA is established by integrating a detailed patient history and physical exam with the results of imaging and laboratory tests (see discussion in Classification below). As axSpA progresses, the entheses of the vertebrae may become inflamed, leading to the formation of syndesmophytes and, eventually, fusion of the vertebrae and apophyseal joints of the spine. Deformities of the spine such as flattening of the normal lumbar lordosis, kyphosis of the thoracic spine, and hyperextension of the cervical spine can occur;⁶ and fusion of the SI joints can be seen.

Classification

Axial SpA can be divided into radiographic axSpA (ankylosing spondylitis or AS) and nonradiographic axSpA. However, it has been recognized that both of these entities may represent different points on a spectrum of the same disease. Many, but not all patients with nonradiographic axSpA eventually develop radiographic axSpA.⁷

In 2009, the Assessment of Spondyloarthritis international Society (ASAS) published improved criteria for the classification of SpA.^{8,9} Although these classification criteria were designed to be used for clinical trials, they are often applied as diagnostic criteria in clinical practice and are helpful in deciding which patients should be treated for axSpA.

According to the ASAS criteria, patients <45 years of age with ≥ 3 months of back pain with or without peripheral complaints can be classified as having radiographic axSpA or AS, if they have sacroiliitis on imaging (radiographs or magnetic resonance imaging [MRI]) and ≥ 1 of the SpA findings listed in Table 1; patients can be classified as having nonradiographic axSpA, if they have no imaging signs of sacroiliitis and test positive for human leukocyte antigen B27 (HLA-B27) and have ≥ 2 of the findings listed in Table 1.^{8,9} The classification system for axSpA has been put into a simple and easy-to-follow algorithm in Figure 2.⁸

Table 1. Clarification of the additional findings required to establish the diagnosis of axSpA

Additional Findings	Comments
IBP	At least four of the following must be present to establish the diagnosis of IBP: <ul style="list-style-type: none"> • Age <40 years old • Insidious onset • Improves with exercise • Does not get better with rest • Pain at night that improves upon getting up
Peripheral oligoarthritis mostly in the lower extremities	Past or present active synovitis diagnosed by a physician
Enthesitis (heel)	Past or present pain or tenderness at the insertion of the Achilles tendon or plantar fascia at the calcaneus
Uveitis	Past or present diagnosis by an ophthalmologist
Dactylitis	Past or present diagnosis by a physician
Psoriasis	Past or present diagnosis by a physician
IBD (Crohn's disease or UC)	Past or present diagnosis by a physician
Good response to NSAIDs	Back pain relieved after 24 to 48 hours of full-dose NSAID
Family history of SpA	Presence of AS, psoriasis, acute uveitis, reactive arthritis, ^a or IBD in first-degree, ^b or second-degree ^c relative
HLA-B27	Positive test
CRP	Elevated

^aReactive arthritis, previously known as Reiter's syndrome

^bFirst-degree relative: mother, father, sister, or brother

^cSecond-degree relative: maternal and paternal grandparents, aunts, uncles, nieces, or nephews

AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; CRP, C-reactive protein; HLA-B27, human leukocyte antigen B27; IBD, inflammatory bowel disease; IBP, inflammatory back pain; NSAID(s), nonsteroidal anti-inflammatory drug(s); SpA, spondyloarthritis; UC, ulcerative colitis

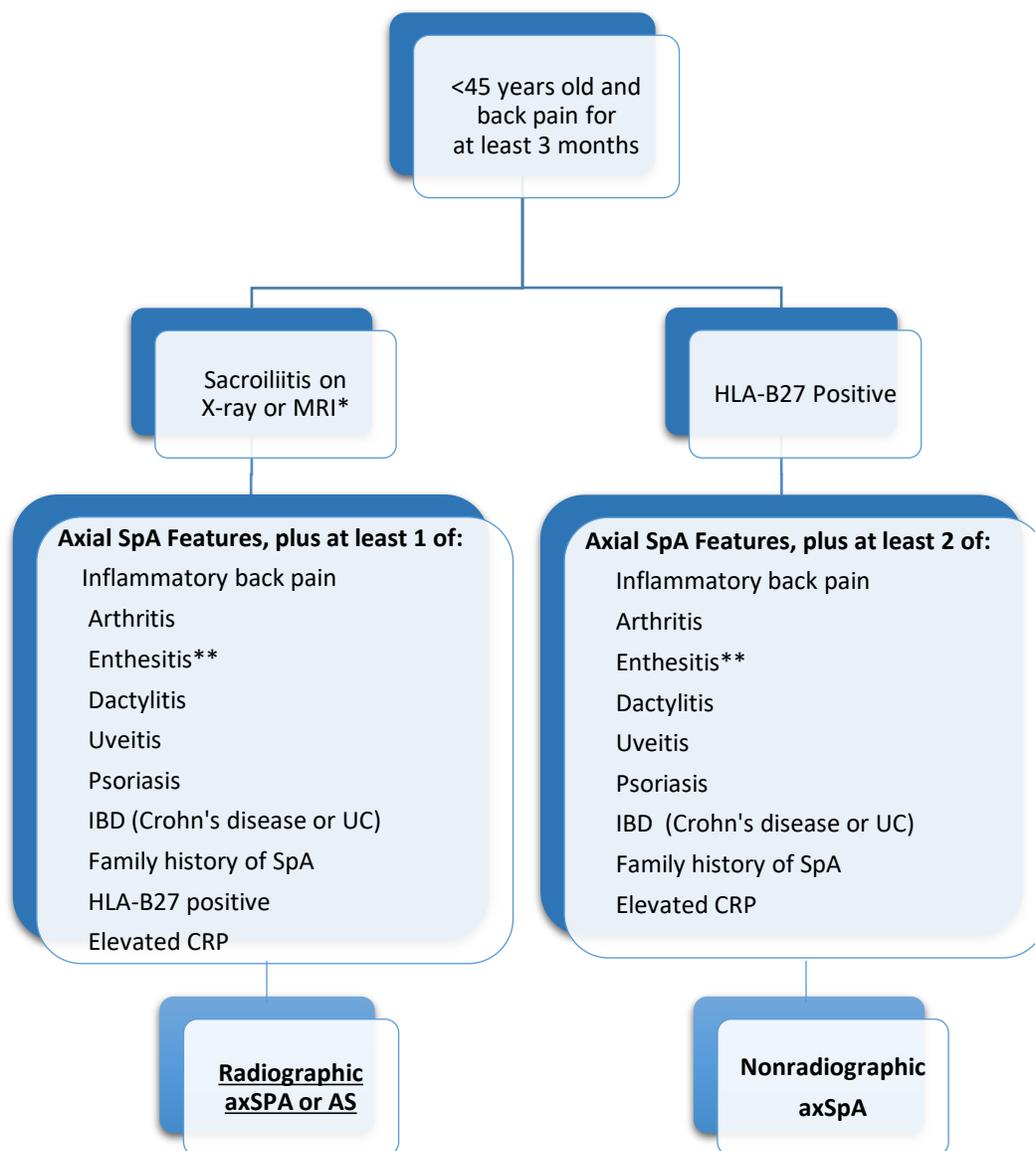


Figure 2. Chart demonstrating the ASAS classification system for axial SpA

*MRI findings of active inflammatory lesions of the SI joints with bone marrow edema and/or osteitis suggestive of sacroiliitis.

**Only enthesitis of the heel is acceptable.

AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; CRP, C-reactive protein; HLA-B27, human leukocyte antigen B27; IBD, inflammatory bowel disease; MRI, magnetic resonance imaging; SpA, spondyloarthritis; UC, ulcerative colitis

The ASAS classification was found to have considerably better sensitivity (79.5%) and specificity (83.3%) than prior classification systems. Using this system, Strand et al.¹⁰ demonstrated that approximately 25% of patients meeting the ASAS criteria for axSpA were missed by rheumatologists who used only clinical expertise to make a diagnosis.

Often, there is an up to 8- to 12-year delay between the onset of symptoms, establishment of the diagnosis of axSpA,¹¹ and the start of appropriate therapy. The most common reason for this delay is that primary care providers who see these patients initially are not familiar with the early signs and symptoms of axSpA. As a result, they frequently fail to refer at-risk patients for a rheumatology evaluation early in the course of the disease. The delay in diagnosis can negatively impact the outcome of the disease, especially in view of the recent advances in drug therapy that can slow disease progression. Primary care providers must learn to identify patients who are at risk for axSpA. Patients presenting with a history of at least 3 months of chronic back pain who are younger than 45 years of age must be evaluated carefully to determine if they have inflammatory back pain (IBP) (see Inflammatory Back Pain below).

If a patient has IBP, then X-rays of the SI joints and/or a HLA-B27 blood test should be performed. A patient with IBP who has (an) abnormal X-ray(s) of the SI joint(s) or is HLA-B27 positive should be referred for a complete rheumatology evaluation.^{12, 13}

Inflammatory Back Pain

Back pain is one of the most common reasons for people to seek medical attention. Approximately 19.2% of the US population between the ages 20 and 69 years reported a history of axial back pain (cervical, upper thoracic, mid- and lower-back, or SI joint area) for <3 months in the *2009-2010 National Health and Nutrition Examination Survey*.¹⁴ In this survey, 40% of the population with axial pain reported that the pain had started before the age of 30, and two thirds reported that it was constant. In addition, using four different sets of criteria for IBP, the report found that between 5% and 6% of 20- to 69-year-olds with back pain met criteria for IBP. However, in the group reporting chronic axial pain (pain for ≥3 months), 28% to 38% met the criteria for IBP.

Seventy percent to 80% of patients with axSpA have IBP. To identify patients at risk for axSpA, providers must be able to recognize when back pain is inflammatory. Back pain is considered to be IBP, if it has been present for at least 3 months and the patient meets four of the following five conditions:⁸

- Age <40 years old
- Insidious onset
- Back pain that improves with exercise
- Back pain that does not improve with rest
- Pain at night that improves when getting up

Comorbidities which have been identified in patients with SpA include pulmonary fibrosis in the apex of the lungs (has not been reported in women), renal amyloidosis, cardiovascular disease (CVD), aortic insufficiency, cardiac conduction changes, asthma, hyperlipidemia, multiple sclerosis, uveitis, diabetes, hypertension, sleep apnea, and spinal fractures.^{15, 16}

Initial Laboratory Testing

More than 90% of patients with axSpA test positive for HLA-B27.¹⁷ A HLA-B test should be performed as part of the initial work-up of patients considered at risk for this condition, if not already done. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are both non-specific measures of inflammation, but baseline levels should be obtained as they may be useful in monitoring response to treatment later. According to the National Institute for Health and Care Excellence (NICE),¹⁸ a negative HLA-B27 or a normal CRP or ESR does not rule out the diagnosis of spondyloarthritis.

Imaging for the Diagnosis of axSpA

According to the European League Against Rheumatism (EULAR), plain films of the SI joints are the initial imaging test that should be obtained in patients whose history, exam, and laboratory findings (HLA-B27) suggest axSpA.¹⁹ If the films do not show evidence of SI disease and clinical suspicion is high, then MRI of the SI joints should be obtained. The findings on MRI suggesting axSpA are:¹⁹

- Bone marrow edema/osteitis
- Structural abnormalities
 - Bone erosions
 - New bone formation
 - Sclerosis
 - Fatty infiltration

No other imaging modalities are recommended by EULAR, with the possible rare exception of computed tomography, if the plain films are negative and MRI is contraindicated.¹⁹

In patients with evidence of sacroiliitis on initial plain films, additional radiographs of the cervical and lumbar spine should be performed. The presence of syndesmophytes on those images predict the future development of additional syndesmophytes.¹⁹

Treatment

Goals of Therapy

A treat-to-target (T2T) approach has been advocated for treating many chronic diseases (diabetes, CVD, RA, etc.) including axSpA. When an evidenced-based T2T paradigm is followed, outcomes improve.²⁰

Targets for the management of axSpA were first established in 2014. The first recommendations, established by an international Task Force, were based primarily on a systematic review of the literature and the consensus of Task Force participants.²⁰ The Task Force noted that the literature available at the time was weak, but they did publish both principles and recommendations for treating axSpA to target. The members agreed that the target should be either remission or low disease activity. They also encouraged researchers to do better and more complete clinical studies to support this hypothesis.²⁰

The recommendations for a T2T strategy in patients with axSpA were reviewed again in 2017.²¹ The 2017 Task Force was composed of 36 members from both Europe and North America, and included rheumatologists, dermatologists, patients, and a nonphysician health professional. According to these recommendations, treatment should aim at providing the best care possible, using a combination of pharmacologic and nonpharmacologic interventions individualized for each the patient.²² The plan should also consider the patient’s general medical status, drug risks, existing comorbidities, current medications, and psychosocial factors (Table 2). Care for patients with comorbidities should be coordinated with the appropriate medical specialists.

Table 2. Treatment goals in patients with axSpA

Control Signs and Symptoms
<ul style="list-style-type: none"> • Pain • Morning stiffness • Fatigue • Extra-articular disease such as uveitis, IBD
Preserve Function
<ul style="list-style-type: none"> • Mobility of the spine • Activities of daily living
Minimize Structural Damage
<ul style="list-style-type: none"> • Osteoproliferation and ankylosis • Bone destruction
Minimize Socioeconomic Impact
<ul style="list-style-type: none"> • Decrease or eliminate need for sick days off from work • Decrease or minimize disability claims
Laboratory Results
<ul style="list-style-type: none"> • Normal ESR and/or CRP

axSpA, axial spondyloarthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease

The target for the management of axSpA is complete remission (absence of clinical or laboratory evidence of inflammation, including normal values of the acute-phase reactants ESR and/or CRP and the absence of extra-articular disease). The target should always be documented in the medical record.

Disease activity should be measured by a validated measure of “musculoskeletal disease activity, and assessment of cutaneous and/or other relevant extra-articular manifestations should be used in clinical practice to define the target and to guide treatment decisions; the frequency of the measurements depends on the level of disease activity.” (Page 9).²¹ Imaging results may be considered in evaluating disease activity but are not encouraged. When the target is reached, it is important that it be maintained throughout the course of the disease.

United Rheumatology recommends the use of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) to measure disease activity in patients with axSpA. With this system, the patient and physician are asked to evaluate the following six parameters (with six questions [Q1-Q6]) on a scale of 1 to 10:²³

- Fatigue and/or tiredness experienced by the patient (Q1)
- Spinal pain (Q2)
- Peripheral joint pain or swelling (Q3)
- Enthesitis (Q4)
- Intensity of morning stiffness (Q5)
- Duration of morning stiffness (Q6)

The BASDAI score is calculated according to the following formula:

$$\frac{\{Q1+Q2+Q3+Q4+\frac{Q5+Q6}{2}\}}{5} = \text{BASDAI}$$

With a minimum score of 0 and a maximum of 10. Scores of ≥ 4 suggest suboptimal control; patients with these scores are good candidates for a change in their medical therapy. The BASDAI score can also be calculated using the Medal online service or the *British Columbia Ministry of Health Form*.

An important principle for the treatment of patients with axSpA advocated by the Task Force is shared decision making between the patient and the rheumatologist with respect to the treatment target. Another important principle is treating to target, which requires the use of a disease activity measure (see discussion above) and changing treatment, as appropriate, if the target is not met within a reasonable amount of time. For those patients with nonrheumatologic comorbidities, care should be coordinated with the appropriate medical specialists. Controlling symptoms and limiting inflammation is important to prevent further bone destruction and disability. Maximizing QoL and minimizing comorbidities are also important. In addition, the Task Force noted that treatment of axSpA is expensive with high medical and societal costs, which must also be considered when developing a treatment plan for each individual patient.²²

Nonpharmacologic Management of Radiographic and Nonradiographic axSpA

In the 2010 and 2016 updates of their joint recommendations for the management of axSpA, the ASAS and EULAR provided the following general nonpharmacologic recommendations:^{22, 24}

- Patient education is strongly encouraged so that the patient can make informed decisions about his/her health care.
- Encourage a regular exercise regimen.
 - This may include physical therapy and:¹⁸
 - Stretching and strengthening exercises
 - Postural exercises
 - Spinal extension
 - Aerobic exercise
 - Range-of-motion exercises for the spine
 - Supervised exercises, on land or in the water, are preferred to home exercises, because they have been found to be more effective than a home exercise program.
 - If supervised exercise is not an option, then a home exercise program should be initiated.
 - Supervised water exercise therapy in a hydrotherapy pool (water temperature between 32°C and 36°C) is also encouraged.²⁵
- Patients may find joining patient associations and self-help groups to be useful.
- Extra-articular manifestations should be managed collaboratively by the appropriate medical specialists.
- Patients should be educated about the increased risk for both CVD and osteoporosis.
- Smoking cessation strategies should be recommended to patients with axSpA, because there has been an association between smoking and disease activity.

It should be stressed to the patient that these nonpharmacologic treatments are essential for obtaining optimal results. However, using only nonpharmacological methods will not provide maximum disease control.

Pharmacologic Treatment

The initial drug of choice for patients with axSpA is a nonsteroidal anti-inflammatory drug (NSAID). The ASAS/EULAR recommendations state that NSAIDs should be given continuously up to the maximum dose and not on an “as needed” basis.²² However; the physician should be aware of the gastrointestinal (GI), cardiovascular, and renal risks of such medications and make the appropriate modifications in dosage; when needed. The latest American College of Rheumatology (ACR) treatment recommendations published in 2016 also strongly recommend continuous NSAIDs as the initial treatment, stating that the benefits “far outweighed” (Page 6) the risks.²⁶ Contraindications to the use of these drugs should always be taken into account. If a patient fails to adequately respond to the initial NSAID, another NSAID should be tried for a total of 4 weeks. Cyclooxygenase-2 (COX-2) NSAIDs should be used in patients with a history of peptic ulcer disease or inflammatory bowel disease (IBD). Caution is advised in patients with heart disease.

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide are not recommended for the treatment of patients with axSpA with one exception:^{24, 26} for patients with peripheral arthritis, sulfasalazine (up to 3 g/day) may be considered. The results of this treatment should be evaluated after 3 months. If the patient fails to adequately respond to this drug after 3 months, a biologic DMARD (bDMARD) should be tried, starting with a tumor necrosis factor inhibitor (TNFi)²² or an interleukin-17 inhibitor (IL-17i) drug. Long-term systemic glucocorticoids should not be used.^{22, 26}

For patients with high disease activity despite treatment with NSAIDs, a bDMARD (biologic originator disease-modifying antirheumatic drug [boDMARD] or biosimilar disease-modifying antirheumatic drug [bsDMARD]) should be given. A TNFi or an IL-17i drug is usually tried first. Elevated CRP or MRI-evidence of sacroiliitis may be an indication that a patient has a reasonable chance of having a good response (applies to both, patients with radiographic and nonradiographic axSpA). Different patients with the same disease activity may respond differently to the same TNFi drug. Therefore, if a patient fails to improve on a particular TNFi or IL-17i drug after a trial of at least 12 weeks with either no change or an increase in BASDAI, either another TNFi drug or an IL-17i should be tried. Conversely, if the patient shows an improvement in the BASDAI score of ≥ 2 after 12 weeks, the current treatment should be continued (Figure 3A and Figure 3B).^{22, 27}

If the patient has a durable remission (≥ 6 months), then tapering drugs slowly should be considered by the treating provider and the patient.¹⁹

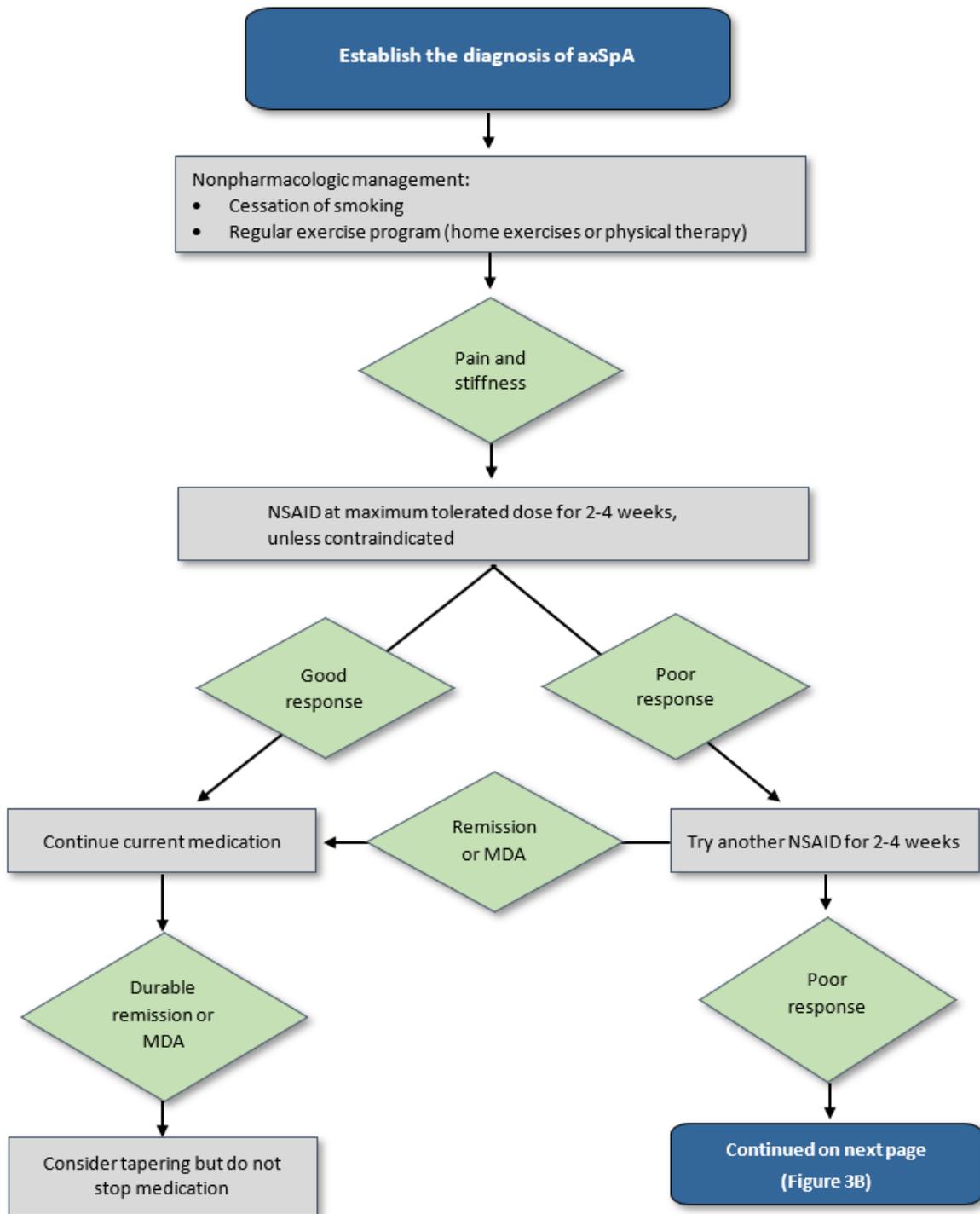


Figure 3A. Management of patients with axSpA

axSpA, axial spondyloarthritis; MDA, minimal disease activity; NSAID, nonsteroidal anti-inflammatory drug

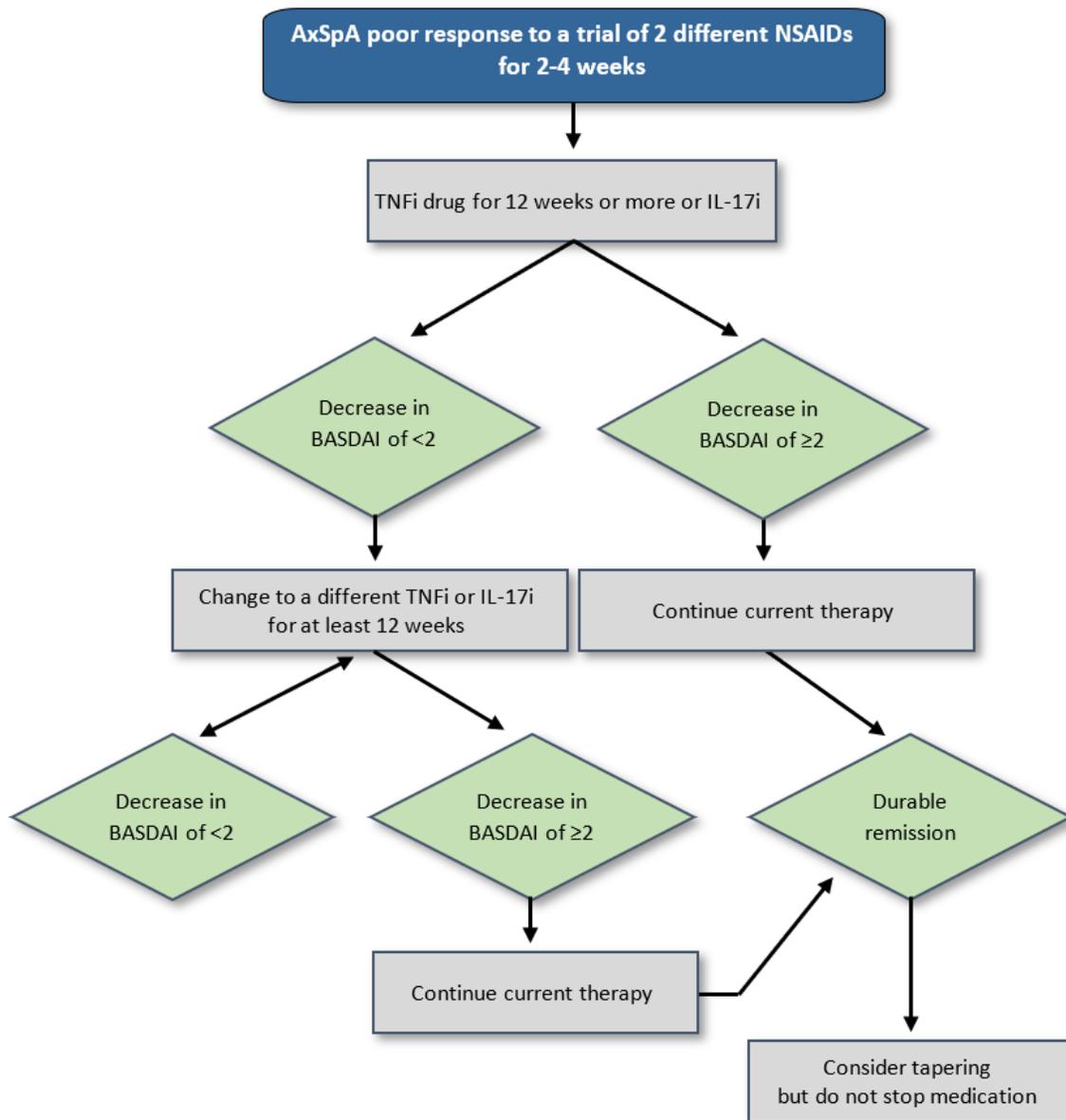


Figure 3B Management of patients with axSpA and poor response to NSAIDs

axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; IL-17i, Interleukin-17 inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; TNFi, tumor necrosis factor inhibitor

van der Heijde D, et al. *Ann Rheum Dis* 2017;76:978-991.²²

No difference in efficacy has been shown between different TNFi medications. However, in patients with IBD or recurrent iritis, infliximab or adalimumab are preferred over etanercept (Table 3).²⁶

If a patient is in a sustained remission (no clinical symptoms or evidence of inflammation for 6 months or more), tapering a bDMARD can be considered, taking into account the predefined treatment target, and

after a discussion between the rheumatologist and the patient. If tapering is considered, either increasing the interval of the dose or decreasing the dose may be considered.

Table 3. Pharmacologic management of axSpA

Medication	Comments
NSAIDs including Coxibs	<ul style="list-style-type: none"> NSAIDs should be given continuously during the period of active disease. Experts suggest that benefit outweighs the risk. NSAIDs should not be used, if there is a contraindication to these drugs. A gastroprotectant should be considered, if using traditional NSAIDs continuously. Dose-modification depending on severity of symptoms should be considered. The possible increased risk of CVD with Coxibs must be considered when choosing one of these drugs over traditional NSAIDs.
TNFi Infliximab Certolizumab pegol Golimumab Adalimumab Etanercept	<ul style="list-style-type: none"> Certolizumab pegol is approved for use in nonradiographic^{28, 29} and radiographic axSpA. There is no data to support the use of one TNFi drug over another, except if the patient has IBD or recurrent iritis. In the presence of IBD or recurrent iritis, infliximab or adalimumab are preferred over etanercept. If the response to one drug is not adequate, switch to a different TNFi drug or to an IL-17i.
IL-17i Secukinumab	<ul style="list-style-type: none"> Can be used as the first line drug. If there is a contraindication to TNFi drugs, use an IL-17i drug as first-line treatment.

axSpA, axial spondyloarthritis; Coxibs, cyclooxygenase-2 (COX-2) inhibitors; CVD, cardiovascular disease; IBD, inflammatory bowel disease; IL-17i, Interleukin-17 inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; TNFi, tumor necrosis factor inhibitor

The effect of etanercept (a TNFi drug) versus sulfasalazine (a conventional DMARD) on active inflammatory lesions in early axSpA was compared by Song et al.³⁰ in a 48-week randomized controlled study. The study showed a 69.2% decrease in MRI-detected inflammation with etanercept, which was almost double the rate observed in the sulfasalazine group. Half of the TNFi-treated patients experienced a clinical remission, whereas remission was seen in only 19% of the patients treated with sulfasalazine.

In addition to pharmacologic treatment; the ACR, EULAR, and ASAS recommend total hip arthroplasty for patients with refractory pain or disability and structural damage to the hip.^{22, 26} Based on expert consensus, the ACR also recommends interval blood tests for ESR and CRP.²⁶

Monitoring

Frequency of follow-up visits should be individualized and based on the course of symptoms, disease severity, and the prescribed treatment. Monitoring should include:²²

- Clinical findings
- Patient Global Assessment
- Patient-reported morning stiffness (severity and duration)
- Fatigue, back pain and/or tenderness
- Peripheral joint pain and/or tenderness
- Swollen joint count
- Results of ESR and CRP as appropriate
- Imaging as appropriate (Table 4)

When patients on a bDMARD drug are in a durable (≥ 6 months) remission, the provider might consider drug tapering.²² However, stopping the drug completely is not recommended, because these patients have a heightened incidence of flares. Unfortunately, the 2016 ASAS-EULAR management recommendations do not define “remission” but suggest that “inactive disease” on an activity measure can be used.²² Tapering can be done by increasing the interval between doses or decreasing the dose at each treatment.

Activity measures are important for tracking a patient’s progress toward the treatment target and are extremely important in monitoring outcomes. They should be recorded at every patient visit together with CRP and/or ESR.

Women's Reproductive Health and axSpA

Spondyloarthritis has traditionally been thought of as a predominately male disorder; however, a recent study in Ontario, Canada, found that the prevalence of SpA has been increasing in the female population. In 1995, the male to female prevalence of this disorder was 1.7 to 1; by 2010, it had decreased to 1.2 to 1.³¹ The study also found that the prevalence of SpA increased almost threefold between 1999 and 2010. Forty five percent of the patients with SpA in this study were women. The age at diagnosis was between 15 and 45 years.

Early in the relationship between a woman of reproductive age with axSpA and her healthcare provider(s), it is important to understand her future plans for a family and to discuss the importance of integrating her axSpA treatment into her program for family planning.³² Regardless of whether or not a patient wants to have children, it is important to discuss the risks of an unintended pregnancy. Half of the pregnancies in the US are unplanned. If the patient wishes to avoid a future pregnancy, referral to her obstetrician/gynecologist or primary care provider for effective family planning is necessary (if she does not yet have a reliable plan with an obstetrician/gynecologist or primary care provider). Some women may wish to become pregnant very soon after the diagnosis of axSpA or in the not too distant future. These patients also benefit from referral to their obstetrician/gynecologist to discuss and start an effective program of family planning. It is very important to impress upon the patient that her axSpA and any associated comorbidities must be well controlled prior to conception to achieve the best possible outcome. If there is an unplanned pregnancy, the patient should be instructed to contact her rheumatologist immediately.

Patients planning for a pregnancy must avoid any medications that could be harmful to a fetus for at least 3 to 6 months prior to conception and during the entire pregnancy. Management of these patients requires close collaboration between the patient's rheumatologist, primary care provider, and obstetrician (or maternal fetal specialist) to achieve the best possible outcome of the pregnancy. Comorbidities such as asthma; CVD including but not limited to aortic insufficiency, hyperlipidemia, multiple sclerosis, osteoporosis, sleep apnea, spinal fractures, depression, uveitis, high blood pressure, diabetes, and malignancy should be under maximum control prior to conception.^{15, 33-35}

In 2014 and 2018, the ACR published information about rheumatic diseases and pregnancy that included the following recommendations:³⁶

- Rheumatic/autoimmune diseases should be controlled for at least 3 to 6 months before trying to conceive.
- Patients can stay on their medications, if they are safe for the fetus; however, this should be discussed with both the patient's rheumatologist and obstetrician. No changes in medications used to treat rheumatic/autoimmune diseases should be made by any treating physician without the approval of the patient's rheumatologist.
- Women with known pulmonary hypertension are advised not to become pregnant, because the underlying lung disease may worsen during pregnancy.

When a patient's axSpA is under control for at least 3 to 6 months, she may consider planning for a pregnancy. Drugs that decrease fertility or can cause congenital anomalies, fetal death, or spontaneous abortions during pregnancy should not be taken during this time and should not be taken during pregnancy. However, in some cases, it may be necessary for a woman with axSpA to take some medication(s) to control her disease and prevent or limit long-term disability. Medication choices should be discussed with the patient, and she and her providers(s) should decide which treatment is most appropriate for her (Table 4).³²

Contraception

Selection of the most effective and appropriate contraception should be a decision that is reached jointly by the patient and her physician(s).

Most of the information about contraception for patients with autoimmune diseases comes from studies of patients with RA, systemic lupus erythematosus (SLE), and IBD. According to Mitchell et al.,³⁷ most forms of birth control are safe for women with autoimmune disorders. These include barrier methods, intrauterine devices (IUDs), and some forms of hormonal contraception.³⁸ However, this may not apply to women with SLE (please refer to the *United Rheumatology Clinical Practice Guideline—Systemic Lupus Erythematosus*).

Multiple different IUDs are available. The pros and cons of each device should be discussed with the patient, if she chooses this method. Some of the issues to be considered for IUDs include potential pregnancy as well as changes in menstrual flow, dysmenorrhea, expulsion, and a risk of infection that is especially important in a patient who may be on immunosuppressive therapy. However, according to Sammaritano et al.,³⁸ there is insufficient data to support a concern for infection.

Oral contraceptives (the pill) usually contain a combination of estrogen and progesterone. Transdermal patches, which usually contain a combination of estrogen and progestin, can be used as well. In a study published in 2001, adherence to the patch was reported to be better than that to oral contraceptives.³⁹ Subdermal implants using progestin only are considered to be the most effective form of hormonal contraception.⁴⁰ Other possible forms of hormonal contraception include a vaginal ring or injections of depot medroxyprogesterone acetate (DMPA), which are given every 3 months by either the patient or her provider. Barrier methods such as male and female condoms, diaphragms, and cervical caps are among the least effective methods of contraception.

It is important to remember that **any contraceptive containing estrogen is not safe for women who test positive for anti-phospholipid antibodies.**

No method is perfect; therefore, as mentioned above, patients must be counseled about the risks of unplanned pregnancies.

Pregnancy

A pregnancy is considered to be high risk, if the mother has any of the following medical problems:^{41, 42}

- Preterm labor
- Preeclampsia
- Placental problems
- Twins or other multiples
- Diabetes
- Hypertension
- Renal Disease
- Epilepsy
- Problems in a prior pregnancy, including but not limited to genetic abnormalities of the baby
- History of multiple miscarriages
- Fetal heart, lung, or kidney problems in a prior pregnancy
- Human immunodeficiency virus (HIV) or hepatitis C, cytomegalovirus, chicken pox, rubella, toxoplasmosis, or syphilis
- Sickle cell anemia
- Asthma
- Autoimmune disease such as SLE, RA, or AS
- Antiphospholipid syndrome
- Age of mother at delivery of >35 years or adolescence
- Thyroid disease
- Obesity
- Zika infection
- Alcohol use
- Smoking
- Substance abuse

Pregnancy in women with (a) rheumatic/autoimmune disease(s) is considered to be high risk, but additional problems can further increase their risk. These include but are not limited to:

- Flare of known rheumatic/autoimmune disease
- History of prior blood clots
- In-vitro fertilization (IVF)
- Presence of anti-Sjögren's syndrome-related antigen A (SSA) and/or antigen B (SSB) antibodies

As stated above, it is important for women have their disease and comorbidities under good control before conception. This may require the use of medications, because not all patients can be adequately controlled without drugs. The Food and Drug Administration (FDA) has not designated any medication used to manage patients with AS or axSpA safe for use in pregnancy. The provider and patient should

carefully review the safety profile of the appropriate drugs and, together, determine which one is best for that patient.

Placental transfer of certolizumab pegol, a TNFi drug, was studied prospectively in the CRIB study, which examined 16 pregnant women with rheumatic disorders who were 30 or more weeks pregnant.⁴³ Two neonates were not included in the final analysis, because they did not meet the study protocol. The drug was not detectable in 13 neonates at birth, and one had minimally detectable levels of the drug (.09% of the level detected in the mother). All of the mothers had the expected blood levels of the drug at delivery. Three infants had very low levels of certolizumab pegol detected in cord blood. The drug was not detectable in the infants at 4 and 8 weeks after delivery. This study concluded that there was either no transfer or minimal transfer of certolizumab pegol to the infants via the placental circulation, and that treatment with certolizumab pegol was safe during pregnancy.⁴³

According to the British Society for Rheumatology (BSR) and the British Health Professionals in Rheumatology (BHPR) guideline,⁴⁴ TNFi drugs can be used in pregnancy, but with caution. The systematic review published by EULAR indicates that TNFi drugs should be considered to control disease activity in the “first part of pregnancy” (Page 797), but that only etanercept and certolizumab pegol can be considered for use throughout pregnancy, because only small amounts of these drugs are transported across the placenta.³² This is consistent with the recommendations above from the BSR and the findings of the CRIB study. According to EULAR, other biologics such as rituximab, abatacept, and tocilizumab should be used only when no other safer drug can control the mother’s disease (Table 4).^{32, 36}

Patients should be cautioned about the use of nonsteroidal anti-inflammatory drugs (NSAIDs) while trying to conceive and during pregnancy. In 2003, Li et al.⁴⁵ published a report on the effects of NSAIDs on pregnancy. The patients in this study did not have AS, axSpA, or any other inflammatory arthritis or autoimmune disease. The authors reported that, if NSAIDs were used early in pregnancy (especially near the time of conception) or for more than 1 week, the risk of miscarriage was increased. The risk for miscarriage was reported to be 10% for any NSAID use; 35% for use near conception, and 52% for more than 1 week of use. In a more recent study, the researchers confirmed that women who had used NSAIDs near conception had a greater risk for miscarriage than those who had not used NSAIDs.⁴⁶ The association of NSAID use and miscarriage was stronger for women who had a low body mass index. The risk of miscarriage increased with increasing exposure to NSAIDs during pregnancy.

Nonsteroidal anti-inflammatory drugs should not be taken in the third trimester because of their association with stenosis of the ductus arteriosus in late pregnancy.⁴⁷

Data about AS or axSpA during pregnancy is limited, but most women are likely to carry their babies to term, especially if the disease was controlled before and during the pregnancy.⁴⁸ If the disease is not well controlled, the symptoms may become worse during pregnancy. It is not always possible to discontinue all medications that are taken to control AS or axSpA. In some cases, it may be necessary for the patient to continue some form of medication for symptom control. The selection of medications should be made after a discussion between the patient and her provider(s). Everyone treating the patient (rheumatologist, primary care provider, or obstetrician/gynecologist) must be kept informed of any changes to

medications. No medications used to treat AS or axSpA should be stopped or changed without the agreement of the patient's rheumatologist.

There are no reports of any improvement in disease activity during pregnancy in women with AS or axSpA. In fact, pregnant patients with AS or axSpA may experience increased pain and morning stiffness in the second trimester. They also may have a higher risk for gestational diabetes, preeclampsia, infection, preterm rupture of membranes, babies small for gestational age, and preterm delivery than women without this disorder. Active disease at any time during pregnancy is associated with an increased risk of preterm delivery.⁴⁹ The incidence of a postpartum flare is very high (up to 87%) in women with AS or axSpA.^{49, 50}

Lactation

There is limited information regarding medication use by nursing mothers with AS or axSpA. Healthcare providers should refer to the section below, *Medications Used to Treat axSpA and Their Potential Effects on Pregnancy and Lactation*. The decision to use any drug during lactation should be made by the patient and her provider(s) together, based on their current understanding of the drug, including but not limited to the amount of the drug found in breast milk and its potential effects on a neonate or infant.

The only TNFi drug for which there is a human study assessing the excretion of the drug into breast milk is certolizumab pegol. This drug has been found to be minimally excreted in breast milk.³⁶ The CRADLE study looked at the level of drug in the breast milk of 17 lactating mothers after three or more doses of certolizumab pegol.⁵¹ Multiple samples were taken over a single dosing period. In 56% of the samples, no drug was detected. In the remaining samples, very low levels of drug were detected (less than 1% of the expected mean drug plasma level in the mother). The authors concluded that treatment with certolizumab pegol was compatible with nursing.

Nonsteroidal anti-inflammatory drugs may be taken during lactation. If corticosteroids are needed, they should be given at the lowest possible dose.³⁶

Medications Used to Treat axSpA and Their Potential Effects on Pregnancy and Lactation

Corticosteroids may be used at the lowest possible dose throughout pregnancy, if needed.³² As discussed above, NSAIDs should be used with caution during conception and early pregnancy. They should not be used in the third trimester.

Certolizumab pegol (Cimzia®; a TNFi drug) is the only medication for which a small amount of data from clinical studies is available.^{43, 51} In the CRIB study,⁴³ 16 pregnant women, all of whom had a rheumatic disorder and were 30 or more weeks pregnant, were followed. Two neonates were not included in the final analysis, because they did not meet study-protocol requirements. In 13 neonates, no drug was detected at birth; in the remaining infant, the level of the drug was .09% of the level detected in the mother. All of the mothers had the expected blood levels of the drug at delivery. In three infants, very low

levels of certolizumab pegol were detected in cord blood. The drug was not measurable in any of the infants at 4 and 8 weeks after delivery. This study concluded that there was no transfer or minimal transfer of certolizumab pegol to the infants via the placental circulation and that treatment with certolizumab pegol was safe during pregnancy.

The other study (CRADLE) followed 17 nursing mothers who had received three or more doses of certolizumab pegol while nursing.⁵¹ Multiple samples of breast milk were taken over a single dosing period. In 56% of the samples, no drug was detected. In the remaining samples, very low levels of drug were detected. The authors concluded that treatment with certolizumab pegol was acceptable for nursing mothers.

According to the EULAR recommendation, certolizumab pegol should be considered in both pregnant and nursing mothers if needed to control the mother's disease.³² However, larger studies are required to confirm these observations.

Adalimumab (Humira®) is transferred across the placenta, and small amounts can be found in human milk.⁵² However, according to the National Institutes of Health (NIH) LactMed database, this drug is most likely destroyed in the infant's GI tract, but caution is advised. According to EULAR, this drug is acceptable during nursing.³²

It is not known whether infliximab (Remicade®) can affect fertility. It crosses the placenta and can be detected in the blood of infants for up to 6 months after birth when mothers took it during pregnancy. Children exposed to infliximab may have an increased risk for infection and should not receive a live virus vaccination until 6 months after birth. It is not known, whether this drug is excreted in human milk. The prescribing information recommends against breast feeding while taking infliximab, but the final decision whether to discontinue the drug or not to nurse should be made by the patient in consultation with her provider(s).^{32, 53}

Small amounts of etanercept (Enbrel®) have been found to cross the placenta and can also be found in cord blood at delivery. According to the prescribing information,⁵⁴ etanercept should be used during pregnancy only if there is no other safer drug available. Information regarding whether or not this drug is found in human milk is inconsistent. According to EULAR's systematic review, there is low excretion of this drug into breast milk; therefore EULAR considers its use to be safe during nursing.³² If a mother has taken etanercept during pregnancy and is nursing, she needs to discuss with her provider(s) whether the drug should be stopped or changed to a different, safer medication or whether she should stop nursing.³²

Golimumab (Simponi®, Simponi® Aria) is a monoclonal antibody that is transported across the placenta during the third trimester of pregnancy.⁵⁵ It is recommended that a woman take this drug during pregnancy only if there is no other option. Infants born to women who have taken this drug while pregnant have an increased risk of infection and should not be given live virus vaccines until 6 months after birth. It is unknown whether this drug is excreted in human milk. If a mother taking golimumab plans to breastfeed her infant, she should discuss with her provider(s) whether or not to continue this drug or to discontinue breast feeding.

Secukinumab (Cosentyx®) is an IL-17 antagonist. According to the FDA, there is inadequate information regarding the use of this drug during pregnancy; therefore, it should be used only if the benefits outweigh the risks. It should be used in nursing mothers with caution.⁵⁶

There are pregnancy registries designed to gather information on maternal-fetal outcomes in patients taking Enbrel and Cimzia. Information on how to provide information to the registries is listed in the prescribing information for each drug. Providers are encouraged to register their patients. The telephone number for the registry may be obtained from the prescribing information at the URLs provided in the References.

United Rheumatology encourages that rheumatologists work closely with high-risk obstetricians and/or maternal fetal specialists, dermatologists, and primary care providers when they are treating women of child bearing age who are pregnant or plan to become pregnant.

Table 4. Medications used in the treatment of patients with AS or axSpA

Medication	Type of Medication	Effects on Fertility	Passes Through the Placenta	Teratogenic	Adverse Effects on Fetus	Long-term effects in children
Etanercept ⁵⁴ (Enbrel®)	TNFi	Unknown	+	Not reported	Unknown	Not reported
Infliximab ⁵³ (Remicade®)	TNFi	Unknown	+	Not reported	Unknown	Not reported
Certolizumab pegol ^{43, 56} (Cimzia®)	TNFi	None to date	Low	Unknown	Unknown	Unknown
Adalimumab ⁵² (Humira®)	TNFi	Unknown	Unknown	Unknown	Unknown	Unknown
Golimumab ⁵⁵ (Simponi®)	TNFi	Unknown	+	Unknown	Unknown	Unknown
Secukinumab ⁵⁶ (Cosentyx®)	IL-17i	Unknown	Unknown	Unknown	Unknown	Unknown
	NSAIDs ⁴⁵⁻⁴⁷	<ul style="list-style-type: none"> Cases of inhibition of follicle rupture 	+	-	<ul style="list-style-type: none"> Decreased renal blood flow Late narrowing of the ductus arteriosus in the fetus 	Unknown
Prednisone ⁵⁷	Glucocorticoid	Unknown	Limited	Increase in oral clefts	<ul style="list-style-type: none"> Rare cataracts Adrenal insufficiency Infection 	Unknown
Dexamethasone ⁵⁸	Glucocorticoid	Unknown	+	Unknown	<ul style="list-style-type: none"> Neuro-developmental abnormalities 	Unknown

+ = yes - = no

AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; IL-17i, interleukin 17 inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; TNFi, tumor necrosis factor inhibitor

Anxiety and Depression

Depression is common in both men and women with AS or axSpA, but it is more common in women, with rates of 46% in women versus 26% in men, according to one study.⁵⁹ In addition, when it occurs, depression is more severe in women than in men. In both women and men, depression is probably related to the level of pain and disability. However, pain contributes less to depression in men than in women. Different than in men, there was a poor correlation between depression and low self-esteem or limited exercise in women. A study compared physician-diagnosed depression in male and female patients with AS to that in the general population.⁶⁰ The investigators found an 80% increase in depression in women with AS and a 50% higher rate in men with AS when compared to the general population.

Shen et al.⁶¹ performed a controlled study of psychiatric disorders in patients with AS compared to those in the general population. Among patients with AS, the investigators reported depression in 3.1%, anxiety disorder in 2.7%, and a sleep disorder in 1.7%; all these rates were higher than those observed in the control group. There was also a greater incidence of sleep disorders than in the control group.

A 2005 study divided 50 patients with AS into two groups—an exercise group and a wait-list or control group.⁶² The researchers wanted to see if 8 weeks of a daily 20-minute home exercise program could improve function, joint mobility, and depression. They found that the exercise group had 33% less pain, a 46% improvement in functional capacity, and a 31% decrease in depression than the control group. When compared to the start of the study, the control group showed no change in functional capacity but increased pain and depression.

United Rheumatology strongly suggests that all patients with a diagnosis of AS or axSpA be evaluated for the presence of anxiety and/or depressive disorders as well as for sleep disturbances. Patients with these disorders should be referred to the appropriate healthcare provider(s) and encouraged to participate in a supervised or at home exercise program.

Glossary

Bone marrow edema	<p>A lesion* within trabecular bone, with signal characteristics consistent with water content** and often with ill-defined margins.</p> <p>*May occur alone or surrounding an erosion or other bone abnormalities.</p> <p>**High-signal intensity and short tau inversion recovery (STIR) images and low-signal on T1 non-contrast images.</p>
Ankylosis	<p>Decreased signal intensity on all sequences, but may be surrounded by increased signal intensity on T1.</p>
Dactylitis	<p>A sausage-shaped digit associated with psoriatic arthritis (PsA).</p>
Enthesitis	<p>Inflammation where tendons, ligaments, or joint capsules attach to bone. In axSpA, this is found at the site of ligamentous insertions to the vertebrae, Achilles tendon and plantar fascial insertion to the calcaneus, patellar tendon insertion on the tibial tubercle, metatarsal heads, superior and inferior borders of the patella, and the base of the 5th metatarsal bone.</p> <p>On MRI, this has high signal intensity on STIR images and/or contrast-enhanced T1 images. The abnormal signal may extend into the bone marrow or soft tissues.</p>
Erosions	<p>On MRI, these are low-signal on T1 images and, if they are active, they will appear as increased signal intensity on STIR images. They may be seen more clearly on T1 fat saturated images or T2 images.</p>
HLA-B27	<p>Also known as human leukocyte antigen with subtypes B 2701-2759. It is a Class I surface antigen detected in blood and found on the surface of white blood cells.</p> <p>It is positive in 70% to 90% of patients with axSpA and in a very high percentage of patients with AS, but it is also found in patients with IBD, reactive arthritis, uveitis, and psoriasis.</p>
IBP	<p>Defined by the ASAS as back pain that has been present for >3 months and meeting four of the following five parameters:</p> <ol style="list-style-type: none">1. Age <40 years old2. Insidious onset3. Back pain that improves with exercise4. No improvement with rest5. Pain at night that improves when getting up.

Sacroiliitis	<p>Inflammation of the SI joints. For the purposes of the ASAS criteria for SpA, the following must be met on MRI:</p> <p>If bone marrow edema/osteitis in subchondral or periarticular bone is seen on only one MRI slice, then more than one lesion must be involved on that slice. If there is only one area of bone marrow edema/osteitis, then it must be seen on at least two contiguous slices.</p>
Subchondral sclerosis	<p>Sclerosis secondary to axSpA should extend at least 5 mm from the SI joint space. It is of decreased signal intensity on all sequences.</p>
Synovitis	<p>An area in the synovial compartment that shows increased post-gadolinium enhancement* of a thickness greater than the width of the normal synovium.</p> <p>*Enhancement (signal intensity increase) is judged by comparison between T1 images obtained before and after intravenous gadolinium contrast.</p>

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