OTHER SPONDYLO-ARTHROPATHIES

(REACTIVE ARTHRITIS and ENTEROPTHIC SP

CHI Formulary Indication Review

INDICATION UPDATE

ADDENDUM- January 2024

To the CHI Original Spondyloarthritis Clinical Guidance- Issued March 2020

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Abbreviations

ADA	Adalimumab
bDMARD	Biologic Disease-Modifying Antirheumatic Drug
CD	Crohn's disease
cDMARD	Conventional Disease-Modifying Antirheumatic Drug

COX-2	Cyclooxygenase 2
Ct	Chlamydia trachomatis
DMARD	Disease-Modifying Antirheumatic Drug
EA	Enteropathic Arthritis or enteroarthritis
ECCO	European Crohn's and Colitis Organization
ERA	Enthesitis-Related Arthritis
ETN	Etanercept
IBD	Inflammatory Bowel Disease
IFX	Infliximab
IL	Interleukin
JAK	Janus Kinase
JSpA	Juvenile Spondyloarthritis
MTX	Methotrexate
NAAT	Nucleic Acid Amplification Testing
NSAID	Non-Steroidal Anti-Inflammatory Drug
PCR	Polymerase Chain Reaction
pSpA	Peripheral Spondyloarthritis
ReA	Reactive Arthritis
SARA	Sexually Acquired Reactive Arthritis
SpA	Spondyloarthritis
SSZ	Sulfasalazine
STI	Sexually Transmitted Infection
TNF	Tumor Necrosis Factor
TNFi	Tumor Necrosis Factor inhibitors
UC	Ulcerative Colitis

Executive Summary

Spondyloarthritis (SpA) is a collective term used to describe a group of rheumatic diseases that share some common characteristics with other inflammatory arthritides, particularly rheumatoid arthritis, while also having distinct features. SpA includes conditions like ankylosing spondylitis (AS), reactive arthritis, psoriatic

arthritis, inflammatory bowel disease-related arthritis, and undifferentiated SpA. These conditions are linked by certain features such as an association with HLA-B27, a specific pattern of peripheral arthritis characterized by its asymmetry, oligoarticular nature, lower extremity predominance, and the potential presence of sacroiliitis, spondylitis, enthesitis, dactylitis, and inflammatory eye disease[2].

SpA is divided into two overlapping categories[3]:

- **Axial spondyloarthritis**, which is characterized by inflammatory pain and arthritis in the spine and hips.
- **Peripheral spondyloarthritis**, characterized by inflammatory pain and arthritis in peripheral joints and tendons other than the spine.

The global prevalence of SpA, including both axial and peripheral SpA, has been estimated at approximately 1%[4]. The prevalence of HLA-B27 was studied in the general population and in patients with axial spondyloarthritis in Saudi Arabia in 2017. HLA-B27 was positive in 60.4, 69, and 25.9% of patients with axSpA, AS, and non-radiographic axSpA (nr-axSpA), respectively[5].

This report will detail the management of peripheral spondyloarthritis other than psoriatic arthritis. For more information regarding the management of axial spondyloarthritis and psoriatic arthritis, please refer to their respective reports.

The clinical signs of peripheral SpA include many of the features shared with other types of SpA. Not all these features may be present in a particular patient. According to the peripheral SpA classification criteria, the most significant manifestations include three peripheral musculoskeletal conditions: arthritis (primarily in the lower extremities and/or asymmetric), enthesitis, and dactylitis. Equally important are other factors such as uveitis and the presence of psoriasis, inflammatory bowel disease (IBD), or a previous infection that could lead to reactive arthritis[4].

There are no specific laboratory findings that definitively indicate peripheral spondyloarthritis (SpA) or SpA as a whole. However, individuals carrying the human leukocyte antigen B27 (HLA-B27) have a higher likelihood of developing SpA. In some patients, markers of acute-phase inflammation may show increased levels. On occasion, laboratory tests can detect microbial infections that have the potential to initiate reactive arthritis[4].

The selection of treatment is determined by choosing agents that can effectively address the specific clinical symptoms in an individual patient, either on their own or in combination. In the case of peripheral spondyloarthritis (SpA), many patients experience peripheral arthritis as a predominant symptom, and most of the available treatments can be applied to various clinical features. However, certain treatments may be more effective for specific symptoms. The main treatment options for the different subtypes and manifestations include non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), glucocorticoids,

tumor necrosis factor inhibitors (TNFis), interleukin (IL) 17 inhibitors, and Janus Kinase (JAK) inhibitors[6].

Enteropathic arthritis, a spondyloarthritis linked to inflammatory bowel disease (IBD) and other gastrointestinal disorders, is an immune-driven inflammatory process. Joint involvement stands out as the most common and impactful extraintestinal manifestation of IBD. Distinct guidelines govern the treatment of IBD, axial spondyloarthritis, and peripheral spondyloarthritis. In the case of enteropathic arthritis, the therapeutic approach must be personalized to consider the diverse intestinal and extraintestinal manifestations of IBD and the clinical features of spondyloarthritis. The use of NSAIDs as first-line agents in enteropathic arthritis is a subject of controversy. Studies examining the relationship between NSAIDs and IBD relapse or flare have yielded conflicting data[7].

Systemic glucocorticoids can be employed for acute flares involving peripheral joints and acute inflammatory bowel symptoms. Conventional DMARDs like methotrexate and sulfasalazine are effective in addressing peripheral joint manifestations of enteropathic arthritis but are not suitable for axial involvement. Numerous randomized controlled trials have shown the efficacy of tumor necrosis factor (TNF) inhibitors in enteropathic arthritis, addressing multiple disease manifestations such as peripheral and axial arthritis, dactylitis, enthesitis, and uveitis[7].

While interleukin-17 (IL-17) inhibitors like secukinumab and ixekizumab are commonly used in spondyloarthritis, they are not recommended in enteropathic arthritis due to the potential risk of inducing new cases of IBD or causing flares in previously quiescent IBD. Ustekinumab, which inhibits interleukins 12 and 23 (IL-12/23), is effective in treating inflammatory bowel disease. Janus kinase (JAK) inhibitors, including tofacitinib and 8padacitinib, play a role in managing enteropathic arthritis for both peripheral and axial symptoms[7].

Reactive arthritis (ReA) is an inflammatory arthritis that appears several days to weeks following a gastrointestinal or genitourinary infection. This condition is typically triggered by bacterial infections, particularly those affecting the genitourinary tract (such as Chlamydia trachomatis, Neisseria gonorrhea, Mycoplasma hominis, and Ureaplasma urealyticum) or the gastrointestinal tract (including Salmonella enteritidis, Shigella flexneri, S. disenteriae, Yersinia enterocolitica, Campylobacter jejuni, and Clostridium difficile)[8].

When an infectious agent is identified as the cause of reactive arthritis, antimicrobial therapy is strongly recommended, often for an extended duration of 3 to 6 months. In the acute phase, NSAIDs are the preferred initial treatment. In cases of mono/oligoarthritis, intra-articular or local glucocorticoids can be used, particularly for enthesitis or bursitis[8].

The systemic use of glucocorticoids is reserved for severe polyarthritis, along with cardiac and ocular manifestations. DMARDs, primarily sulfasalazine, have proven effective in both acute and chronic cases of ReA. Other agents, such as methotrexate and azathioprine, have shown utility in chronic arthritis and are recommended for patients who do not respond to NSAID therapy. Biologicals, including TNF blocking agents like infliximab and etanercept, have been suggested for the treatment of reactive arthritis. However, further studies are required to determine their definitive indications[8].

CHI issued Spondyloarthritis guidance after thorough review of renowned international and national clinical guidelines in March 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an **addendum** to the prior CHI Spondyloarthritis clinical guidance and seeks to offer guidance for the effective management of **other spondyloarthropathies** provides an **update on the guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized being **the addition of new guidelines and review articles** Spondyloarthritis in over 16s **(NICE Guidelines)**: diagnosis and management **(2017)**, **2014** Update of the **Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada** Treatment Recommendations for the Management of Spondyloarthritis. Part II: Specific Management Recommendations, **British Association of Sexual Health and HIV National Guideline** on the Management of Sexually Acquired Reactive Arthritis **(2021)**, **2021** clinical practice guidelines for the diagnosis, treatment, and follow-up of patients with peripheral spondylarthritis the **Colombian Association of Rheumatology: Consensus statement**, **Current Clinical Microbiology Reports**: Reactive Arthritis Article: **Update (2020)**, **Enteropathic Spondyloarthritis**: From Diagnosis to Treatment **2013 (Review article)**, **Expert Review of Clinical Pharmacology**: Management of patients with inflammatory bowel disease and spondyloarthritis **(2017)** and **Italian Expert Panel** on the management of patients with coexisting spondyloarthritis and inflammatory bowel disease **(2014).**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is recommended to include the SFDA registered drugs **Upadacitinib (RINVOQ®)**, **Azathioprine (IMURAN®)** and **Cyclosporine (Effyren®)** in the CHI formulary while removing Acemetacin since it is no longer registered in the SFDA Drug list of November 2023. **Golimumab, Ixekizumab, Rituximab, Certolizumab pegol, Secukinumab** and **Ustekinumab.** Should also be delisted since they have no role in the treatment of the forms of spondyloarthritis detailed in this report (more details

regarding the removal of these drugs can be found in Section 2.3 Delisting). Furthermore, there was some changes made to the previously listed drugs: **NSAIDs (Aceclofenac, Celecoxib, Dexketoprofen, Diclofenac Potassium, Diclofenac Sodium, Etoricoxib, Flurbiprofen, Ibuprofen, Indomethacin, ketoprofen, Mefenamic acid, Meloxicam, Naproxen, Piroxicam, Tenoxicam), leflunomide, methotrexate** and **sulfasalazine** (more details regarding the modifications for these drugs can be found in Section 2.2 Modifications).

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in Spondyloarthritis management.

Below is a table summarizing the major changes based on the spondyloarthritis guidelines used to issue this report:

Table 1. General Recommendations for the Management of Other Forms of Spondyloarthritis (Reactive Arthritis and Enteropathic Spondyloarthritis)

Management of Other Spondyloarthropathies		
Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Enteropathic arthritis		
For cases of peripheral or axial SpA with quiescent inflammatory bowel disease, NSAIDs should be generally avoided, however, a short-term course of selective COX-2 inhibitor for no more than two weeks and systemic steroids as a bridge to SSZ is an acceptable option.	N/A	Italian Expert Panel on the management of patients with coexisting spondyloarthritis and inflammatory bowel disease (2014)[9]
In specific cases, patients with peripheral arthritis and other extraintestinal manifestations have found immunosuppressive drugs such as methotrexate, azathioprine, cyclosporine, and leflunomide to be beneficial and effective.	N/A	Enteropathic Spondyloarthritis: From Diagnosis to Treatment 2013 (Review article)[9]
Anti-tumor necrosis factor-alpha (anti-TNFα) drugs, notably infliximab and	N/A	Enteropathic Spondyloarthritis:

adalimumab, have shown efficacy not only in controlling intestinal inflammation but also in alleviating joint-related symptoms, encompassing both axial and peripheral manifestations.		From Diagnosis to Treatment 2013 (Review article)[1]
Sulfasalazine is a suitable choice for addressing peripheral spondyloarthritis (SpA) because it has demonstrated its effectiveness in managing this condition in these patients.	N/A	Expert Review of Clinical Pharmacology: Management of patients with inflammatory bowel disease and spondyloarthritis (2017)[10]
In terms of immunomodulators, both methotrexate and thiopurines are found to be ineffective for the treatment of axial SpA. For instances of active, non-complicated luminal Crohn's Disease (CD) linked with axial Spondyloarthritis (axial SpA), the use of anti-TNFα agents is advised.	N/A	Italian Expert Panel on the management of patients with coexisting spondyloarthritis and inflammatory bowel disease (2014)[9]
TNF inhibitors are second-line agents for axial symptoms after NSAIDs. In case of primary nonresponse within 12 weeks or loss of response, consider switching to another TNF inhibitor.	N/A	Italian Expert Panel on the management of patients with coexisting spondyloarthritis and inflammatory bowel disease (2014)[9]
Peripheral arthritis with active IBD responds well to treatment of the underlying disease (IBD) in addition to physiotherapy and simple analgesia.	N/A	Italian Expert Panel on the management of patients with

Local injection of corticosteroids may be required if symptoms don't resolve rapidly. A short-term course of selective COX-2 inhibitor for no more than two weeks and systemic steroids as a bridge to SSZ is an acceptable option. If arthropathy becomes persistent even after control IBD, sulfasalazine, methotrexate, or anti-TNF therapy can be started. In case of primary nonresponse within 12 weeks or loss of response, consider switching to another TNF inhibitor.		coexisting spondyloarthritis and inflammatory bowel disease (2014)[9]
Reactive arthritis		
Initial treatment for adult patients diagnosed with peripheral spondyloarthritis (pSpA) should involve the use of conventional disease-modifying antirheumatic drugs (cDMARDs).	Conditional recommendation in favor of cDMARDs intervention. Certainty of the evidence low ⊕⊕ ○○	The Colombian Association of Rheumatology (2021)[13]
Adult patients with peripheral spondyloarthritis (pSpA) who do not respond positively to their treatment or cannot tolerate conventional disease-modifying antirheumatic drugs (cDMARDs) should consider commencing therapy with either an anti-TNFα or an anti-IL17A agent, as recommended.	Strong recommendation in favor. Certainty of the evidence moderate ⊕⊕⊕○	The Colombian Association of Rheumatology (2021)[13]
Nonsteroidal anti-inflammatory drugs (NSAIDs) have gained widespread recognition as the primary treatment for numerous inflammatory arthritic conditions. Ensuring a steady and consistent usage of these drugs is crucial to fully utilize their anti-inflammatory properties. In these situations, no specific NSAID has demonstrated a distinct advantage	Grade 1B	The British Association of Sexual Health and HIV National Guideline (2021)[12]

over the others, and individual responses to them can vary.		
Topical corticosteroid preparations are suitable for addressing skin or mucous membrane lesions.	Grade 1C	The British Association of Sexual Health and HIV National Guideline (2021)[12]
It is imperative to administer antimicrobial therapy when a genital infection is detected in cases of reactive arthritis. The treatment should align with the recommendations for uncomplicated infections specified in relevant infection management guidelines.	Not Graded	The British Association of Sexual Health and HIV National Guideline (2021)[12]
Prolonged antimicrobial treatment for sexually acquired reactive arthritis (SARA) lacks confirmation of its efficacy and is, therefore, not advisable.	Grade 1C	The British Association of Sexual Health and HIV National Guideline (2021)[12]
General Recommendations		
Non-pharmacological approaches for spondyloarthritis (SpA) should include patient education and routine physical activity, preferably supervised by experienced physiotherapists in specialized facilities. It is crucial to consider both individual and group physical therapy, and patients may find value in participating in patient organizations and self-support groups.	Patient education (I, A), physical activity (II, B), individual and group physical therapy (I, A), self-support (IV, D) groups.	Canadian Rheumatology Association/ Spondyloarthritis Research Consortium of Canada (2014)[11]
Consider employing corticosteroid injections in specific sites of inflammation, such as the sacroiliac (SI) joints, peripheral joints, and entheses.	Sacroiliac joints: (I, A), Psoriatic arthritis joint (II, B), All other sites (IV, D)	Canadian Rheumatology Association/ Spondyloarthritis Research Consortium of Canada (2014)[11]
If patients experience ongoing, treatment-resistant pain or disability in	IV, D	Canadian Rheumatology

addition to X-ray or imaging evidence of structural hip joint damage, total hip arthroplasty should be considered, regardless of the patient's age.		Association/ Spondyloarthritis Research Consortium of Canada (2014)[11]

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

A. Guidelines for Axial Spondyloarthritis

Please refer to the axial spondyloarthritis (ankylosing spondylitis) report.

B. Guidelines for Psoriatic Arthritis

Please refer to the psoriatic arthritis report.

C. Guidelines for Other Forms of Peripheral Spondyloarthritis

This section is divided into two parts: one part includes recommendations from **updated versions of guidelines** mentioned in the previous CHI spondyloarthritis report, and another part includes **newly added guidelines** that have helped generate this report.

C.1 Revised Guidelines

There was no mention of guidelines related to the management of other forms of peripheral spondyloarthritis.

The guidelines in the previous CHI spondyloarthritis report mainly focused on the management of axial spondyloarthritis.

Therefore, the aim of this report is to focus on the management of types of spondyloarthritis other than axial spondyloarthritis and psoriatic arthritis.

It will mainly cover the guidelines related to the management of **reactive arthritis** and **enteropathic spondyloarthritis**.

C.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Spondyloarthritis report, along with their recommendations.

Table 2. List of Additional Guidelines

Additional Guidelines
Spondyloarthritis in over 16s **(NICE Guidelines):** diagnosis and management **(2017)**
2014 Update of the Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada Treatment Recommendations for the Management of Spondyloarthritis. Part II: Specific Management Recommendations
British Association of Sexual Health and HIV National Guideline on the Management of Sexually Acquired Reactive Arthritis **(2021)**
2021 clinical practice guidelines for the diagnosis, treatment, and follow-up of patients with peripheral spondylarthritis the **Colombian Association of Rheumatology: Consensus statement**
Current Clinical Microbiology Reports: Reactive Arthritis Article: **Update (2020)**
Enteropathic Spondyloarthritis: From Diagnosis to Treatment **2013 (Review article)**
Expert Review of Clinical Pharmacology: Management of patients with inflammatory bowel disease and spondyloarthritis **(2017)**
Italian Expert Panel on the management of patients with coexisting spondyloarthritis and inflammatory bowel disease **(2014)**

C.2.1 NICE Guideline on Diagnosis and Management of Spondyloarthritis in Over 16s (2017)

The National Institute for Health and Care Excellence (NICE) published in 2017 its clinical guideline on the diagnosis and management of spondyloarthritis that is suspected or confirmed in adults who are 16 years or older. It aims to raise awareness of the features of spondyloarthritis and provide clear advice on what action to take when people with signs and symptoms first present in healthcare settings. It also provides advice on the range of treatments available[14]. The main recommendations are summarized below:

- Spondyloarthritis comprises a collection of inflammatory disorders with a variety of possible symptoms. These conditions can primarily manifest as:
    A. Axial:
        - Radiographic axial spondyloarthritis (ankylosing spondylitis)
        - Non-radiographic axial spondyloarthritis
    B. Peripheral:

- Psoriatic arthritis
- Reactive arthritis
- Enteropathic spondyloarthritis

- Peripheral presentations are frequently observed as joint or tendon issues that may not initially appear connected, and misdiagnosis can occur due to the potential for symptoms to shift from one joint to another.

Suspecting spondyloarthritis

- Spondyloarthritis can display a wide range of symptoms and may pose challenges in its diagnosis, potentially resulting in delayed or overlooked identification. These symptoms can manifest in musculoskeletal aspects, such as inflammatory back pain, enthesitis, and dactylitis, or extend to extra-articular areas like uveitis and various psoriasis manifestations, including psoriatic nail symptoms. Factors contributing to the risk of spondyloarthritis include recent genitourinary infections and a family history of spondyloarthritis or psoriasis.
- Both axial and peripheral forms of spondyloarthritis may go unnoticed, even if they emerge alongside established comorbidities, such as uveitis, psoriasis, inflammatory bowel disease (like Crohn's disease or ulcerative colitis), or a gastrointestinal or genitourinary infection.

Referral for suspected other peripheral spondyloarthritides

- Individuals with suspected new-onset inflammatory arthritis should be promptly directed to a rheumatologist for an evaluation for spondyloarthritis, unless there are indications of rheumatoid arthritis, gout, or acute calcium pyrophosphate (CPP) arthritis (commonly known as 'pseudogout').
- For individuals with dactylitis, it is advisable to make a referral to a rheumatologist for an assessment of spondyloarthritis.
- In the case of enthesitis without an apparent mechanical cause, a referral to a rheumatologist for a spondyloarthritis assessment is recommended if:
    - It persists.
    - It occurs in multiple locations.
    - Additionally, any of the following conditions are also present:
        - Unexplained back pain.
        - Current or previous episodes of uveitis.
        - Current or previous occurrences of psoriasis.

        - A history of gastrointestinal or genitourinary infections.
        - Inflammatory bowel disease, such as Crohn's disease or ulcerative colitis.

Diagnostic criteria for suspected spondyloarthritis

- In specialist care settings, consider using validated spondyloarthritis criteria to guide clinical judgement when diagnosing spondyloarthritis. Examples include:
    - General spondyloarthritis criteria:
        - Amor
        - European Spondyloarthropathy Study Group (ESSG)
    - Peripheral spondyloarthritis criteria:
        - Assessment of Spondyloarthritis International Society (ASAS) (peripheral)
        - Classification of Psoriatic Arthritis (CASPAR)
    - French Society of Rheumatology (reactive arthritis).
- Even if a person's C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are within the normal range, the possibility of a spondyloarthritis diagnosis should not be dismissed.

Imaging

- Provide individuals with suspected peripheral spondyloarthritis in their hands and feet with plain film X-rays to assess their symptoms in these regions.
- If the plain film X-ray does not yield a definitive diagnosis, contemplate the use of ultrasound for:
    - the hands and feet to assess for joint involvement
    - suspected enthesitis sites
- Evaluate the possibility of using plain film X-rays, ultrasound, and/or magnetic resonance imaging) MRI for examining other symptomatic areas in both the periphery and the axial region.
- Interpret a positive HLA-B27 test result as a factor that heightens the probability of peripheral spondyloarthritis.
- If a diagnosis of peripheral spondyloarthritis is established, provide plain film X-rays of the sacroiliac joints to check for any axial involvement, even if the individual is not experiencing any symptoms in that region.

Antibody testing for suspected reactive arthritis

- Avoid standard testing for infective antibody status as a means to diagnose reactive arthritis in individuals with a prior gastrointestinal infection.

Education about spondyloarthritis

- Provide information and explanations regarding spondyloarthritis, such as:
    - What spondyloarthritis entails.
    - Diagnosis and the expected course of the condition.
    - Available treatment options, encompassing pharmaceutical and non-pharmaceutical approaches, along with potential side effects.
    - Common symptoms and strategies for their management.
    - Dealing with flare-ups and symptoms outside the joints.
    - Self-help techniques.
    - Opportunities for individuals with spondyloarthritis to participate in research.
    - An outline of the healthcare professionals involved in their care and how to contact them.
    - Information about employment rights and the ability to work while managing the condition.
    - Details about local support groups, online forums, national charities, and how to connect with them.

Information about disease flares

- Inform individuals with spondyloarthritis regarding the potential for encountering flare-ups and symptoms beyond joint involvement.
- Contemplate the creation of a personalized plan for managing flare episodes, taking into account the individual's specific requirements, preferences, and situation.
- When discussing any strategy for handling flare-ups, offer details on:

- access to care during flares (including details of a named person to contact [for example, a specialist rheumatology nurse])
- self-care (for example, exercises, stretching and joint protection)
- pain and fatigue management
- potential changes to medicines
- managing the impact on daily life and ability to work.

Management of other peripheral spondyloarthritides

- For non-progressive monoarthritis, contemplate the use of local corticosteroid injections as a standalone treatment.
- Provide standard disease-modifying antirheumatic drugs (DMARDs) to individuals with the following conditions: peripheral polyarthritis, oligoarthritis, or persistent or progressive monoarthritis linked to peripheral spondyloarthritis.
- When determining which standard DMARD to offer, take into consideration factors such as the individual's preferences, needs, and circumstances (including pregnancy planning and alcohol consumption), any existing comorbidities like uveitis, psoriasis, and inflammatory bowel disease, the characteristics of the disease, and the potential side effects.
- If a standard DMARD, administered at the maximum tolerable dose for a minimum of three months, does not deliver sufficient relief from symptoms, consider the possibility of switching to or incorporating another standard DMARD.
- Think about the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in conjunction with standard DMARDs or biological DMARDs to address symptoms. Administer oral NSAIDs at the lowest effective dose for the shortest duration, while also considering the need for appropriate clinical evaluation, continuous monitoring of risk factors, and the potential use of gastroprotective measures.
- In cases where NSAIDs fail to offer sufficient relief from symptoms, contemplate the use of steroid injections (either locally or intramuscularly) or short-term oral steroid therapy as an adjunct to standard DMARDs or biological DMARDs for symptom management.
- If extra-articular disease is effectively controlled by an existing standard DMARD, but peripheral spondyloarthritis remains uncontrolled, consider adding another standard DMARD to the treatment regimen.

Reactive arthritis

- Antibiotics: Once the initial infection has been addressed, refrain from providing extended antibiotic treatment (lasting 4 weeks or more) as the sole approach to manage reactive arthritis triggered by a gastrointestinal or genitourinary infection.

Non-pharmacological management of spondyloarthritis

- Consider directing individuals with spondyloarthritis, encountering challenges in their daily routines, to a specialized therapist, which may include physiotherapists, occupational therapists, hand therapists, orthotists, or podiatrists. The specialist therapist should:
    - assess people's needs
    - provide advice about physical aids
    - arrange periodic reviews to assess people's changing needs.

Managing flares

- Handle flare-ups in either specialized medical care or general healthcare, depending on the individual's requirements.
- Seek guidance from specialized care as necessary when managing flare-ups in primary care, especially for individuals who:
    - have recurrent or persistent flares
    - are taking biological DMARDs
    - have comorbidities that may affect treatment or management of flares.

Long-term complications

- Consider the potential side effects linked to NSAIDs, standard DMARDs, and biological DMARDs when overseeing spondyloarthritis in primary care.
- Inform individuals that the use of TNF-alpha inhibitors may elevate the risk of developing skin cancer.
- Engage in conversations about risk factors for cardiovascular conditions with all individuals diagnosed with spondyloarthritis.

C.2.2 Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada Treatment Recommendations for the Management of Spondyloarthritis. Part II: Specific Management Recommendations (2014)

The Canadian Rheumatology Association (CRA) and the Spondyloarthritis Research Consortium of Canada (SPARCC) have collaborated to update the recommendations for the management of spondyloarthritis (SpA). Part II: Specific Management Recommendations addresses management with nonpharmacologic methods, nonsteroidal antiinflammatories and analgesics, disease-modifying antirheumatic drugs, antibiotics, tumor necrosis factor inhibitors, other biologic agents, and surgery[11]. The main recommendations are summarized below:

Table 3. Levels of Evidence

Level of Evidence	
I	Meta-analysis, systematic reviews of RCT, or an individual RCT
II	Meta-analysis, systematic reviews of observational studies (cohort/case control studies), or individual observational studies, OR RCT subgroup/posthoc analysis
III	Nonanalytic studies (case reports, case series)
IV	Expert opinion
NR	Recommendation is not linked to evidence

Table 4. Strengths of Recommendation

Strength of Recommendation	
A	Strong recommendation: Direct level 1 evidence
B	Moderate recommendation: Direct level 2 or extrapolated level 1 evidence

A. Spondyloarthritis in adults

Non-Pharmacological treatment

- Non-Pharmacological for SpA should encompass patient education (I, A) and regular exercise (II, B), preferably under the guidance of expert physiotherapists at specialized centers. Both individual and group physical therapy (I, A) should be taken into account, and patients can benefit from involvement in patient associations and self-help (IV, D) groups.

Corticosteroids

- Consider using corticosteroid injections in specific areas of inflammation, such as the SI joints, peripheral joints, and entheses. (Sacroiliac joints: I, A), (Psoriatic arthritis joint, II, B), (All other sites, IV, D)
- Consider using short periods of systemic corticosteroids for particular symptoms. It is not advised or endorsed to use systemic steroids over an extended period. (Ankylosing spondylitis: I, A) (Other forms of spondyloarthritis: IV, D).

DMARDs

- Sulfasalazine (SSZ), methotrexate (MTX), and leflunomide could be options for patients with peripheral SpA, although the evidence supporting their effectiveness is limited to moderate at best. The dosage and monitoring of these medications should be customized to each patient and follow the standard care protocols. (I, A)
- In cases of peripheral SpA, combining DMARD therapy should be contemplated, especially in patients exhibiting unfavorable prognostic factors, experiencing moderate to high disease activity, or those with recently diagnosed conditions. Combining therapy should also be considered for patients who do not respond adequately to single-drug treatment. (IV, D)

Antibiotics

- In cases of confirmed post-Chlamydia chronic reactive arthritis, it is advisable to consider a six-month trial of rifampin in combination with either doxycycline or azithromycin. (IV, D)

Tumor Necrosis Factor inhibitors (TNFi)

- TNFi treatment, for patients with persistent high disease activity despite prior therapy, should be supervised by a rheumatologist. (IV, D)
- Patients with mainly peripheral SpA should be considered for TNF inhibitors if they continue to have inflammation that doesn't subside after trying NSAIDs and one DMARD. (TNFi efficacy: I, A), (Post NSAID and DMARD: IV, D)
- For individuals with stubborn enthesitis or dactylitis, TNF inhibitors should be considered if they have persistent inflammation. (Enthesitis: I, A), (dactylitis: II, B)
- Various TNFi medications are available to treat SpA, which includes infliximab, etanercept, adalimumab, golimumab, and certolizumab. The choice of TNFi should be made through discussion between the physician and the patient.

Dosage and monitoring of these drugs should be customized to each patient and adhere to standard care practices. (I, B)

- For maintenance on TNFi, the decision should be based on achieving a clinical response 16 weeks after starting the treatment. In peripheral SpA, a clinical response is defined as a 30% reduction in the number of active joints. (IV, D)
- When deciding on a TNFi treatment, consider whether there are extraarticular manifestations present or not. If feasible, the selected TNFi should effectively address both SpA and the specific extraarticular symptoms. (I, A)
- The combination of MTX and TNFi does not affect clinical effectiveness significantly, although in cases of peripheral SpA, it might be linked to a longer-lasting response to the drug. (II, B)
- For individuals who do not respond well to TNFi treatment, there may be benefits to switching to a different TNFi medication. (II, B)

Other biologic agents

- At present, there is no supporting evidence for utilizing alternative biologic agents in the treatment of SpA, including drugs such as ABA (abatacept), TCZ (tocilizumab), and anakinra. (ABA: II, B), (TCZ: I, A), (Anakinra: II, B).

Surgery

- In cases where patients have persistent, treatment-resistant pain or disability along with X-ray or imaging indications of structural damage in the hip joint, total hip arthroplasty should be contemplated, without regard to the patient's age. (IV, D)

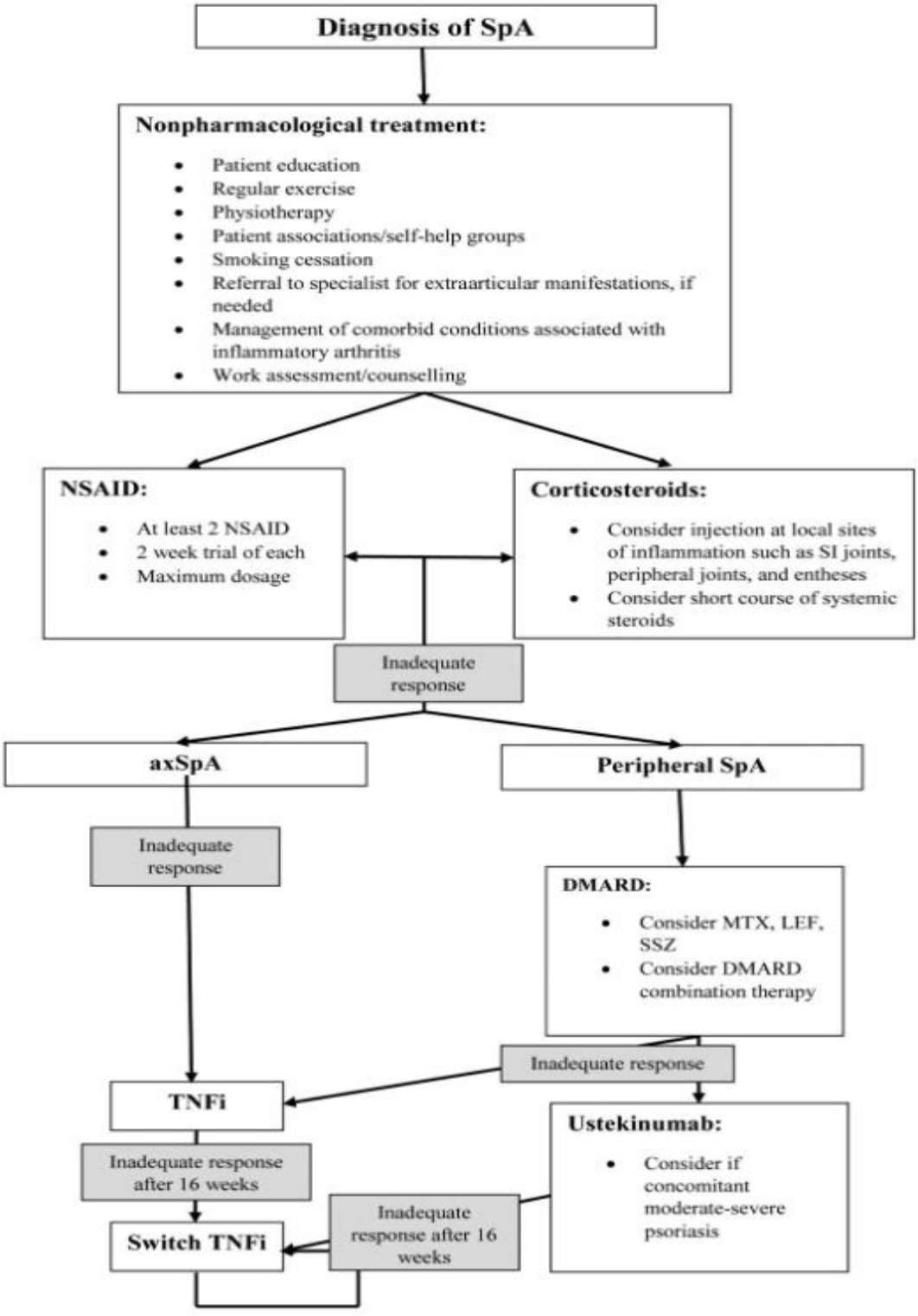

Figure 1. *Treatment Algorithm for Spondyloarthritis. Retrieved from the 2014 Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada Guideline*

B. Juvenile Spondyloarthritis (JSpA)

Non-Pharmacological

- It is highly advisable to motivate children with JSpA (specifically Enthesitis-Related Arthritis or ERA) to engage in routine physical activities that align with their overall capabilities and age-appropriate development. (I, B)
- Frequent occurrences of peripheral arthritis and enthesitis in the foot and ankle are typical in juvenile spondyloarthritis (specifically Enthesitis-Related Arthritis or ERA). Therefore, it is advisable to contemplate the utilization of comfortable, cushioning, and supportive foot orthotics for these patients. (I, B)

NSAID and analgesics

- Peripheral SpA is more prevalent in JSpA (specifically Enthesitis-Related Arthritis or ERA) and should be addressed by initially providing a sufficient trial of NSAIDs for a duration of 1 to 2 months. (IV, D)

Corticosteroids

- No alterations are made. A single study focuses on JSpA, while the majority of data is inferred from studies involving juvenile idiopathic arthritis (JIA).

DMARDs

- There are no modifications to the adult recommendations. (SSZ: I, A), (MTX, Leflunomide: III, C)

Antibiotics

- There are no trials of antibiotics in the treatment of JSpA (ERA). There are no modifications (IV, D)

TNF inhibitors (TNFi)

- TNF inhibitors are advantageous in the context of JSpA (specifically ERA) and should be prescribed based on the specific guidelines for predominantly axial or peripheral SpA. The TNFi options available for treating JSpA (ERA) are presently limited to etanercept (ETN), adalimumab (ADA), and infliximab (IFX). (IFX, ADA: I, A), (ETN: II, B)

Other biologic agents

- The use of these agents in JSpA (ERA) has not been studied. (IV, D)

Surgery

- There are no specific modifications to the adult SpA recommendations with, to our knowledge, no studies found in JSpA (ERA). (IV, D)

C.2.3 British Association of Sexual Health and HIV National Guideline on the Management of Sexually Acquired Reactive Arthritis (2021)

The British Association of Sexual Health and HIV published the UK national guideline on the management of sexually acquired reactive arthritis in 2021[12]. The main recommendations are summarized below:

Table 5. Levels of Evidence

Levels of evidence	
A	A body of evidence of high-quality meta-analyses, systematic reviews of and RCTs directly applicable to the target population
B	As above but relating to high quality case control or cohort studies with low risk of bias or confounding and high probability that a relationship is causal
C	As B but trials may have some flaws
D	Non-analytic evidence e.g., case reports or series or expert opinion

Table 6. Strength of Recommendations

Strength of recommendations	
1	Strong
2	Weak

Definition

- Reactive arthritis belongs to the group of seronegative spondyloarthropathies.
- It involves a non-infectious inflammation of the synovial membranes, fascia, and tendons, which is triggered by an infection that originates from a distant site.
- This infection is often associated with gastrointestinal pathogens, such as Salmonella, Shigella, and Campylobacter, or it can result from a sexually transmitted infection (STI), in which case it is referred to as sexually acquired reactive arthritis (SARA).

Infective pathogens

- The exact mechanisms that connect infectious pathogens to sexually acquired reactive arthritis (SARA) are not entirely clear, and it remains uncertain why some individuals develop SARA in response to a sexually transmitted infection (STI) while others do not.
- It is believed that SARA arises from an immune response to the infectious agent, and DNA and/or surface pathogens have been detected in the joint material of individuals with SARA.
- Chlamydia trachomatis has been found to exist in an unusual and persistent state in patients with SARA. In this atypical form, it suppresses the production of the major outer membrane protein (MOMP) and generates heat shock proteins, which contribute to the inflammatory response.
- The most common STI that can cause SARA include *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma genitalium* and sexual transmission of enteric pathogens (e.g., Shigella).

Risk factors and associations

- Sexually acquired reactive arthritis (SARA) is more frequently observed in men, with a male-to-female ratio of over 10 to 1. However, the possibility of under recognition or differences in the disease presentation in women should not be discounted.
- The presence of the HLA-B27 gene increases the susceptibility to SARA and is linked to the severity of the condition.
- There have been reports indicating an increased incidence of reactive arthritis in the sub-Saharan population living with HIV, where almost all cases of HIV-associated reactive arthritis are HLA-B27 negative. Nevertheless, similar observations have not been reported in Caucasian populations with HIV.

Clinical features

A. History

- It is crucial to conduct a comprehensive sexual history when evaluating cases.
- Typically, there is a reported history of engaging in sexual activity with a new partner within three months of the onset of arthritis symptoms.
- On average, genital symptoms manifest about 14 days before the onset of arthritis symptoms.

B. Symptoms and signs

- In terms of genital symptoms, women are more likely than men to show no apparent signs. However, they may report changes in vaginal discharge, pelvic discomfort, deep pain during intercourse, bleeding between menstrual periods, or after sexual intercourse. During clinical examination, mucopurulent cervicitis may be observed, with or without bleeding upon cervical contact, and tenderness during abdominal or bimanual examination.
- Male genital symptoms can include urethral discharge, pain during urination, and testicular discomfort or swelling. During examination, visible urethral discharge, testicular pain, and/or swelling may be evident.
- Arthritis is characterized by inflammation, resulting in joint pain, often more pronounced at night, potential joint swelling, and early morning stiffness.
- Peripheral joint involvement typically presents as asymmetrical arthritis, typically an oligoarthritis, primarily affecting the lower limbs, specifically the knees, ankles, and feet.
- Additional musculoskeletal symptoms may include discomfort or difficulty while walking due to inflammation of the Achilles tendon insertion (Achilles enthesitis) and/or inflammation of the plantar fascia (plantar fasciitis), affecting approximately 20-40% of cases.
- Painful movements may arise due to inflammation of the tendon sheaths (tenosynovitis), seen in about 30% of cases, while fusiform swelling of a finger or toe with dactylitis may occur in 16% of cases.
- If sacroiliitis is present during an acute episode, individuals may experience lower back pain and stiffness.
- Other rare extra-articular features which may have few or no symptoms or signs:
    - ✓ Cardiovascular: tachycardia, left ventricular dilatation, aortic valve disease, cardiac conduction
    - ✓ Renal: proteinuria, microscopic hematuria, aseptic pyuria, glomerulonephritis
    - ✓ Others: cranial nerve palsies, meningoencephalitis, thrombophlebitis of the lower limbs, subcutaneous nodules.
- Non-specific systemic symptoms of malaise, fatigue, weight loss, and fever are seen in some patients.

C. Diagnosis

- The diagnosis of SARA relies on clinical observations, particularly the presence of characteristic features associated with spondyloarthritis in the context of a sexually transmitted genital infection. There are no distinct diagnostic criteria for this condition.
- All patients should be offered screening for STIs (Grade 1A), as follows:
    - ✓ Male genital samples:
        - Urine nucleic acid amplification testing (NAAT) for C. trachomatis and N. gonorrhoeae
        - Urethral gram-stained smear (if urethral symptoms)
        - Urethral culture and sensitivity testing for *N. gonorrhoeae*
    - ✓ Female genital samples:
        - Vulvovaginal NAAT for *C. trachomatis* and *N. gonorrhoeae*
        - Endocervical culture and sensitivity testing for *N. gonorrhoeae* (if microscopy or NAAT positive)
    - ✓ Genital samples in trans people:
        - Urine NAAT for *C. trachomatis* and *N. gonorrhoeae* in all patients
        - If the patient has a vagina (including post genital reconstruction surgery) and is using it for sex, vulvovaginal NAAT for *C. trachomatis* and *N. gonorrhoeae*
        - Urethral and/or endocervical gram-stained smear and culture for *N. gonorrhoeae* as appropriate (depending on symptoms, genital configuration, and any reconstructive surgery)
    - ✓ Samples in both men and women:
        - Pharyngeal and rectal NAAT samples for *C. trachomatis* and *N. gonorrhoeae* where indicated by the sexual history
        - Screening for HIV and syphilis
        - Screening for hepatitis B and C based on risk factors in the sexual history
        - Consider *M. genitalium* NAAT (urine in men/vulvovaginal sample in women)
    - ✓ The following are also useful initial investigations:
        - Acute phase response - erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) or plasma viscosity (PLV)

- Full blood count (FBC)
- Urinalysis

D. Further investigations

- The subsequent tests might prove beneficial in specific circumstances, but they may not be obligatory in every case. It is advisable to maintain close communication with relevant pathology departments to guarantee that the appropriate samples are collected.

1. Biochemistry:
    - Liver and kidney function tests
2. Microbiology:
    - Blood cultures
    - Stool culture
    - Synovial fluid aspirate for cell count, gram stain crystals and culture (to exclude septic arthritis and gout)
3. Radiology:
    - X-rays of affected joints
    - Ultrasonography of affected joints or entheses
    - Magnetic resonance imaging of sacroiliac joints and spine
4. Others:
    - HLA-B27
    - Electrocardiogram (ECG)
    - Echocardiogram
    - Synovial biopsy
    - Exclusion tests for other rheumatological diseases:
        i. Anti-cyclic citrullinated peptide (anti-CCP) (rheumatoid arthritis)
        ii. Autoantibodies (systemic lupus erythematosus)
        iii. Plasma urate (gout)
        iv. Chest x-ray and serum angiotensin-converting enzyme level (sarcoidosis)

Management

A. General advice

- In most instances, sexually acquired reactive arthritis (SARA) may resolve on its own, and the management approach aligns with this characteristic. However, this is not universally the case.
- As is the case with all sexually transmitted infections, patients should be counseled to refrain from all sexual activity until they, as well as their partners, have completed treatment and follow-up.
- Patients should also be advised to steer clear of potential "triggering infections" in the future, whether urogenital or gastrointestinal, in order to prevent a new bout of SARA. As a result, it's essential to discuss safer sexual practices and emphasize the importance of maintaining good food hygiene.

B. Treatment

1. Antibiotics

- It is imperative to provide antimicrobial therapy for any identified genital infection. The treatment should follow the guidelines for uncomplicated infections as outlined by relevant infection management guidelines.
- The potential impact of short-course antibiotic treatment for acute genital infection on the non-genital aspects of sexually acquired reactive arthritis (SARA) is a matter of debate. While it may diminish the risk of recurrent arthritis in individuals with a history of reactive arthritis (ReA), it is unlikely to influence the arthritis once it has manifested. (Grade IB)
- The effectiveness of extended antimicrobial therapy in the treatment of sexually acquired reactive arthritis (SARA) has not been established and, as a result, it is not advised. (Grade 1C)

2. Physical therapy

- Rest is beneficial for alleviating constitutional symptoms, enthesitis, and arthritis, especially in weight-bearing joints and tendons where limiting activity is part of the initial treatment approach.
- Physiotherapy should be employed as needed to prevent muscle atrophy and, as symptoms improve, to enhance muscle strength and increase the range of motion in the affected joints and tendons. Physiotherapy and exercise are particularly vital when axial involvement is present. (Grade 1D)
- The use of cold pads can be considered to relieve joint pain and reduce swelling, and ultrasound may also be beneficial. Additionally, orthotics

equipped with insoles, cushioning, and heel supports might assist in managing enthesitis. (Grade 1D)

3. Non-Steroidal Anti-inflammatory drugs (NSAIDs)

- Nonsteroidal anti-inflammatory drugs (NSAIDs) have long been established as the primary treatment for numerous inflammatory arthritic conditions. It is crucial to use them regularly to maximize their anti-inflammatory benefits. In these situations, no specific NSAID has demonstrated superiority over others, and individual responses may vary. (Grade 1B)
- NSAIDs can also be beneficial for addressing associated constitutional symptoms, and there are both oral and topical options available to manage enthesitis symptoms. (Grade 1D)
- However, it's essential to consider potential side effects associated with NSAIDs, particularly gastrointestinal, renal, and cardiovascular effects. NSAIDs should be prescribed for the shortest possible duration, especially in individuals with other underlying risk factors for adverse reactions. (Grade 1A)
- For individuals at a high risk of gastrointestinal bleeding, a cyclooxygenase (COX-2) selective drug should be chosen. (Grade 1A)
- COX-2 selective medications have been associated with an elevated cardiovascular risk, irrespective of the presence of preexisting cardiovascular risk factors. The highest risk is likely associated with prolonged and high-dose usage, especially in individuals who have multiple risk factors for cardiovascular or cerebrovascular conditions. Among COX-2 inhibitors, naproxen is perceived to have the most favorable cardiovascular safety profile.

4. Corticosteroids

- Intra-articular corticosteroid injections are particularly beneficial for addressing single problematic joints. It's worth noting that there are no randomized placebo-controlled trials (RPCTs) specifically assessing their use in sexually acquired reactive arthritis (SARA). (Grade 1C)
- Local corticosteroid injections can be considered for enthesitis, although they should be used judiciously, especially at weight-bearing sites. (Grade 2C)
- Topical corticosteroid preparations are suitable for addressing cutaneous or mucosal lesions. (Grade 1C) Low-potency options are preferable for treating mucosal lesions. Alternative treatments for mild to moderate lesions include topical salicylic acid ointments and vitamin D3 analogs like calcitriol. (Grade 1C) For more severe lesions, retinoids such as acitretin may be considered. (Grade 1C)

- The management of uveitis involves the use of topical corticosteroid eye drops, oral corticosteroids, and mydriatics. Posterior uveitis usually requires more aggressive therapy. All patients with eye symptoms should undergo a slit lamp examination and be managed with specialized ophthalmological guidance. (Grade 1A)
- Systemic corticosteroids may prove valuable in cases with multiple affected joints or when severe constitutional symptoms are present. They can be administered orally, as a single intramuscular injection, or occasionally as an intravenous bolus. There have been no RPCTs specifically focused on corticosteroid use in SARA, but they have demonstrated efficacy in reducing inflammation in rheumatoid arthritis. (Grade 2D)
- If systemic corticosteroids are employed, consideration should be given to osteoporosis prophylaxis, although this is less likely to be necessary for short courses or single injections.

5. Disease Modifying Anti-Rheumatic Drugs (DMARDs)

- These treatments are recommended when there are persistent and disabling joint symptoms lasting over 3 months or in cases of severe disease or identified erosive joint damage.
- **Sulfasalazine** has been shown to reduce the severity and duration of synovitis in peripheral joints, although its influence on long-term recovery may be limited. It may also offer some benefits in early sacroiliitis but doesn't appear effective in established ankylosing spondylitis. High doses of 3g daily may be associated with significant toxicity, particularly gastrointestinal, while 2g daily seems to be equally effective and better tolerated. The dosage of sulfasalazine should be gradually increased until an effective dose is achieved. (Grade 1B)
- Many physicians prefer **methotrexate** due to its ease of weekly oral administration and the positive responses seen in conditions like rheumatoid disease and psoriatic arthritis. Methotrexate primarily affects peripheral joints and the enthesis. It may also be helpful in managing severe mucous membrane and skin lesions, although it can lead to side effects such as mouth ulceration and gastrointestinal intolerance. There is no confirmed efficacy of methotrexate in treating axial or spinal joint disease. Published randomized placebo-controlled trials (RPCTs) of methotrexate's use in sexually acquired reactive arthritis (SARA) are lacking. Dosages typically range from 7.5-15mg orally as a single weekly dose, which can be increased to 25mg orally in cases of resistant arthritis. It may also be administered as an intramuscular preparation. Importantly, oral folic acid, typically given as a single weekly dose of 5-15mg, should be administered 24 hours after the methotrexate dose. (Grade 1B)

6. Biologic agents

- **Tumor necrosis factor (TNF) alpha blockers**, of which there are several, have demonstrated high efficacy in treating a range of conditions, including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, skin lesions, other spondyloarthritides, and related enthesitis. They have also been reported to reduce the frequency of uveitis episodes when used to treat ankylosing spondylitis.
- However, TNF alpha blockers come with potential side effects, such as infusion reactions, an increased risk of infections (including tuberculosis), the development of autoantibodies, and the potential for systemic lupus erythematosus, vasculitis, demyelinating disease, and worsening congestive cardiac failure. While there is no proven risk for solid cancer and lymphoma development, caution is advisable for cutaneous malignancies, and frequent skin examinations are recommended.
- The use of biological agents in treating reactive arthritis (including sexually acquired reactive arthritis, SARA) is still limited, and no large or controlled studies are available. Although early reports show promise and suggest that they do not reactivate the infective trigger in patients with reactive arthritis, the role of such therapy in SARA remains to be firmly established. (Grade 2C)
- New treatments for seronegative spondyloarthritis, including axial spondyloarthritis and psoriatic arthritis, involve IL-17A inhibitors and JAK inhibitors, which have demonstrated effectiveness in rheumatoid arthritis. However, there is currently no available data on their potential effects in SARA.

7. Rare treatments

- Medical synovectomy: Procedures involving isotopes like Yttrium-90, Osmic acid, Samarium-153, or Rhenium-186 have shown short-term benefits in treating symptomatic chronic single joint synovitis. However, their advantages over intra-articular corticosteroids have not been definitively confirmed. (Grade 2D)
- Radiotherapy is only exceptionally used, typically in cases of severe and disabling heel pain caused by enthesitis. (Grade 2D)
- In certain circumstances, surgical procedures like synovectomy and arthroplasty may be valuable. There have been suggestions to provide a 3-month course of azithromycin alongside the synovectomy, but this trial lacked a placebo arm, so the exact benefit cannot be confirmed. (Grade 2D)
- For individuals experiencing severe post-inflammatory pain and fatigue, low-dose tricyclic drugs, such as amitriptyline at a dosage of 10-25mg at night, can be used as part of the treatment plan. (Grade 2D)

Pregnancy and breast feeding

- Several medications are not approved for use during pregnancy or while breastfeeding and should be avoided unless the potential benefits outweigh the associated risks.
- NSAIDs have the potential to induce temporary sub-fertility through a condition called luteinized unruptured ovarian follicle syndrome. If used regularly during pregnancy, especially in the third trimester, they can lead to premature closure of the fetal ductus arteriosus, oligohydramnios, delayed onset, and prolonged duration of labor. Guidance on breastfeeding while using NSAIDs depends on the specific NSAID being used.
- Prolonged use of corticosteroids carries a risk of intrauterine growth restriction and fetal adrenal suppression. Systemic effects on the baby during breastfeeding are unlikely unless the mother is taking more than 40mg of prednisolone (or equivalent) per day. With higher doses, appropriate monitoring of infant adrenal function is recommended. (Grade 1A)
- Sulfasalazine carries a theoretical risk of neonatal hemolysis in the third trimester, so it should be used cautiously during pregnancy and breastfeeding, along with maternal folate supplementation. (Grade 1A)
- Methotrexate and retinoids are both teratogenic and are, therefore, contraindicated during pregnancy and breastfeeding. Women and men, along with their female partners, should avoid conception for at least 6 months after using methotrexate, according to the manufacturer's recommendations. Women taking retinoids should be advised on the use of effective contraception for at least 1 month before, during, and at least 1 month after using these medications, and in some cases, such as acitretin, for up to 3 years after. (Grade 1A)
- The use of TNF blockers and other biologic therapies during pregnancy and breastfeeding should only be considered under the guidance of the appropriate specialist, as the advice varies depending on the specific medication.

HIV positive individuals

- There is no evidence to suggest that treatments should be any different in HIV positive individuals.

Follow-up

- Follow-up for specific STIs should follow the standard protocols for uncomplicated infections. In certain cases, this may involve test-of-cure or repeat screening. Follow-up can be helpful to ensure treatment adherence and assess the risk of reinfection. In cases where a test of cure is not necessary, follow-up could be conducted over the phone.
- For extra-genital features, the follow-up should be conducted under the guidance of the relevant specialist.
- In most individuals, SARA is a self-limiting disease with a mean duration of symptoms lasting 4-6 months. However, 50% of patients may experience recurrent episodes at variable time intervals, particularly those who are HLA-B27 positive, which is a recognized predictor of disease chronicity and severity in spondyloarthritis.
- Up to 17% will develop chronic symptoms lasting over 12 months, and 15% will experience persistent locomotor disability.
- The latter is primarily due to erosive joint damage and resulting deformities. Ocular involvement with uveitis can lead to cataracts and rapid vision loss in a minority of cases, highlighting the need for expert ophthalmological assessment.

C.2.4 Colombian Association of Rheumatology Clinical Practice Guidelines for the Diagnosis, Treatment, and Follow-Up of Patients with Peripheral Spondylarthritis (2021)

The aim of this clinical guideline by the Colombian Association of Rheumatology is to develop and formulate a set of specific recommendations based on the best available evidence for the diagnosis, treatment, and monitoring of adult patients with peripheral spondyloarthritis[15]. The main recommendations are summarized below.

Table 7. Certainty of Evidence

Certainty of evidence	
High ⨁⨁⨁⨁	Further research is very unlikely to change our confidence in the estimate of effect
Moderate ⨁⨁⨁O	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low ⨁⨁OO	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low ⨁OOO	Any estimate of effect is very uncertain

Table 8. Strength of Recommendations

Strength of recommendations	
Strong	"The panel recommends…"
Conditional	"The panel suggests…"

Conventional DMARDs (cDMARDs)

- In adult patients with peripheral spondyloarthritis (pSpA), the recommended initial therapy is the use of conventional disease-modifying antirheumatic drugs (cDMARDs). (Conditional recommendation in favor of cDMARDs intervention. Certainty ofthe evidence low ⨁⨁ ○○)
- The panel believes that methotrexate and sulfasalazine can be used interchangeably. It is essential to provide the patient with education regarding the treatment and its impact to enhance treatment adherence and patient satisfaction.

Systemic glucocorticoids

- For patients with pSpA, it is advised to refrain from using systemic glucocorticoids. (Strong recommendation against treatment. Certainty of the evidence low ⨁⨁ ○○)
- Before starting glucocorticoid treatment in patients suspected of having pSpA, it is recommended to promptly refer them to a rheumatologist to ensure their management and diagnosis align with the highest quality standards.

Therapy options after cDMARDs failure

- For patients with peripheral spondyloarthritis (pSpA) who have not responded to therapy or cannot tolerate conventional disease-modifying antirheumatic drugs (cDMARDs), it is recommended to commence treatment with either an anti-TNFα or an anti-IL17A. (Strong recommendation in favor. Certainty of the evidence moderate ⨁⨁⨁○)

- While undergoing treatment with any of these biologic disease-modifying antirheumatic drugs (bDMARDs), it is essential to maintain close patient monitoring and regularly evaluate the treatment's effectiveness. After a reasonable treatment duration, it is advisable to discontinue the current medication and consider switching to a different class of drug, taking into account the patient's specific characteristics.

Therapy options after bDMARDs failure

- In adult patients with peripheral spondyloarthritis (pSpA) who do not respond to their initial biologic disease-modifying antirheumatic drugs (bDMARD) therapy, the recommendation is to consider using another bDMARD as the next treatment option. This can involve either sticking with the same type of bDMARD or switching to one with a different mechanism of action. Another option is to consider a JAK inhibitor. (Conditional recommendation in favor of the intervention. Certainty of the evidence moderate ⊕⊕⊕○)
- The choice to alter or stop the initial bDMARD treatment should be determined by objectively assessing the disease activity, employing reliable clinical measurement tools. (Expert consensus)

Treatment of adult patients with pSpA and associated uveitis as an extra-articular manifestation, cDMARDs

- In adult patients with pSpA and anterior uveitis (associated as an extra-articular manifestation) the suggestion is to use methotrexate or sulfasalazine with a view to reducing flares. (Conditional recommendation in favor of the use of cDMARDs. Certainty of the evidence low ⊕⊕ ○○)
- In adult patients with pSpA and anterior uveitis unresponsive to treatment with immune-modulators, it is recommended to employ azathioprine for the management of ocular inflammation. (Conditional recommendation in favor of the intervention. Certainty of the evidence low ⊕⊕ ○○)

Treatment of adult patients with pSpA and associated uveitis as an extra-articular manifestation

- In adult patients with pSpA and concurrent uveitis (as an extra-articular symptom) who require bDMARD treatment, it is recommended to consider the use of an anti-TNFα medication to lower the occurrence of acute anterior uveitis. (Conditional recommendation in favor of the intervention. Certainty of the evidence very low ⊕ ○○○)

Treatment of adult patients with pSpA and associated inflammatory bowel disease

- For patients with pSpA who also have inflammatory bowel disease (IBD), it is recommended to begin treatment with conventional disease-modifying antirheumatic drugs (cDMARDs). (Conditional recommendation in favor of the intervention. Certainty of the evidence very low ⊕ ○○○)
- If patients with pSpA and comorbid inflammatory bowel disease do not show improvement with conventional disease-modifying antirheumatic drugs (cDMARDs), the advice is to opt for an anti-TNF treatment rather than using other biologic disease-modifying antirheumatic drugs like anti-IL-17 or anti-IL 12–23. (Strong recommendation in favor of the use of anti TNF-α, Certainty of the evidence: on anti-IL-17 moderate ⊕⊕⊕○; on anti-IL 12–23 very low ⊕ ○○○)
- When deciding on the anti-TNFα treatment for these individuals, it is recommended to prioritize the use of monoclonal antibodies instead of soluble receptor bDMARDs. (Certainty of the evidence moderate ⊕⊕⊕○)

C.2.5 Review Article: Reactive Arthritis (*Current Clinical Microbiology Reports*, 2020)

The association between microbiome changes and spondyloarthropathies is becoming increasingly evident. The results regarding the biologic treatment on refectory reactive arthritis (ReA) are promising. The aim of this paper published by Bentaleb et al. is to provide an overview about reactive arthritis, with an update regarding pathophysiology and therapeutic approach of the disease, outlining the clinical features and diagnostic approach, based on recent literature review[16].

Clinical Manifestations

A. Osteoarticular manifestations

- The most frequent presentation of ReA is the oligoarthritis.
- ReA can affect any peripheral joint, but the knee is the most involved.
- Additional manifestations include low back pain, sacroiliitis and enthesitis.

B. Extra-articular manifestations

- Genitourinary symptoms: May include urethritis, cervicitis, salpingo-oophoritis, cystitis, or prostatitis. In the post venereal form of ReA, urethritis and cervicitis are the most observed symptoms.
- Ocular symptoms: Conjunctivitis is seen more in patients with acute ReA and arises rarely in chronic disease. Uveitis is more often observed in chronic ReA but less frequently seen in acute ReA.

- Skin manifestations: The most observed are keratoderma blennorrhagicum, circinate balanitis, aphthous ulcers (up to 60%), and erythema nodosum (rare).
- Cardiac manifestations: It has been suggested that pericarditis is more seen in chronic stage of ReA, while heart block and valvular disease may arise in the acute ReA.

Diagnosis of ReA

- Currently, there is no consensus on diagnostic criteria for Reactive Arthritis (ReA). Therefore, the diagnosis primarily relies on clinical evaluation, involving a thorough review of the patient's medical history and a physical examination.
- During this evaluation, healthcare providers will inquire about prior infections and look for signs of musculoskeletal involvement and potential extra-articular infections. Rheumatologists also need to investigate whether there are symptoms indicative of Spondyloarthritis (SpA).
- Due to the wide range of clinical presentations associated with ReA and the need to rule out other conditions, clinicians should be diligent in excluding more common differential diagnoses like septic arthritis, gout, psoriatic arthritis, and rheumatoid arthritis.

A. Diagnostic criteria

- While a consensus on diagnostic criteria for Reactive Arthritis (ReA) is generally lacking, the diagnosis of ReA is typically made by considering a combination of clinical and microbiological criteria in most cases.
- During the fourth International Workshop on ReA, Berlin, Germany, in 1999, the lists of general guidelines concerning the classification and diagnosis of ReA have been issued.

Table 9. Diagnosis Criteria of Reactive Arthritis (ReA)

Major criteria	Minor criteria
Arthritis, meeting 2 of the following 3 characteristics: • **Asymmetric** • **Mono- or oligoarthritis** • Lower limb involvement	Presence of a triggering infection, as evidenced by positive urine culture, cervical/urethral swab, or stool culture
Preceding symptomatic infection, meeting one of the following characteristics:	Presence of persistent synovial infection, as evidenced by positive immunohistology or PCR

• **Enteritis, defined as at least 1 day of diarrhea occurring 3 days to 6 weeks before the onset of arthritis** • Urethritis, defined as dysuria or discharge for at least 1 day occurring 3 days to 6 weeks before the onset of arthritis	

- Patients with definite diagnosis of ReA must have both major criteria and at least one minor criterion.
- Patients with probable diagnosis for ReA must have both major criteria or one major and one minor criterion.

B. Laboratory testing

1. <u>Confirmation of triggering infection</u>

- Commonly, enteric pathogens such as Campylobacter, Salmonella, Shigella, or Yersinia are typically identified through a combination of stool enzyme immunoassay and culture.
- To diagnose Chlamydia trachomatis (Ct) infection, various techniques are employed, including:
- Nucleic acid amplification of urine or a urethral swab specimen.
- Urinary polymerase chain reaction (PCR) can detect rapidly Ct. DNA
- Semi-nested PCR (snPCR) and nested PCR (nPCR) are used to detect Ct DNA in synovial fluid.
- Antibody testing can help identify infections, but positive antibody test results don't always differentiate between past and recent infections.
- Moreover, serology results are often delayed by several days after the sample is collected, which limits their clinical utility.

2. <u>Inflammatory markers</u>

- In the acute phase of ReA, the inflammatory markers such us erythrocyte sedimentation rate (ESR) and CRP tend to be higher, but they can be normal in the case of Chlamydia-induced ReA (CiReA).

C. Radiological findings

- There are no particular diagnostic tests available to definitively confirm this condition. Nevertheless, an increasing number of publications have

highlighted the advantages of ultrasound, especially in diagnosing ReA within the spectrum of spondyloarthritis (SpA).

Therapeutic approach

- It's important to take into account the underlying infections as well as the joint-related and non-joint-related manifestations of the disease when determining how to manage ReA.
- The treatment of the underlying infections varies depending on the specific type of triggering infection.
- The approach to managing ReA is influenced by the phase of the disease, whether it is in an acute or chronic stage.

A. Treatment of acute ReA

1. <u>Non-steroidal anti-inflammatory drugs</u>

Nonsteroidal anti-inflammatory drugs (NSAIDs) are typically the initial medications recommended for managing SpA and ReA.

Based on the experiences of healthcare providers, NSAIDs have demonstrated their clinical effectiveness in treating ReA, even though there have been only two limited prospective trials to formally assess their use.

It is generally believed that ReA is unresponsive to NSAIDs when at least two different NSAIDs prove ineffective, each prescribed at the maximum dosage for a minimum of 2 weeks.

2. <u>Glucocorticoids</u>

In cases of acute ReA where patients exhibit an inadequate response to or cannot tolerate NSAIDs, it may be advisable to contemplate intra-articular glucocorticoid therapy. This approach can offer relief from symptoms and minimize the potential side effects associated with systemic steroids.

3. <u>Antibiotics</u>

Despite numerous studies examining antibiotics as a therapeutic option for ReA, there continues to be a discussion regarding their effectiveness.

B. Treatment of chronic ReA

1. <u>Disease-modifying antirheumatic drugs</u>

Radiographic damage observed in ReA shows similarities to that of other types of SpA, with PsA being a notable example. Consequently, conventional disease-modifying antirheumatic drugs (DMARDs) are frequently employed in the treatment of ReA.

Sulfasalazine (SSZ) has demonstrated its effectiveness in the treatment of ReA, with supporting evidence from two prospective, double-blind studies.

Methotrexate (MTX) is among the most used DMARDs for managing chronic ReA, despite the absence of proven efficacy in clinical trials.

2. Biological agents

Biological treatments have shown promise in managing treatment resistant ReA, although the available studies are typically case reports and small-scale open clinical trials. Patients who underwent biological treatment experienced relief from symptoms and saw improvements in the inflammatory markers associated with arthritis.

TNF Alpha Antibody: in terms of the underlying mechanisms of ReA, research has indicated that chronic ReA may exhibit elevated levels of TNF-α. This finding underscores the utilization of anti-TNF alpha therapies as a treatment strategy. When ReA does not respond well to properly administered conventional therapies (such as NSAIDs and DMARDs) or when it has persisted for 6 months, anti-TNF alpha treatments are recommended.

Interleukin-6 Receptor Antibody: According to a case report, the rapid improvement of symptoms in ReA that does not respond to conventional medications is achieved with tocilizumab. This is the initial case that validates the effectiveness of tocilizumab in the treatment of ReA.

Interleukin-17a Monoclonal Antibody: There have been limited clinical trials and documented experiences with IL-17a monoclonal antibodies in ReA. In one study, secukinumab was administered to address an active ReA case. The patient's clinical symptoms showed swift improvement, and there were no significant adverse events over the 12-week study period.

Evolution and Prognosis

- In general, the progression of ReA can exhibit significant variability in terms of disease duration, the frequency of occurrences, and the severity of relapses. As research suggests, most patients typically experience full remission within 6 to 12 months. Nevertheless, a substantial portion, ranging from 30% to 63% of patients, may develop chronic ReA that persists for more than 6 months, necessitating further treatment.
- When considering the factors that can predict a more unfavorable prognosis for ReA, being positive for HLA-B27, contracting a Chlamydia-induced infection, having a family history of spondyloarthropathy, and experiencing chronic bowel inflammation are the most influential factors contributing to the severity and progression of the disease.

C.2.6 Review Article: Enteropathic Spondyloarthritis: From Diagnosis to Treatment (*Clinical and Developmental Immunology*, 2013)

The aim of this review published by Peluso et al. is to describe clinical and pathophysiological data about enteropathic arthritis or enteroarthritis (EA). However, because of the significant lack of studies on this specific issue, most of results are derived from studies on IBD or other types of spondyloarthritis[9].

Definition

- Enteropathic arthritis or enteroarthritis (EA) is a type of spondyloarthritis (SpA) that develops in individuals with inflammatory bowel diseases (IBDs) and various gastrointestinal conditions, including Whipple's disease (WD), celiac disease (CD), and intestinal bypass surgery.

Classification Criteria

- The diagnosis is typically established based on a patient's medical history and physical examination because there is currently no universally accepted set of criteria for diagnosing enteropathic arthritis (EA). This is due to the fact that spondyloarthritis (SpA) comprises a range of distinct conditions with similar clinical features and a shared genetic predisposition.
- In the absence of definitive criteria, the diagnosis of EA has traditionally been made following the guidelines provided by the European Spondyloarthropathy Study Group (ESSG) criteria.
- Notably, one of these criteria for SpA includes the presence of inflammatory bowel disease (IBD). Therefore, individuals with IBD who also exhibit symptoms like inflammatory back pain and synovitis (primarily in the lower limbs) are categorized as having spondyloarthropathy.

Pathogenesis

- While the exact cause of EA remains unclear, the fact that joint inflammation occurs in individuals with a genetic predisposition following bacterial gut infections has provided significant evidence of a potential connection between inflammation of the gut lining and arthritis.
- Genetic factors contribute to a predisposition, while environmental factors, such as infectious agents, might have a causative role.
- Besides genetic susceptibility, significant emphasis has been placed on environmental factors in initiating the onset of the disease.

- The joint involvement observed in IBD is classified in two subsets: peripheral and axial (including sacroiliitis with or without spondylitis).
- There may be other periarticular manifestations such as enthesopathy, dactylitis, tendonitis, periostitis, clubbing, granulomatous lesions (in joints and bones), osteoporosis, and osteomalacia.
- The arthritic manifestations of IBD are divided into different clinical subsets: peripheral and axial joint involvement (including sacroiliitis with or without spondylitis).

Table 10. Classification and Features of Articular Involvement Subsets in Inflammatory Bowel Disease (IBD). Adapted from Peluso et al. (2013)

Peripheral			**Axial**	
Type 1	**Type 2**	**Type 3**	**Isolated sacroiliitis**	**Spondylitis**
(i) Pauciarticular (less than 5 joints)	(i) Polyarticular (5 or more joints)	(i) Both axial and peripheral involvement	(i) Asymptomatic	(i) Usually precede the onset of IBD
(ii) Asymmetric involvement	(ii) Symptoms persist for months or even years		(ii) Usually non progressive disease	(ii) Runs a course independent of IBD
(iii) Acute, self-limiting attack (< 10 weeks)	(iii) May be erosive			(iii) Clinical course is similar to idiopathic ankylosing spondylitis
(iv) Usually coincides with relapse of IBD	(iv) Runs a course independent of IBD			(iv) Disease progression leads to increasing immobility and ankylosing
(v) Strongly associated with other	(v) Affects both large and small joints			(v) Associated with uveitis

extra-intestinal manifestations				
(vi) Lower limbs more affected	(vi) Strongly associated with uveitis			(vi) Strongly associated with HLA B27
(vii) Associated with HLA DRB1, B35, B27	(vii) Associated with HLA B44			

Other Rheumatic and Extra-Articular Manifestations

- In addition to less frequent associations with other rheumatic diseases such as rheumatoid arthritis, Sjogren syndrome, Takayasu arteritis, and fibromyalgia, inflammatory bowel disease (IBD) is linked with several extra-articular manifestations.
- These include enthesitis, dactylitis, and buttock pain, which are characteristic of enteropathic arthritis (EA) and have a similar occurrence rate as seen in other spondyloarthritis conditions.
- Furthermore, the extra-articular manifestations of EA encompass acute anterior uveitis, aortic insufficiency, and cardiac conduction disturbances.

Cardiovascular Disease and EA

- Despite the shared inflammatory origins and the documented higher risk of cardiovascular issues in both inflammatory bowel disease (IBD) and spondyloarthritis (SpA), there is currently a lack of literature on the cardiovascular risk in patients with enteropathic arthritis (EA).

Treatment

- The effective management of patients with enteropathic arthritis (EA) requires close collaboration between a gastroenterologist and a rheumatologist.
- Treatment often involves the use of corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and/or anti-TNFα medications, which not only help control intestinal inflammation but also typically result in a reduction of symptoms related to peripheral type I arthritis. These symptoms often respond well to rest, physiotherapy, and localized steroid injections.

- In contrast, managing types II and III EA can be more complex, and these forms may persist even after reducing inflammatory bowel disease (IBD) activity.
- In our experience, most patients promptly respond to anti-inflammatory drugs, which are effective in controlling joint and entheses inflammation. However, it's important to note that these medications do not halt the progression of joint damage and may also have significant side effects on the bowel, potentially exacerbating IBD and leading to the development of ulcers in the small intestine and colon.
    - ✓ As a result, to address joint symptoms, it is advisable to prescribe anti-inflammatory drugs for patients experiencing mild exacerbations. However, their usage should be restricted to the minimal effective dose and for short durations.
- Sulfasalazine and 5-aminosalicylic acid are frequently employed in the treatment of inflammatory bowel disease (IBD). Their effectiveness has also been verified in managing mild peripheral arthritis, especially in patients with ulcerative colitis (UC). However, their efficacy in treating Crohn's disease (CD) has not been definitively established. It's important to note that these medications do not influence the progression of joint damage to more severe forms of arthritis, and their utility in the axial subset is limited. Furthermore, they do not appear to prevent the potential development of intestinal inflammation in patients with spondyloarthritis (SpA).
- Immunosuppressive medications like methotrexate, azathioprine, cyclosporine, and leflunomide have proven to be effective in certain patients who have peripheral arthritis and other extraintestinal manifestations. Recently, our research team has been investigating the effectiveness and tolerability of a 20 mg/week dose of methotrexate in individuals with peripheral arthritis associated with UC. Our findings have demonstrated a prompt and effective reduction of joint symptoms along with notable improvements in laboratory results and disease activity measures.
- Anti-tumor necrosis factor-alpha (anti-TNFα) medications, particularly infliximab and adalimumab, have demonstrated effectiveness in not only managing intestinal inflammation but also in addressing joint symptoms, including both axial and peripheral involvement. This is particularly notable in patients with Crohn's disease (CD), and these drugs are currently extensively employed in the treatment of enteropathic arthritis. In contrast, etanercept appears to be effective in controlling joint symptoms but does not seem to have the same impact on intestinal symptoms.

- Certain researchers have suggested the use of probiotics to address individuals with both inflammatory bowel disease and arthritis. Probiotics can modify the composition of the gut microbiota and alleviate patients' enduring joint pain in the initial phases of the disease, particularly before the onset of significant joint damage. This approach can enhance the overall quality of life and have a favorable impact on the progression of the disease. Additionally, some studies have indicated potential improvements in experimental colitis in mouse models and in individuals with inflammatory bowel disease.
- Given the elevated cardiovascular risk observed in individuals with inflammatory bowel disease (IBD), commonly used cardiovascular medications such as statins and angiotensin-converting enzyme inhibitors have the potential to serve a dual purpose. They can be effective in both preventing or managing coronary artery disease and in controlling IBD.

C.2.7 Review Article: Management of Patients with Inflammatory Bowel Disease and Spondyloarthritis (*Expert Review of Clinical Pharmacology*, 2017)

This review article published in 2017 by Pouillon et al.[17] includes the main recommendations of the following guidelines: the Delphi consensus amon Itaian experts on the multidisciplinary management of patients with coexisting inflammatory bowel disease and spondyloarthritis (2014)[18] and the first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease (ECCO consensus, 2016)[19].

Classification of Spondyloarthritis

- Spondyloarthritis (SpA) is categorized based on the criteria established by the Assessment in SpondyloArthritis international Society, which differentiates between peripheral and axial forms of SpA.

Table 11. Classification Criteria for Peripheral and Axial SpA According to the Assessment in SpondyloArthritis International Society. Adapted from Pouillon et al. (2017).

Peripheral SpA		
Arthritis or Enthesitis or Dactylitis		
PLUS		
≥ 1 of	**OR**	**≥ 2 of the remaining**
Psoriasis		Arthritis
IBD		Enthesitis

Preceding infection		Dactylitis
HLA-B27		Inflammatory back pain in the past
Uveitis		Positive family history for SpA
Sacroiliitis on imaging		
Axial SpA (in patients with back pain ≥ 3 months and age of onset < 45 years)		
Sacroiliitis on imaging*	**OR**	HLA B-27
PLUS		**PLUS**
≥ 1 SpA feature**		≥ 2 other SpA features**

* Sacroiliitis on imaging:
- Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
OR
- Definite radiographic sacroiliitis according to modified New York criteria

** SpA features:
- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- CD/UC
- Good response to NSAIDs
- Family history of SpA
- HLA-B27
- Elevated CRP

Diagnosing SpA in IBD patients

- The European Crohn's and Colitis Organisation (ECCO) consensus outlines a diagnostic strategy for arthritis in individuals with inflammatory bowel disease (IBD).

Table 12. Classification of IBD-Related Arthritis According to ECCO Consensus (2016). Adapted from Pouillon et al. (2017).

Localization	Disease characteristics	Subtypes
Peripheral	• Signs of inflammation And • Exclusion of other specific forms of arthritis	<u>Type 1</u> • Affecting ≤ 5 joints • Predominantly lower limbs • Mostly acute and self-

		limiting • Parallels IBD activity <u>Type 2</u> • Affecting > 5 joints • Predominantly upper limbs • Can persist months/years • Independently from IBD activity
Axial	• Inflammatory back pain And • Magnetic resonance imaging or radiographic features of sacroiliitis	Sacroiliitis +/- spondylitis

- Due to the non-destructive nature of peripheral arthritis, particularly in cases of oligoarthritis, standard X-rays typically show no abnormalities.
- The identification of peripheral SpA associated with IBD is primarily reliant on clinical assessment, such as the presence of joint swelling and tenderness.
- In instances where clinical examination alone is inconclusive, ultrasound (US) evaluation or magnetic resonance imaging (MRI) can be employed to confirm peripheral enthesitis or to identify peripheral arthritis, tenosynovitis, and bursitis.
- Symptoms of SpA are sometimes overlooked in individuals with IBD. Consequently, patients displaying SpA symptoms may not receive a timely diagnosis, resulting in delayed effective treatment. This delay can contribute to a chronic and disabling disease progression, ultimately reducing their quality of life.
- The use of a self-reported SpA questionnaire in IBD patients has been shown to enhance the identification of SpA.
- The gastroenterologist should be prompted to refer the patient for a more comprehensive rheumatologic evaluation when specific diagnostic indicators are observed as listed in table 13.

Table 13. Diagnostic Clues for Referral of the IBD Patient to the Rheumatologist. Adapted from Pouillon et al. (2017)

Diagnostic clues that should trigger the gastroenterologist to refer the IBD patient for further rheumatologic evaluation
• Chronic (>3 months) back pain • Peripheral joint pain/swelling • Presence of signs of enthesitis • History or evidence of dactylitis

Treatment goals in SpA

- In the management of SpA, the treatment objectives include preserving physical function, managing disease activity, and averting organ damage.

Treatment options

- Sulfasalazine is a viable option for the treatment of peripheral SpA due to its proven effectiveness in these individuals.
- Administering localized steroid injections is a beneficial therapeutic choice specifically for patients with peripheral SpA who have oligoarthritis (involving four or fewer joints). In cases of a peripheral flare, systemic corticosteroids can also be employed, but it is essential to swiftly reduce the dosage.
- Methotrexate has been established as an effective treatment approach for individuals with psoriatic arthritis and rheumatoid arthritis. Therefore, it can be contemplated as a potential therapy for patients with peripheral SpA.
- Anti-TNF agents, such as adalimumab, certolizumab, and etanercept, have shown their effectiveness in treating psoriatic arthritis. Additionally, adalimumab has displayed encouraging outcomes in two placebo-controlled studies involving patients with peripheral SpA.
- There is a need for large cohort studies exploring the potential benefit of vedolizumab on IBD-associated SpA.
- The selection of a pharmaceutical treatment hinges on the prevailing condition.
- Steroids and 5-aminosalicylates are suitable only when specifically needed for IBD but not for SpA.
- Sulfasalazine and methotrexate may be applicable for managing concurrent (particularly peripheral) SpA.

- The initiation of anti-TNF blockers should align with the treatment recommendations for the primary disease.
- NSAIDs for SpA can be contemplated solely in patients without active IBD and should be utilized for brief durations.
- NSAIDs are an initial therapeutic choice for SpA. However, their usage raises the likelihood of a relapse in IBD. There is some evidence to propose that the utilization of COX-2 inhibitors might be less risky compared to traditional NSAIDs, although further verification is required to substantiate this.

Table 14. Key Components of the Current Available Treatment Guidelines in IBD Patients with Coexisting SpA. Adapted from Pouillon et al. (2017)

Multidisciplinary management of patients withcoexisting inflammatory bowel disease and spondyloarthritis: A Delphi consensus among Italian experts (2014)[18]
Peripheral SpA (≤ 4 joints, enthesitis, dactylitis) and active IBD
○ Systemic steroids and/or sulfasalazine according to IBD indications. ○ Anti-TNF according to IBD guidelines. ○ Consider stopping anti-TNF only after complete IBD remission.
Peripheral SpA (> 4 joints) and active IBD
○ Systemic steroids and/or sulfasalazine according to IBD indications. ○ NSAIDs should be avoided. ○ Anti-TNF according to IBD guidelines. ○ Consider stopping anti-TNF only after complete IBD remission.
Peripheral SpA and IBD in remission
○ Local steroid injections, short- term (≤ 15 days) NSAIDs and oral sulfasalazine are appropriate options in peripheral oligoarthritis (≤ 4 joints, enthesitis, dactylitis). ○ Short-term (≤ 15 days) NSAIDs/systemic steroids may be considered as a bridge to oralsulfasalazine in peripheral polyarthritis (> 4 joints). ○ Anti-TNF according to rheumatological indications. ○ Anti-TNF can be gradually suspended according to rheumatologist's opinion in case of prolonged remission.
The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. J Crohn's Colitis (ECCO Consensus) 2016[19]
Peripheral SpA
○ Treatment of underlying gut inflammation is often sufficient to treat

peripheral arthritis.
  - Short-term NSAID or local steroid injection can be used to provide symptomatic relief.
  - Short-term oral corticosteroïds are effective but should be discontinued as soon as practicable.
  - Sulfasalazine and methotrexate may have a role the treatment.
  - Anti-TNF therapy is appropriate and effective in resistant cases.

C.2.8 Italian Expert Panel on the Management of Patients with Coexisting Spondyloarthritis and Inflammatory Bowel Disease (2014)

In this paper, the expert panel presents some red flags to guide clinicians – both rheumatologists and gastroenterologists – to make a correct diagnosis of IBD-associated SpA in clinical practice. IBD-associated SpA classification, clinical presentation and diagnostic work-up are also presented. When IBD and SpA coexist, the therapeutic strategy should be modulated to take into account the variable manifestations of IBD in terms of intestinal and extra-intestinal features, and the clinical manifestations of SpA, with particular attention to peripheral enthesitis, dactylitis and anterior uveitis[9].

IBD-associated SpA: disease classification, diagnosis, and manifestations

- The current categorization of Spondyloarthritis (SpA) encompasses both established and emerging entities, such as Ankylosing Spondylitis (AS), non-radiographic axial SpA (nr-axSpA), Psoriatic Arthritis (PsA), Inflammatory Bowel Disease (IBD)-associated SpA, Reactive Arthritis (ReA), undifferentiated SpA (uSpA), as well as B27-related uveitis. Additionally, aortic insufficiency and conduction disturbances are included.
- Various sets of criteria have been devised to classify all forms of SpA, including undifferentiated SpA. However, there are currently no validated criteria specifically designed for the classification of IBD-associated SpA.
- Typically, the diagnosis relies on utilizing criteria such as the European Spondyloarthropathy Study Group (ESSG) or the Assessment in SpondyloArthritis (ASAS) criteria.
- Consequently, IBD-associated SpA is identified in individuals with Ulcerative Colitis (UC) or Crohn's Disease (CD) who present with inflammatory back pain (IBP) and/or synovitis, primarily affecting the lower limbs.

IBD-associated SpA clinical presentation and diagnostic work-up

- Two primary patterns of IBD-associated SpA have been identified: peripheral arthritis and axial manifestations linked to sacroiliitis, either with or without concurrent spondylitis.
- It is possible for these subsets to coexist within the same patient. Similar to other forms of SpA, manifestations like enthesitis, dactylitis/tenosynovitis, and extra-articular symptoms, particularly anterior uveitis, may manifest.
- Notably, skin-related manifestations, including erythema nodosum, pyoderma gangrenosum, and aphthous stomatitis, are observed in at least 10% of patients.

IBD-associated SpA combined therapy: a patient-tailored approach

- When both IBD and SpA are present concurrently, the treatment approach should be adjusted.
- This adjustment should consider the diverse manifestations of IBD, encompassing both intestinal and extra-intestinal features.
- Simultaneously, careful attention should be given to the clinical manifestations of SpA, with a specific focus on peripheral enthesitis, dactylitis, and anterior uveitis.

Axial SpA and active luminal CD and UC

1. **Axial SpA and active not complicated luminal CD**

- Considering the potential for gastrointestinal toxicity and the activity of the intestinal disease, the use of traditional NSAIDs is not recommended for the treatment of axial SpA. Additionally, selective COX-2 inhibitors (COXIBs) are discouraged due to a lack of data supporting their use in active IBD.
- Sulfasalazine (SSZ) is not advisable for the management of axial SpA and ileal CD.
- While systemic steroids may find use in the short-term treatment of moderate-to-severe CD, they are not effective in addressing axial symptoms associated with axial SpA. In terms of immunomodulators, both methotrexate and thiopurines are found to be ineffective for the treatment of axial SpA.
- For instances of active, non-complicated luminal CD linked with axial SpA, the use of anti-TNFα agents is advised. However, it is noteworthy that etanercept is not recommended in this context, as it has been reported to be ineffective in treating active CD and could potentially serve as a triggering factor for the onset of new CD.

- Induction and maintenance doses should be those that are effective for both diseases: 5 mg/kg at weeks 0, 2 and 6, and then every 8 weeks for infliximab; 160 mg at week 0, 80 mg at week 2 and then 40 mg every 2 weeks for adalimumab.
- Adjusting the dosage of anti-TNFα is considered an appropriate step in addressing the loss of response (LOR) to biological therapy. This involves either increasing the doses or reducing the interval between administrations as necessary. If these adjustments prove ineffective, or in cases of primary nonresponse (PNR), transitioning to an alternative anti-TNFα agent should be contemplated.
- For individuals who have not previously undergone immunomodulator therapy, a combined treatment strategy involving both an anti-TNFα agent and a thiopurine should be considered. This approach may yield more favorable outcomes for those with moderate-to-severe CD compared to relying on monotherapy alone.
- In instances where patients experience prolonged and stable remission with both axial and intestinal manifestations, especially considering the heightened risk of axial SpA relapse, it is advisable to continue the use of anti-TNFα agents. There is also the option to contemplate reducing anti-TNFα doses based on treatment recommendations for SpA in CD patients who exhibit prolonged and stable clinical, radiological, endoscopic, and biochemical remissions.
- Irrespective of the presence of intestinal symptoms, physical therapy and rehabilitation are consistently recommended as supportive treatments in the management of axial SpA. This recommendation aligns with the guidelines provided by ASAS/EULAR (European League Against Rheumatism).

a. SpA and complicated CD

CD can become complex when issues such as obstructive symptoms, intestinal perforation, or intra-abdominal abscesses arise.

In such instances, surgical interventions should take precedence over any medical therapy, addressing both intestinal and musculoskeletal symptoms.

Following surgery and the full resolution of complications, the initiation of anti-TNFα agents is recommended for the treatment of SpA, as well as for addressing any remaining active luminal disease, especially in cases where intestinal resection has not resulted in a cure.

Additionally, biological therapy may prove beneficial in preventing the post-operative recurrence of CD.

b. SpA and active perianal CD

- Treating active perianal CD necessitates a comprehensive approach involving both surgical and medical interventions.
- Following a thorough clinical and radiological assessment of lesions, surgery becomes crucial for resolving septic complications.
- Procedures like seton placement and fistulectomy should be performed when deemed appropriate.
- In cases where complex perianal CD coexists with SpA, the primary medical option is biological therapy using an anti-TNFα agent. This choice is supported by recent evidence demonstrating its efficacy in both inducing and maintaining the healing of fistulas.
- Additionally, antibiotics may serve as a beneficial adjunctive treatment, especially in the periods just before and after surgery.

2. Axial SpA and active UC

- Avoid traditional NSAIDs and selective COXIBs.
- SSZ is not recommended for managing axial SpA. However, use mesalazine compounds in all UC patients unless contraindicated, as they are effective for maintenance therapy and preventing colorectal cancer.
- For short-term treatment of moderate-to-severe UC, systemic steroids may be employed, but they do not address axial symptoms.
- Methotrexate is ineffective for axial SpA and not the first-line therapy for UC.
- In steroid-dependent UC cases, consider thiopurines. However, due to the inefficacy of azathioprine (AZA) and 6-mercaptopurine (6-MP) on axial SpA, opt for biological therapy with anti-TNFα.
- Adjusting anti-TNFα dosage is acceptable for loss of response to biological therapy, either by increasing doses or shortening administration intervals. If these measures fail and in cases of PNR, switching to a different anti-TNFα agent should be considered.
- If axial symptoms recur during biological treatment, switching to another anti-TNFα agent is a valid therapeutic option.
- Physical therapy and rehabilitation are consistently recommended as supportive interventions in the care of axial SpA.

Axial SpA and quiescent IBD

- Focus on treating the axial disease in patients with active axial SpA and quiescent UC or CD.

- While avoiding traditional NSAIDs and selective COXIBs in active IBD patients, a brief course (no more than 2 weeks) of selective COXIBs may be acceptable for those with quiescent IBD.
- Initiate anti-TNFα agents when NSAIDs are inadequate for controlling axial symptoms. Choose a specific anti-TNFα considering its potential impact on underlying IBD; avoid etanercept due to reported associations with new-onset CD, while infliximab and adalimumab can be administered according to EULAR/ASAS recommendations.
- In cases of primary nonresponse or loss of response, transitioning to another anti-TNFα agent is recommended.
- For patients experiencing stable and prolonged remission of axial disease, continue long-term biological therapy to mitigate the high likelihood of axial SpA relapse.

Peripheral SpA (oligoarthritis and/or enthesitis and/or dactylitis) and active luminal CD and UC

Peripheral SpA and active not complicated luminal CD or active UC

- The management of peripheral oligoarthritis (≤4 joints), peripheral enthesitis, and dactylitis involves local steroid injections. If this approach proves ineffective, SSZ (2 g/day for CD, 2-3 g/day for UC) and low systemic steroid doses may be considered.
- In cases where active CD is present, traditional NSAIDs and selective COXIBs should be avoided.
- The selection of systemic therapies depends on the IBD activity, and their effectiveness in addressing musculoskeletal manifestations should be taken into account.
- For moderate-to-severe luminal CD, systemic steroids, anti-TNFα agents, and immunomodulators may be valid therapeutic options following national and international IBD management guidelines. TNF-blockers are also beneficial for musculoskeletal manifestations resistant to conventional therapy.
- In cases of prolonged and stable remission for both musculoskeletal and IBD manifestations, consider an exit strategy allowing for the discontinuation of anti-TNFα.

Polyarthritis (N4 joints) and active luminal UC and CD

Polyarthritis and not complicated luminal CD or active UC

- **Polyarthritis and not complicated luminal CD:** In cases where polyarthritis is linked with mild to moderate CD, the use of systemic steroids and/or SSZ depends on the activity of the intestinal disease. Specifically, SSZ at a dosage of 4 g/day is recommended for mild Crohn's colitis and should be prioritized over other mesalazine compounds when peripheral arthritis is associated with IBD.
- **Polyarthritis and active UC:** For mild-to-moderate UC accompanied by polyarthritis, the preferred treatment is oral SSZ within a dose range of 2–3 g/day, if well-tolerated (refer to Fig. 2 BOX B). In instances of active distal colitis, topical mesalazine compounds, with or without topical steroids, are recommended.
- Avoid the utilization of NSAIDs and selective COXIBs. For individuals with moderate-to-severe UC, initiate biological treatment with anti-TNFα, potentially in combination with SSZ.

Peripheral SpA and IBD in remission

1. **Peripheral SpA (oligoarthritis and/or enthesitis and/or dactylitis) and quiescent IBD**

- A brief course (limited to 2 weeks) of selective COXIBs may be deemed acceptable for individuals with quiescent IBD. However, for patients experiencing oligoarthritis, dactylitis, and/or enthesitis, it is safer to initiate local steroid injections as the first-line therapeutic approach.
- In cases of treatment failure and when musculoskeletal manifestations are associated with UC or Crohn's colitis, oral SSZ is recommended at a dosage of 2 g/day.
- If there is a lack of response or inadequate response to steroid injections and SSZ within a 12-week period, initiate biologic treatment at rheumatologic doses.
- The choice of a specific anti-TNFα should consider its potential impact on underlying digestive disease: avoid etanercept due to reported associations with new-onset CD, while infliximab and adalimumab can be administered following EULAR and ASAS guidelines.
- For cases of primary non-response (PNR) within 12 weeks or loss of response (LOR) during anti-TNFα treatment, transitioning to another anti-TNFα is a valid therapeutic option.
- As specific recommendations are unavailable, in instances of prolonged remission of musculoskeletal disease, consider gradual tapering and

suspension of anti-TNFα treatment as an exit strategy, in line with the rheumatologist's guidance.

2. Polyarthritis (N4 joints) and quiescent IBD

- The management of patients with polyarthritis in association with quiescent UC or CD should primarily focus on addressing the articular disease.
- While steering clear of traditional NSAIDs and selective COXIBs in individuals with active IBD, it may be deemed acceptable to administer a short-term course (no more than 2 weeks) of selective COXIBs in those with quiescent IBD.
- Both low doses of systemic steroids and selective COXIBs can be contemplated as a "bridge therapy" leading to oral SSZ at a dosage of 2–3 g/day.
- In cases of loss of response (LOR), inadequate response, or intolerance to SSZ, initiate biologic treatment at rheumatologic doses.
- The selection of a specific anti-TNFα should consider its potential impact on underlying digestive disease: avoid etanercept due to reported associations with new-onset CD, while infliximab and adalimumab can be administered following EULAR and ASAS guidelines.
- For cases of primary non-response (PNR) within 12 weeks or LOR during biological treatment, switching to another anti-TNFα is a viable option.
- In instances where specific recommendations are lacking, and in the scenario of prolonged and stable remission of polyarthritis, contemplate gradual tapering and suspension of anti-TNFα treatment as an exit strategy, aligning with the rheumatologist's judgment.

Section 2.0 Drug Therapy in Spondyloarthritis

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market and the fourth details other drugs that have been approved by the FDA/Ema but have not yet been registered by the SFDA.

2.1 Additions

On March 16, 2022, the U.S. Food and Drug Administration (FDA) approved RINVOQ® (Upadacitinib) for the treatment of adults with moderately to severely active ulcerative colitis (UC) who have had an inadequate response or intolerance to one or more tumor necrosis factor (TNF) blockers[20].

On May 18, 2023, The U.S. Food and Drug Administration (FDA) announced that the (FDA) has approved RINVOQ® (Upadacitinib) for the treatment of adults with moderately to severely active Crohn's disease who have had an inadequate response or intolerance to one or more TNF blockers[21].

The use of JAK inhibitors (such as tofacitinib and upadacitinib) is recommended for the treatment of adult patients with peripheral spondyloarthritis (pSpA) who do not respond to their initial biologic disease-modifying antirheumatic drugs (bDMARD) therapy (Conditional recommendation in favor of the intervention. Certainty of the evidence moderate ⊕⊕⊕○)[13]. However, Upadactinib has not gained FDA approval for this indication yet. Relevant information pertaining to this drug can be found below.

Furthermore, azathioprine, tocilizumab, and cyclosporine are possible options used in the treatment of different types and manifestations of peripheral arthritis are registered on the SFDA. Hence, relevant information pertaining to these drugs can also be found below.

2.1.1 Upadacitinib

This section includes pertinent information regarding the use of Upadacitinib (RINVOQ®)[22] in patients with peripheral spondyloarthritis.

Table 15. Upadacitinib Drug Information

SCIENTIFIC NAME UPADACITINIB	
SFDA Classification	Prescription
SFDA	No
US FDA	No
EMEA	No
MHRA	No
PMDA	N/A
Indication (ICD-10)	FA92.1, M48.8
Drug Class	Immunosuppressants
Drug Sub-class	Selective immunosuppressants
ATC Code	L04AA
Pharmacological Class (ASHP)	92:36; Disease-modifying Antirheumatic Agents
DRUG INFORMATION	
Dosage Form	Prolonged-release tablet

Route of Administration	Oral use
Dose (Adult) [DDD]*	**Crohn's-associated inflammatory arthritis:** Oral: 15 mg once daily[23]
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	*Dosing: Kidney Impairment: Adult* eGFR ≥15 mL/minute/1.73 m^2: No dosage adjustment necessary. eGFR <15 mL/minute/1.73 m^2: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). *Dosing: Hepatic impairment: Adult* Severe impairment (Child-Pugh class C): Use is not recommended. *Dosing: Adjustment for Toxicity: Adult* **Hematologic:** Absolute lymphocyte count (ALC) <500/mm^3: Interrupt therapy until ALC ≥500/mm^3. ANC <1,000/mm^3: Interrupt therapy until ANC ≥1,000/mm^3. Hemoglobin <8 g/dL: Interrupt therapy until hemoglobin ≥8 g/dL. **Hypersensitivity reaction (severe):** Discontinue therapy. **Infection (serious), including herpes zoster:** Interrupt treatment until the infection is controlled.
Prescribing edits*	ST, MD, PA
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Should be prescribed by rheumatology specialists.
PA (Prior Authorization):	Should be prior authorized since it is a costly medication, used as an

	alternative therapy and needs to be prescribed by a rheumatology specialist.
QL (Quantity Limit):	N/A
ST (Step Therapy):	The use of JAK inhibitors (such as tofacitinib and upadacitinib) is recommended for the treatment of adult patients with peripheral spondyloarthritis (pSpA) who do not respond to their initial biologic disease-modifying antirheumatic drugs (bDMARD) therapy.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	>10%: Dermatologic: Acne vulgaris Respiratory: Upper respiratory tract infection 1% to 10%: Dermatologic: Skin carcinoma Endocrine & metabolic: Hypercholesterolemia, weight gain Gastrointestinal: Abdominal pain, nausea Hematologic & oncologic: Lymphocytopenia, neutropenia. Hepatic: Increased liver enzymes
Drug Interactions*	5-Aminosalicylic Acid Derivatives: May enhance the myelosuppressive effect *Risk C: Monitor therapy*. Abrocitinib: May enhance the immunosuppressive effect of upadacitnib *Risk X: Avoid combination*. Baricitinib: Immunosuppressants may enhance the immunosuppressive effect of Baricitinib. *Risk X: Avoid combination*.
Special Population	N/A

Pregnancy	Based on data from animal reproduction studies, in utero exposure to upadacitinib may cause fetal harm.
Lactation	It is not known if upadacitinib is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during treatment and for 6 days following the last dose of upadacitinib.
Contraindications	Hypersensitivity to upadacitinib or any component of the formulation.
Monitoring Requirements	• Monitor CBC at baseline and periodically thereafter. • Monitor LFTs at baseline and periodically thereafter; interrupt therapy if LFTs increased and drug-induced liver injury is suspected. • Assess lipids 12 weeks after upadacitinib initiation and manage lipid abnormalities according to current clinical guidelines.
Precautions	• GI perforation: Use with caution in patients at increased risk for GI perforation. • Hematologic toxicity: Hematologic toxicity, including lymphopenia, anemia, and neutropenia, may occur. • Hepatic effects: Liver enzyme elevation has been observed. • Hypersensitivity reactions • Infections: Patients receiving upadacitinib are at increased risk for serious infections. • Lipid abnormalities: Increased lipid parameters • Malignancy: Lymphoma and other malignancies have been reported in patients receiving upadacitinib.

	• Medication residue in stool: Medication residue in stool or ostomy output has been reported in patients with anatomical conditions (eg, ileostomy, colostomy, intestinal resection) • Immunizations: Immunization status should be current before initiating therapy.
Black Box Warning	Serious infections including Active TB, invasive fungal infections, bacterial and viral infections.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of *upadacitinib* for the treatment of peripheral spondyloarthritis**.

CONCLUSION STATEMENT - UPADACITINIB

Upadacitinib (JAK inhibitor) is a possible option for the management of peripheral spondyloarthritis in patients who do not respond to their initial biologic disease-modifying antirheumatic drugs (bDMARD) therapy as mentioned in the guidelines. However, this recommendation is not supported by strong evidence and there were no HTA conducted for this medication. Therefore, **more evidence is needed to be able to assess the role of upadacitinib in peripheral spondyloarthritis.**

2.1.2 Tocilizumab

This section includes pertinent information regarding the use of Tocilizumab (ACTEMRA®)[24] in reactive arthritis.

Table 16. Tocilizumab Drug Information

SCIENTIFIC NAME Tocilizumab	
SFDA Classification	Prescription

SFDA Approval	No
US FDA	No
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	M02. 9, M48.8
Drug Class	Antirheumatic, Disease Modifying, Monoclonal Antibody
Drug Sub-class	Interleukin-6 Receptor Antagonist
ATC Code	L04AC07
Pharmacological Class (ASHP)	92:36 - Disease-modifying Antirheumatic Agents
DRUG INFORMATION	
Dosage Form	Concentrate for solution for infusion
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Reactive arthritis:** 8 mg/kg every 4 weeks[25]
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal Impairment: CrCl ≥ 30 mL/minute: No dosage adjustment necessary. CrCl < 30 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); however, based on tocilizumab's molecular weight (148 kDa), it is unlikely to be significantly renally eliminated. Hepatic Impairment: Hepatic impairment prior to treatment initiation: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).
Prescribing edits*	ST, MD, PA
AGE (Age Edit): N/A	

CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by rheumatology specialists.	
PA (Prior Authorization): Should be prior authorized since it is a costly medication, used as an alternative and should be prescribed by a rheumatology specialist.	
QL (Quantity Limit): N/A	
ST (Step Therapy): According to few case reports, the rapid improvement of symptoms in ReA that does not respond to conventional medications is achieved with tocilizumab.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common: Increased serum cholesterol, constipation, neutropenia, increased serum alanine aminotransferase, increased serum aspartate aminotransferase, infusion-related reaction Most serious: Deep vein thrombosis, hypertension, peripheral edema, septic shock, hyperglycemia, hypoglycemia, leukopenia, thrombocytopenia, antibody development, acute kidney injury
Drug Interactions*	Risk X interactions: - Abrocitinib - Anifrolumab - Anti-TNF Agents - Baricitinib - BCG Products - Biologic Disease-Modifying Antirheumatic Drugs (DMARDs) - Brivudine - Cladribine - Dengue Tetravalent Vaccine (Live) - Deucravacitinib - Filgotinib

	- Mumps- Rubella- or Varicella-Containing Live Vaccines - Nadofaragene Firadenovec - Natalizumab - Pimecrolimus - Poliovirus Vaccine (Live/Trivalent/Oral) - Ritlecitinib - Ruxolitinib (Topical) - Tacrolimus (Topical) - Tertomotide - Tofacitinib - Typhoid Vaccine - Upadacitinib - Vaccines (Live) - Yellow Fever Vaccine
Special Population	N/A
Pregnancy	Tocilizumab crosses the placenta. Tocilizumab is a humanized monoclonal antibody (IgG_1). Human IgG crosses the placenta. Fetal exposure is dependent upon the IgG subclass, maternal serum concentrations, placental integrity, newborn birth weight, and gestational age, generally increasing as pregnancy progresses. The lowest exposure would be expected during the period of organogenesis and the highest during the third trimester. Tocilizumab was not detected in umbilical cord blood, infant serum, or maternal serum at delivery in a patient who received her last dose 23 weeks prior to delivery. Postmarketing data reviewed through 2014 have not shown an increased rate of congenital malformations or a pattern of specific malformations following in utero exposure to tocilizumab. The review included pregnancy outcome data from

	288 women who received tocilizumab for rheumatic disorders; the majority received a dose during the first trimester or within 6 weeks of conception. Using these data, the incidence of preterm birth and spontaneous abortion may be increased when compared to the background rate, but these outcomes may also be influenced by maternal disease and concomitant medications. Additional outcome data is limited. Until additional data is available, tocilizumab is not currently recommended for the treatment of rheumatic and musculoskeletal diseases during pregnancy. Tocilizumab should be discontinued once pregnancy is confirmed. Data collection to monitor pregnancy and infant outcomes following exposure to tocilizumab is ongoing.
Lactation	Tocilizumab is present in colostrum and breast milk. In a report of 2 cases, breast milk concentrations peaked ~3 days after an IV maternal dose, then gradually decreased. In a third case, tocilizumab was detected in the serum of 1 infant at birth following in utero exposure; however, concentrations rapidly decreased and were not detectable by 4 weeks of age, even though the infant was exclusively breastfed. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. Although data related to use in lactating patients are limited,

	adverse events have not been reported in breastfed infants. Concentrations of tocilizumab are expected to be limited in breast milk due to large molecular weight. Also, because tocilizumab is unlikely to be absorbed via the infant GI tract, use of tocilizumab may be considered in patients who are breastfeeding.
Contraindications	Hypersensitivity to prednisolone or any component of the formulation; administration of live or live attenuated virus vaccines (with immunosuppressive doses of corticosteroids); systemic fungal infections. Canadian labeling: Additional contraindications (not in US labeling): Hepatitis; herpes; shingles; varicella; measles; uncontrolled active infections; uncontrolled psychotic states.
Monitoring Requirements	Chronic therapy: Latent TB screening prior to therapy initiation (all patients); neutrophils, platelets (prior to therapy, 4 to 8 weeks after start of therapy, and every 3 months thereafter [rheumatoid arthritis {RA}, giant cell arteritis {GCA}, systemic sclerosis (scleroderma)-associated interstitial lung disease {SSC-ILD}]); ALT/AST, alkaline phosphatase, and total bilirubin (prior to therapy, every 4 to 8 weeks after start of therapy for the first 6 months, and every 3 months thereafter [RA, GCA, SSc-ILD]); neutrophils, platelets, ALT/AST (prior to therapy, at second administration, and every 2 to 4 weeks [systemic juvenile idiopathic arthritis] or 4 to 8 weeks [polyarticular juvenile idiopathic arthritis] thereafter); additional liver function tests (eg, bilirubin) as clinically

	indicated; lipid panel (prior to and 4 to 8 weeks following initiation of therapy, then subsequently according to current guidelines); monitor all patients for signs and symptoms of infection (prior to, during, and after therapy); signs and symptoms of CNS demyelinating disorders; new onset abdominal symptoms.
Precautions	• Herpes zoster reactivation: Herpes zoster reactivation has been reported. • Hyperlipidemia: Therapy is associated with increases in total cholesterol, triglycerides, low-density lipoprotein, and/or high-density lipoprotein. • Malignancy: Use of tocilizumab may affect defenses against malignancies; impact on the development and course of malignancies is not fully defined; however, malignancies were observed in clinical trials. • Demyelinating CNS disease: Use with caution in patients with preexisting or recent onset CNS demyelinating disorders; rare cases of CNS demyelinating disorders (multiple sclerosis and chronic inflammatory demyelinating polyneuropathy) have occurred. • Hepatic impairment: Use with caution in hepatic impairment; see "Dosage: Hepatic Function Impairment" for additional information. • Tuberculosis: Consider anti-tuberculosis (TB) treatment in patients with a history of latent or active TB infection or disease (latent

	or active TB) if adequate treatment course cannot be confirmed, and for patients with risk factors for TB despite a negative test.
Black Box Warning	Risk of serious infections
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of *tocilizumab* for the treatment of reactive arthritis**.

CONCLUSION STATEMENT – TOCILIZUMAB

Tocilizumab can be used as a potential option for the treatment of reactive arthritis in patients who do not respond to conventional medications. However, this assumption is based on few case studies, therefore, larger studies and RCTs are needed to confirm its effectiveness in the management of reactive arthritis. Therefore, **stronger evidence is needed to be able to assess the role of tocilizumab in reactive arthritis management.**

2.1.3 Azathioprine

This section includes pertinent information regarding the use of Azathioprine (IMURAN®)[26] in patients with peripheral spondyloarthritis and anterior uveitis.

Table 17. Azathioprine Drug Information

SCIENTIFIC NAME Azathioprine	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	No
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	H20.043, M48.8
Drug Class	Immunosuppressant Agent

Drug Sub-class	Anti-CD20
ATC Code	L04AX01
Pharmacological Class (ASHP)	92:44 - Immunosuppressive Agents
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	**Uveitis, noninfectious (alternative agent) (off-label use):** 2 to 3 mg/kg once daily; some experts may use up to 4 mg/kg once daily, however, they do not exceed 250 mg/day
Maximum Daily Dose Adults*	Maximum dose has not been established
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal Impairment: **Altered kidney function:** • CrCl ≥30 mL/minute: Initial: No dosage adjustment necessary. • CrCl 10 to <30 mL/minute: Initial: Administer 75% to 100% of the usual indication-specific dose. If the initial dose is a dose range, then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 75% to 100% of 2 mg/kg once daily as an initial dose is recommended). • CrCl <10 mL/minute: Initial: Administer 50% to 100% of the usual indication-specific dose. If the initial dose is a dose range, then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 50% to 100% of 2 mg/kg once daily as an initial dose is recommended).

	Hemodialysis, intermittent (thrice weekly): Dialyzable (45% removed during 8 hours of hemodialysis): Initial: Administer 50% to 100% of the indication-specific dose; if the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 50% to 100% of 2 mg/kg once daily as an initial dose is recommended). When scheduled dose falls on a dialysis day, administer after hemodialysis. If not administered after hemodialysis, provide a 50% supplemental dose. **Peritoneal dialysis:** Initial: Administer 50% to 100% of the indication-specific dose. If the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 50% to 100% of 2 mg/kg once daily as an initial dose is recommended). **CRRT:** Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Recommendations are based on high-flux dialyzers and effluent flow rates of 20 to 25 mL/kg/hour (or ~1,500 to 3,000 mL/hour) unless otherwise noted. Close monitoring of response and adverse reactions (eg, hematologic toxicity) due to drug accumulation is important. Initial: Administer 75% to 100% of the indication-specific dose. If the initial dose is a dose range then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then

	administering 75% to 100% of 2 mg/kg once daily as an initial dose is recommended). **PIRRT (eg, sustained, low efficiency diafiltration)**: Drug clearance is dependent on the effluent flow rate, filter type, and method of renal replacement. Appropriate dosing requires consideration of adequate drug concentrations (eg, site of infection) and consideration of initial loading doses. Close monitoring of response and adverse reactions (eg, hematologic toxicity) due to drug accumulation is important. Initial: Administer 75% to 100% of the indication-specific dose. Administer the dose after PIRRT therapy ends on PIRRT days. If the initial dose is a dose range, then it is recommended to begin with the lowest end of the dose range (eg, if the usual dose is 2 to 3 mg/kg once daily then administering 75% to 100% of 2 mg/kg once daily as an initial dose is recommended) Hepatic Impairment: There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	ST, MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by rheumatology specialists.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Considered as an alternative in adult patients with pSpA and anterior uveitis unresponsive to treatment with immune-modulators.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	

SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common: Nausea, vomiting, leukopenia, infection (renal transplant; rheumatoid arthritis; includes bacterial infection, fungal infection, protozoal infection, viral infection, opportunistic infection, and reactivation of latent infections) Most serious: Leukopenia, thrombocytopenia, hepatotoxicity, malignant lymphoma, hepatosplenic T-cell lymphoma (HSTCL), hemophagocytic lymphohistiocytosis (HLH), acute myelocytic leukemia, myelodysplastic syndrome, and malignant neoplasm of skin, pancreatitis.
Drug Interactions*	Risk X interactions: - Abrocitinib - Baricitinib - BCG (Intravesical) - BCG Products - Brivudine - Cladribine - Dengue Tetravalent Vaccine (Live) - Deucravacitinib - Dipyrone - Febuxostat - Fexinidazole - Filgotinib - Mercaptopurine - Mumps- Rubella- or Varicella-Containing Live Vaccines - Nadofaragene Firadenovec - Natalizumab - Pimecrolimus - Poliovirus Vaccine (Live/Trivalent/Oral) - Ritlecitinib

	- Ruxolitinib (Topical) - Tacrolimus (Topical) - Talimogene Laherparepvec - Tertomotide - Tofacitinib - Typhoid Vaccine - Upadacitinib - Vaccines (Live) - Yellow Fever Vaccine
Special Population	Patients with systemic lupus erythematosus (SLE) undergoing hip or knee replacement surgery: Patients with severe SLE (referring to patients with severe organ manifestations such as nephritis) should not interrupt therapy when undergoing hip or knee replacement surgery. For patients with SLE without severe disease, hold azathioprine for at least 1 week prior to surgery to reduce infection risk; therapy can be restarted once surgical wound shows evidence of healing (eg, no swelling, erythema, or drainage), sutures/staples are removed, and no ongoing nonsurgical site infections (typically ~14 days to reduce infection risk).
Pregnancy	Azathioprine crosses the placenta. Adverse events, including congenital anomalies, immunosuppression, hematologic toxicities (lymphopenia, pancytopenia), and intrauterine growth retardation have been observed in case reports following maternal use in kidney allograft recipients. Some of these adverse outcomes may be dose-related or a result of maternal disease. Adverse pregnancy outcomes may also be associated with a kidney transplant, including preterm delivery and low birth weight in the infant and

	hypertension and preeclampsia in the mother. Appropriate maternal use of lower risk immunosuppressants may help decrease these risks. Azathioprine can be continued and should be substituted for mycophenolate in patients who become pregnant following a kidney transplant. Azathioprine may also be used in some pregnant patients who have had a liver, heart or uterine transplant. Although use for rheumatoid arthritis in pregnant patients is contraindicated by the manufacturer, available guidelines suggest that use of azathioprine may be acceptable for the management of rheumatic and musculoskeletal diseases during pregnancy. Patients with inflammatory bowel disease who are on maintenance therapy with azathioprine monotherapy may continue treatment during pregnancy; initiating treatment during pregnancy is not recommended. Combination therapy with azathioprine should be avoided due to increased risk of newborn infection. Treatment with azathioprine for autoimmune hepatitis should be continued during pregnancy. Because pregnancy may increase the risk of a flare, monitor closely for 6 months' postpartum. Azathioprine may also be useful for the treatment of immune thrombocytopenia in a pregnant patient refractory to preferred agents. Azathioprine is considered acceptable for the treatment of myasthenia gravis in pregnant patients who are not

	controlled with or unable to tolerate corticosteroids.
Lactation	The azathioprine metabolite 6-mercaptopurine (6-MP) is present in breast milk. Azathioprine is a prodrug which is rapidly metabolized to 6-MP. 6-MP is present in breast milk; however, it is inactive until further metabolized to 6-TGN metabolites which are present only within red blood cells. Peak breast milk concentrations of 6-MP occurred within 4 hours in a study of eight lactating women. Another study measured the active metabolite concentrations in RBCs of four breastfeeding women ≥3 months' postpartum on chronic azathioprine therapy; sampling was conducted at variable times after the dose. Women in the study had normal thiopurine methyltransferase (TPMT) activity. All women had therapeutic concentrations of 6-TGN; however, none of the infants had detectable concentrations. Newborn serum concentrations of 6-MP and 6-TGN were also undetectable in a study which evaluated seven breastfed infants between 1 and 28 days' postpartum. Mothers in this study were taking azathioprine 100 mg/day. Information is available from a report of 29 women taking azathioprine 50 to 175 mg/day throughout pregnancy and postpartum and their 30 breastfed newborns. Among 20 infants with blood cell counts evaluated after delivery, one infant was diagnosed with asymptomatic neutropenia on day 15 of life. Neutropenia fluctuated over 1.5 months of breastfeeding, continued for

	15 days after breastfeeding was discontinued, and resolved 3.5 months later. No adverse outcomes were observed in the remaining infants who were followed for 1 to 17 months .A second study of 11 women taking azathioprine maintenance doses for inflammatory bowel disease (median: 150 mg/day) did not find an increased risk of infection in their 15 breastfed infants. The infants were followed for 6 months to 6 years. Recommendations for breastfeeding during azathioprine therapy vary. Due to the potential for serious adverse reactions in the infant, breastfeeding is not recommended by the manufacturer. The World Health Organization also recommends breastfeeding be avoided during maternal treatment. Recommendations for breastfeeding in females taking azathioprine following a kidney transplant differ; generally breastfeeding may be considered with maternal use of maintenance doses. Azathioprine is considered compatible for use in women with inflammatory bowel disease who wish to breastfeed. Azathioprine may be continued or initiated in patients with rheumatic and musculoskeletal diseases who are breastfeeding. Patients who are concerned with the theoretical risks of immunosuppression may consider pumping and discarding breast milk for the first 4 hours after an azathioprine dose to decrease potential exposure to the breastfed infant.
Contraindications	Hypersensitivity to azathioprine or any component of the formulation;

	pregnancy (in patients with rheumatoid arthritis [see Pregnancy Considerations]); patients with rheumatoid arthritis and a history of treatment with alkylating agents (eg, cyclophosphamide, chlorambucil, melphalan) may have a prohibitive risk of malignancy with azathioprine treatment.
Monitoring Requirements	• CBC with differential and platelets (weekly during first month, twice monthly for months 2 and 3, then monthly thereafter; monitor more frequently with dosage modifications or as clinically indicated), total bilirubin, LFTs (every 3 months), CrCl, monitor for signs/symptoms of infection and malignancy (eg, splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss). Azathioprine has been associated with skin cancer with long-term use after kidney transplantation. Patients taking azathioprine for a prolonged time period should avoid sun exposure and be monitored for skin cancer regularly. • Thiopurine S-methyltransferase (TPMT) genotyping or phenotyping: Consider testing for TPMT deficiency, particularly in patients with abnormally low CBC unresponsive to dose reduction. TPMT genotyping or phenotyping may assist in identifying patients at risk for developing toxicity (CPIC [Relling 2019]). • Nudix hydrolase 15 (NUDT15) genotyping: Consider genotyping for

	NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated myelosuppressive episodes. NUDT15 genotyping may assist in identifying patients at risk for developing toxicity (CPIC [Relling 2019]). • TPMT and NUDT15 testing cannot substitute for monitoring CBC in patients receiving azathioprine.
Precautions	• Hepatic impairment: Use with caution in patients with hepatic impairment. • Renal impairment: Use with caution in patients with renal impairment. • Mercaptopurine: Azathioprine is metabolized to mercaptopurine; concomitant use may result in profound myelosuppression and should be avoided. • Vaccines: Immune response to vaccines may be diminished. Toxicity or adverse reactions to live vaccines may be enhanced (depending on the azathioprine dose).
Black Box Warning	Malignancy
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of *azathioprine* for the treatment of patients with peripheral spondyloarthritis and anterior uveitis.**

CONCLUSION STATEMENT – AZATHIOPRINE

Azathioprine can be used as second-line therapy in patients with peripheral spondyloarthritis and anterior uveitis if other therapies have failed as recommended by the guidelines. Therefore, it is recommended that this drug be added to the CHI formulary for peripheral spondyloarthritis.

2.1.4 Cyclosporine

This section includes pertinent information regarding the use of Cyclosporin (Effyren®)[27] in patients with peripheral spondyloarthritis and extraintestinal manifestations.

Table 18. Cyclosporine Drug Information

SCIENTIFIC NAME Cyclosporine	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	No
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	H20.043, M48.8
Drug Class	Immunosuppressant Agent
Drug Sub-class	Calcineurin Inhibitor
ATC Code	L04AD01
Pharmacological Class (ASHP)	92:44 Immunosuppressive Agents
DRUG INFORMATION	
Dosage Form	Capsule, hard
Route of Administration	Oral use
Dose (Adult) [DDD]*	**Uveitis (off-label use):** Oral: 2.5 to 5 mg/kg/day in 2 divided doses; gradually decrease to maintenance dose; used alone or in conjunction with other corticosteroids. An expert panel recommends initial dose of 3 to 5 mg/kg/day; reducing dose, once inflammation was under control, to 2 to 3 mg/kg/day until a maintenance dose of 1 mg/kg/day is achieved.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal Impairment:

	- **kidney impairment prior to treatment initiation:** **Altered kidney function:** ➢ CrCl ≥60 mL/minute: No dosage adjustment necessary. ➢ CrCl <60 mL/minute: No dosage adjustment necessary (0.1% excreted in the urine unchanged). For nontransplant indications (eg, autoimmune disease), the manufacturer's labeling states use is contraindicated in patients with abnormal renal function (not defined); however, when potential benefits outweigh the risks, may consider cautious use with frequent monitoring of kidney function, or consider use of an alternative agent due to increased risk of worsening kidney function, especially for patients with more severe impairment. **Hemodialysis, intermittent (thrice weekly)**: Not dialyzable: No supplemental dose or dosage adjustment necessary. For nontransplant indications (eg, autoimmune disease) the manufacturer's labeling states use is contraindicated in patients with abnormal renal function (not defined); however, may use with extreme caution if benefits outweigh risks, or consider use of an alternative agent, especially if the patient has residual kidney function. **Peritoneal dialysis:** Unlikely to be significantly dialyzable (large Vd): No dosage adjustment necessary. For nontransplant indications (eg,

	autoimmune disease) the manufacturer's labeling states use is contraindicated in patients with abnormal renal function (not defined); however, may use with extreme caution if benefits outweigh risks, or consider use of an alternative agent, especially if patient has residual kidney function. **CRRT:** No dosage adjustment necessary. However, cyclosporine can potentially worsen acute kidney injury; therefore, avoid use unless benefits outweigh the risks. Monitor kidney function closely. **PIRRT** (eg, sustained, low-efficiency diafiltration): No dosage adjustment necessary. However, cyclosporine can potentially worsen acute kidney injury; therefore, avoid use unless benefits outweigh the risks. Monitor kidney function closely. - **Nephrotoxicity or acute kidney injury during treatment:** **Altered kidney function:** ➢ Nontransplant indications (eg, autoimmune disease): The following general recommendations may be considered; individualize therapy according to risks/benefits and institutional protocols, when available: If serum creatinine increases 25% to 30% above baseline (measured on 2 separate occasions at least 2 weeks apart), or by ≥50% at any time during therapy, reduce dose by 25% to 50% and monitor serum creatinine every 2 weeks for 1 month. If serum creatinine does not decrease to within 25%

	to 30% of baseline, further reduce dose by 25% to 50% and monitor serum creatinine every 2 weeks for 1 month. If serum creatinine does not decrease to within 25% to 30% of baseline, discontinue cyclosporine. - **Patients receiving renal replacement therapies (eg, hemodialysis, peritoneal dialysis, CRRT):** **Nontransplant indications (eg, autoimmune disease):** Consider temporary interruption of therapy or switching to an alternative agent to help promote renal recovery and preserve residual kidney function if other factors (eg, concurrent nephrotoxins, dehydration) contributing to decreased kidney function cannot be mitigated. Continued use should only be considered if benefits outweigh risks of further kidney injury. <u>Hepatic Impairment:</u> - **Mild-to-moderate impairment:** There are no dosage adjustments provided in the manufacturer's labeling; monitor blood concentrations. - **Severe impairment:** There are no dosage adjustments provided in the manufacturer's labeling; however, metabolism is extensively hepatic (exposure is increased). Monitor blood concentrations; may require dose reduction.
Prescribing edits*	ST, MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	

G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by rheumatology specialists.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Should be used as alternative therapy in patients with peripheral spondyloarthritis and extraintestinal spondyloarthritis (uveitis).	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common: Renal dysfunction, liver dysfunction, tiredness, headache, abdominal pain, hypertension, nausea, vomiting, hyperlipidemia, electrolyte changes, muscle cramp. Most serious: Diabetes mellitus, hepatotoxicity, hyperkalemia, hypertension., infections, malignancy, nephrotoxicity, neurotoxicity.
Drug Interactions*	Risk X interactions: - Abrocitinib - Aliskiren - Asunaprevir - Atorvastatin - Baricitinib - BCG Products - Bilastine - Bosentan - Brivudine - Cladribine - Dengue Tetravalent Vaccine (Live) - Deucravacitinib - Disulfiram - DOXOrubicin - Dronedarone - Elagolix - Elagolix, Estradiol, and Norethindrone - Elbasvir and Grazoprevir

	- Erdafitinib - Fexinidazole - Filgotinib - Foscarnet - Fusidic Acid - Grapefruit Juice - Lasmiditan - Lercanidipine - Lovastatin - Methotrimeprazine - Mifamurtide - MiFEPRIStone - Mumps- Rubella- or Varicella-Containing Live Vaccines - Nadofaragene Firadenovec - Natalizumab - Ornidazole - Pacritinib - PAZOPanib - Pimecrolimus - Pimozide - Pitavastatin - Poliovirus Vaccine (Live/Trivalent/Oral) - Potassium-Sparing Diuretics - Red Yeast Rice - Revefenacin - Ritlecitinib - Ruxolitinib (Topical) - Secnidazole - Simeprevir - Simvastatin - Sirolimus (Protein Bound) - Sparsentan - Tacrolimus (Systemic) - Tacrolimus (Topical) - Talimogene Laherparepvec - Taurursodiol - Tertomotide

	- Tofacitinib - Topotecan - Treosulfan - Typhoid Vaccine - Upadacitinib - Vaccines (Live) - VinCRIStine (Liposomal) - Voxilaprevir - Yellow Fever Vaccine - Zavegepant
Special Population	- **Patients with systemic lupus erythematosus (SLE) undergoing hip or knee replacement surgery**: Patients with severe SLE (referring to patients with severe organ manifestations such as nephritis) should not interrupt therapy when undergoing hip or knee replacement surgery. For patients with SLE without severe disease, hold cyclosporine for at least 1 week prior to surgery to reduce infection risk; therapy can be restarted once surgical wound shows evidence of healing (eg, no swelling, erythema, or drainage), sutures/staples are removed, and no ongoing nonsurgical site infections (typically ~14 days to reduce infection risk). - **Transplant recipients:** Make dose adjustments based on blood concentrations; dependent on organ transplanted, time after transplant, organ function, and CsA toxicity.
Pregnancy	Cyclosporine crosses the placenta. In a study of 15 pregnant patients, maternal concentrations did not correlate with those found in the umbilical cord (n=14). Cyclosporine was

	detected in the serum of one newborn for several days after birth. Cyclosporine is not associated with specific teratogenic effects, but maternal use may be associated with an increased risk of intrauterine growth restriction, small for gestational age babies, maternal hypertension, and preeclampsia. Premature births and low birth weight were consistently observed in pregnant transplant recipients (additional pregnancy complications also present). In utero exposure to cyclosporine has not been found to influence renal function or blood pressure in children followed up to 7 years of age (limited data). Some formulations may contain alcohol; the alcohol content should be taken into consideration prior to prescribing to patients who are pregnant. Cyclosporine levels decline during pregnancy and increased monitoring is recommended.
Lactation	Cyclosporine is present in breast milk. Concentrations of cyclosporine in milk vary widely. Due to the potential for serious adverse in the breastfeeding infant, the manufacturer recommends a decision be made to discontinue cyclosporine or to discontinue breastfeeding, considering the importance of treatment to the mother.
Contraindications	Hypersensitivity to cyclosporine or any component of the formulation. IV cyclosporine is contraindicated in hypersensitivity to polyoxyethylated castor oil (Cremophor EL). Rheumatoid arthritis and psoriasis patients with abnormal renal function,

	uncontrolled hypertension, or malignancies. Concomitant treatment with PUVA or UVB therapy, methotrexate, other immunosuppressive agents, coal tar, or radiation therapy are also contraindications for use in patients with psoriasis. *Canadian labeling:* Additional contraindications (not in the US labeling): Concurrent use with bosentan; rheumatoid arthritis and psoriasis patients with primary or secondary immunodeficiency excluding autoimmune disease, uncontrolled infection, or malignancy (excluding non-melanoma skin cancer).
Monitoring Requirements	- Measure creatinine, liver enzymes, electrolytes, blood level of ciclosporin.
Precautions	- Hepatic impairment: Cyclosporine has extensive hepatic metabolism and exposure is increased in patients with severe hepatic impairment. May require dose reduction. - Psoriasis: Appropriate use: If receiving other immunosuppressive agents, radiation or UV therapy, concurrent use of cyclosporine is not recommended.
Black Box Warning	Experienced physician, Immunosuppression, Bioavailability, Hypertension/nephrotoxicity
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided**

specific recommendations regarding the use of *cyclosporine* for the treatment of uveitis (extraintestinal manifestation) in patients with peripheral spondyloarthritis.

CONCLUSION STATEMENT – CYCLOSPORINE

Cyclosporine is recommended for the management of uveitis associated with peripheral spondyloarthritis if other agents have failed as mentioned in the guidelines.

Therefore, it is recommended that this medication be added to the CHI formulary of peripheral spondyloarthritis.

2.2. Modifications

- The ICD-10 Code was changed from M.45 (Spondyloarthritis) to M48.8 (other specified spondylopathies) since this report mainly focuses on forms of spondyloarthritis other than axial spondyloarthritis (discussed in a separate report) and psoriatic arthritis (discussed in a separate report).
- The following table lists the modifications that were made for the different medications.

Table 19. Drug Modifications

Drug	Modification
NSAIDs: Aceclofenac, Celecoxib, Dexketoprofen, Diclofenac Potassium, Diclofenac Sodium, Etoricoxib, Flurbiprofen, Ibuprofen, Indomethacin, ketoprofen, Mefenamic acid, Meloxicam, Naproxen, Piroxicam, Tenoxicam	Removed this part **"BDMARDS FOR AXIAL SPONDYLOARTHRITIS"** from the following sentence "CONSIDER SWITCHING TO ANOTHER NSAID AND IF 2 AGENTS FAILED CONSIDER ADDITION OF" since axial spondyloarthritis is detailed in a separate report. This indication mainly focuses on other forms of spondyloarthritis (enteropathic spondyloarthritis and reactive arthritis).
Leflunomide	Removed the part (in the notes) that details its use in axial spondyloarthritis (discussed in a separate report).
Methotrexate	Removed the part (in the notes) that details its use in axial spondyloarthritis (discussed in a separate report).

Sulfasalazine	Removed the part (in the notes) that details its use in axial spondyloarthritis (discussed in a separate report).

2.3. Delisting

The following table lists the medications that should be delisted with the corresponding reason for each.

Table 20. Delisted Drugs

Delisted Drugs	Reason
Acemetacin	Withdrawn from SFDA and is no longer registered.
Golimumab	This medication is approved for the management of the following conditions: - Axial spondyloarthritis (radiographic and non-radiographic) - Ulcerative colitis - Crohn's Disease - Psoriatic Arthritis All the listed conditions are detailed in separate reports. As for enteropathic spondyloarthritis, golimumab has proved to be effective and may be an alternative therapeutic option for this condition in CD patients who are not responsive to other TNF inhibitors.[28] However, this recommendation is based on low-quality evidence (case series). Therefore, larger studies and more robust evidence are needed in order to recommend this drug for the treatment of enteropathic spondyloarthritis.
Ixekizumab	This medication is approved for the management of the following conditions: - Axial spondyloarthritis (radiographic and non-radiographic) - Plaque psoriasis - Psoriatic arthritis It has no role in the management of the other types of spondyloarthritis discussed in this report.
Rituximab	This medication is indicated for the management of rheumatoid arthritis.

	It has no role in the management of the other types of spondyloarthritis discussed in this report.
Certolizumab pegol	This medication is approved for the management of the following conditions: - Axial spondyloarthritis (radiographic and non-radiographic) - Plaque psoriasis - Psoriatic arthritis - Crohn disease - Rheumatoid arthritis It has no role in the management of the other types of spondyloarthritis discussed in this report.
Secukinumab	This medication is approved for the management of the following conditions: - Axial Spondyloarthritis (radiographic and non-radiographic) - Plaque psoriasis - Psoriatic arthritis As for reactive arthritis, secukinumab has proven to be effective in two in two cases of chronic severe reactive arthritis who initially failed treatment with tumour necrosis factor inhibitor. However, this recommendation is based on low-quality evidence (case series). Therefore, larger studies and more robust evidence are needed in order to recommend this drug for the treatment of enteropathic spondyloarthritis.
Ustekinumab	This medication is approved for the management of the following conditions: - Axial Spondyloarthritis (radiographic and non-radiographic) - Plaque psoriasis - Psoriatic arthritis Ustekinumab may be an appropriate treatment option for patients with inflammatory bowel disease and enteropathic arthritis symptoms group, considering both pathogenesis and successful treatment responses. However, this conclusion is based on results from a systematic literature search performed in the Pubmed database of publications between January 2010 and October 2021 (low-quality evidence) which included 11 patients (small sample size)[11].

	Therefore, larger studies on a higher number of people and more robust evidence are needed in order to recommend this drug for the treatment of enteropathic spondyloarthritis.

Section 3.0 Key Recommendations Synthesis

Enteropathic Spondyloarthritis

- For cases of peripheral or axial SpA with quiescent inflammatory bowel disease, NSAIDs should be generally avoided, however, a short-term course of selective COX-2 inhibitor for no more than two weeks and systemic steroids as a bridge to SSZ is an acceptable option.[9]
- In specific cases, patients with peripheral arthritis and other extraintestinal manifestations have found immunosuppressive drugs such as methotrexate, azathioprine, cyclosporine, and leflunomide to be beneficial and effective.[9]
- Anti-tumor necrosis factor-alpha (anti-TNFα) drugs, notably infliximab and adalimumab, have shown efficacy not only in controlling intestinal inflammation but also in alleviating joint-related symptoms, encompassing both axial and peripheral manifestations.[9]
- Sulfasalazine is a suitable choice for addressing peripheral spondyloarthritis (SpA) because it has demonstrated its effectiveness in managing this condition in these patients.[10]
- In terms of immunomodulators, both methotrexate and thiopurines are found to be ineffective for the treatment of axial SpA. For instances of active, non-complicated luminal Crohn's Disease (CD) linked with axial Spondyloarthritis (axial SpA), the use of anti-TNFα agents is advised.[9]
- TNF inhibitors are second-line agents for axial symptoms after NSAIDs. In case of primary nonresponse within 12 weeks or loss of response, consider switching to another TNF inhibitor.[9]
- Peripheral arthritis with active IBD responds well to treatment of the underlying disease (IBD) in addition to physiotherapy and simple analgesia. Local injection of corticosteroids may be required if symptoms don't resolve rapidly. A short-term course of selective COX-2 inhibitor for no more than two weeks and systemic steroids as a bridge to SSZ is an acceptable option. If arthropathy becomes *persistent* even after control IBD , sulfasalazine, methotrexate, or anti-TNF therapy can be started. In case of primary nonresponse within 12 weeks or loss of response, consider switching to another TNF inhibitor.[9]

Reactive arthritis

- Nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely recognized as the primary therapy for various inflammatory arthritic conditions. Consistent and regular use of these medications is essential to harness their full anti-inflammatory potential. In such cases, no particular NSAID has shown a clear advantage over the rest, and individual reactions to them can differ (Grade 1B).[12]
- It is important to consider the potential adverse effects linked to NSAIDs, notably those affecting the gastrointestinal, renal, and cardiovascular systems. NSAIDs should be recommended for the briefest period feasible, especially in individuals with additional underlying risk factors for unwanted reactions (Grade 1A).[12]
- Based on the experiences of healthcare providers, NSAIDs have demonstrated their clinical effectiveness in treating ReA, even though there have been only two limited prospective trials to formally assess their use. (••)[16]
- In cases where there is a significant risk of gastrointestinal bleeding, it is advisable to opt for a selective cyclooxygenase (COX-2) inhibitor (Grade 1A).[12]
- Topical corticosteroid formulations are appropriate for treating skin or mucous membrane lesions. (Grade 1C)[12]
- Providing antimicrobial treatment for any detected genital infection in instances of reactive arthritis is essential. The therapy should adhere to the recommendations for uncomplicated infections as specified in the pertinent infection management guidelines.[12]
- The efficacy of prolonged antimicrobial treatment for sexually acquired reactive arthritis (SARA) has not been confirmed, and therefore, it is not recommended. (Grade 1C).[12]
- For adult patients diagnosed with peripheral spondyloarthritis (pSpA), the preferred initial treatment approach involves the utilization of conventional disease-modifying antirheumatic drugs (cDMARDs). (Conditional recommendation in favor of cDMARDs intervention. Certainty of the evidence low ⊕⊕ ○○)[13]
- Patients with peripheral spondyloarthritis (pSpA) who do not exhibit a positive response to treatment or are unable to tolerate conventional disease-modifying antirheumatic drugs (cDMARDs) should consider initiating therapy with either an anti-TNFα or an anti-IL17A agent as recommended. (Strong recommendation in favor. Certainty of the evidence moderate ⊕⊕⊕○)[13]

- For adult patients diagnosed with peripheral spondyloarthritis (pSpA) who do not experience a positive response to their initial biologic disease-modifying antirheumatic drugs (bDMARD) treatment, it is advised to contemplate the use of an alternative bDMARD as the subsequent therapeutic approach. This can entail either continuing with the same class of bDMARD or transitioning to one with a distinct mode of action. Another option to consider is the use of a JAK inhibitor. (Conditional recommendation in favor of the intervention. Certainty of the evidence moderate ⨁⨁⨁◯)[13]

General Recommendations

- Non-pharmacological approaches for spondyloarthritis (SpA) should include patient education (I, A) and routine physical activity (II, B), preferably supervised by experienced physiotherapists in specialized facilities. It's important to consider both individual and group physical therapy (I, A), and patients may find value in participating in patient organizations and self-support (IV, D) groups.[11]
- Consider the use of corticosteroid injections in specific areas of inflammation, such as the SI joints, peripheral joints, and entheses. (Sacroiliac joints: I, A), (Psoriatic arthritis joint, II, B), (All other sites, IV, D)[11]
- When patients experience ongoing, treatment-refractory pain or disability in conjunction with X-ray or imaging evidence of structural damage in the hip joint, the consideration of total hip arthroplasty is warranted, regardless of the patient's age. (IV, D)[11]

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Spondylarthritis report** and aims to provide recommendations to aid in the management of other forms of spondyloarthropathies (reactive arthritis and enteropathic spondylarthritis). It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with spondylarthritis. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age

CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Other Forms of Spondyloarthritis Scope

2020	Changes	2024	Rationale
Section 1.0 Other forms of spondyloarthritis Clinical Guidelines			
	Missing	Spondyloarthritis in over 16s: diagnosis and management (2017)	- Classification of spondyloarthritis - Suspecting spondyloarthritis - Referral for suspected other peripheral spondyloarthritides - Diagnostic criteria for suspected spondyloarthritis - Imaging - Antibody testing for suspected reactive arthritis - Education about spondyloarthritis - Information about disease flares - Management of other peripheral spondyloarthritides ✓ For non-progressive monoarthritis, contemplate the use of local corticosteroid injections as a standalone treatment. ✓ Provide standard disease-modifying antirheumatic drugs (DMARDs) to individuals with the following conditions: peripheral polyarthritis, oligoarthritis, or persistent or progressive monoarthritis linked to peripheral spondyloarthritis. ✓ When determining which standard DMARD to offer, take into consideration factors such as the individual's preferences, needs, and circumstances (including pregnancy planning and alcohol

			consumption), any existing comorbidities like uveitis, psoriasis, and inflammatory bowel disease, the characteristics of the disease, and the potential side effects. ✓ If a standard DMARD, administered at the maximum tolerable dose for a minimum of three months, does not deliver sufficient relief from symptoms, consider the possibility of switching to or incorporating another standard DMARD. - Non-pharmacological management of spondyloarthritis - Managing flares - Long-term complications
	Missing	2014 Update of the Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada Treatment Recommendations for the Management of Spondyloarthritis. Part II: Specific Management Recommendations[1] [1]	**C. Spondyloarthritis in adults** **Non-Pharmacological treatment** • Non-Pharmacological for SpA should encompass patient education (I, A) and regular exercise (II, B), preferably under the guidance of expert physiotherapists at specialized centers. Both individual and group physical therapy (I, A) should be taken into account, and patients can benefit from involvement in patient associations and self-help (IV, D) groups. **Corticosteroids** • Consider using corticosteroid injections in specific areas of inflammation, such as the SI joints, peripheral joints, and entheses. (Sacroiliac joints: I, A), (Psoriatic arthritis joint, II, B), (All other sites, IV, D) **DMARDs**

			• SSZ, MTX, and leflunomide could be options for patients with peripheral SpA, although the evidence supporting their effectiveness is limited to moderate at best. The dosage and monitoring of these medications should be customized to each patient and follow the standard care protocols. (I, A) **Antibiotics** • In cases of confirmed post-Chlamydia chronic reactive arthritis, it is advisable to consider a six-month trial of rifampin in combination with either doxycycline or azithromycin. (IV, D) **Tumor Necrosis Factor inhibitors (TNFi)** • TNFi treatment, for patients with persistent high disease activity despite prior therapy, should be supervised by a rheumatologist. (IV, D) **Other biologic agents** • At present, there is no supporting evidence for utilizing alternative biologic agents in the treatment of SpA, including drugs such as ABA (abatacept), TCZ (tocilizumab), and anakinra. (ABA: II, B), (TCZ: I, A), (Anakinra: II, B). **Surgery** • In cases where patients have persistent, treatment-resistant pain or disability along with X-ray or imaging indications of structural damage in the hip joint, total hip arthroplasty should be contemplated, without regard to the patient's age. (IV, D) **D. Juvenile Spondyloarthritis** **Non-Pharmacological**

			• It is highly advisable to motivate children with juvenile spondyloarthritis (JSpA) (specifically Enthesitis-Related Arthritis or ERA) to engage in routine physical activities that align with their overall capabilities and age-appropriate development. (I, B) **NSAID and analgesics** • Peripheral spondyloarthritis (SpA) is more prevalent in juvenile spondyloarthritis (specifically Enthesitis-Related Arthritis or ERA) and should be addressed by initially providing a sufficient trial of nonsteroidal anti-inflammatory drugs (NSAIDs) for a duration of 1 to 2 months. (IV, D) **Corticosteroids** • No alterations are made. A single study focuses on juvenile spondyloarthritis (JSpA), while the majority of data is inferred from studies involving juvenile idiopathic arthritis (JIA). **DMARD** • There are no modifications to the adult recommendations. (SSZ: I, A), (MTX, Leflunomide: III, C) **Antibiotics** • There are no trials of antibiotics in the treatment of JSpA (ERA). There are no modifications (IV, D) **TNFis** • TNF inhibitors (TNFi) are advantageous in the context of juvenile spondyloarthritis (specifically Enthesitis-Related Arthritis or ERA) and should be

			prescribed based on the specific guidelines for predominantly axial or peripheral spondyloarthritis. The TNFi options available for treating juvenile spondyloarthritis (ERA) are presently limited to etanercept (ETN), adalimumab (ADA), and infliximab (IFX). (IFX, ADA: I, A), (ETN: II, B) **Other biologic agents** • The use of these agents in JSpA (ERA) has not been studied. (IV, D) **Surgery** • There are no specific modifications to the adult SpA recommendations with, to our knowledge, no studies found in JSpA(ERA). (IV, D)
	Missing	British Association of Sexual Health and HIV National Guideline on the Management of Sexually Acquired Reactive Arthritis, 2021[29]	**Definition** • Reactive arthritis belongs to the group of seronegative spondyloarthropathies. **Infective pathogens** • The exact mechanisms that connect infectious pathogens to sexually acquired reactive arthritis (SARA) are not entirely clear, and it remains uncertain why some individuals develop SARA in response to a sexually transmitted infection (STI) while others do not. **Risk factors and associations** **Clinical features** • **History** • **Symptoms and signs** • **Diagnosis** • **Further investigations**

			Management • **General advice** • **Treatment** **<u>Antibiotics:</u>** It is imperative to provide antimicrobial therapy for any identified genital infection. The treatment should follow the guidelines for uncomplicated infections as outlined by relevant infection management guidelines. **<u>Physical therapy</u>** **<u>Non-Steroidal Anti-inflammatory drugs (NSAIDs):</u>** • Nonsteroidal anti-inflammatory drugs (NSAIDs) have long been established as the primary treatment for numerous inflammatory arthritic conditions. It is crucial to use them regularly to maximize their anti-inflammatory benefits. In these situations, no specific NSAID has demonstrated superiority over others, and individual responses may vary. (Grade 1B) • **<u>Corticosteroids:</u>** • Intra-articular corticosteroid injections are particularly beneficial for addressing single problematic joints. It's worth noting that there are no randomized placebo-controlled trials (RPCTs) specifically assessing their use in sexually acquired reactive arthritis (SARA). (Grade 1C) • Topical corticosteroid preparations are suitable for addressing cutaneous or mucosal lesions. (Grade 1C)

			• **<u>Disease Modifying Anti-Rheumatic Drugs (DMARDs):</u>** • These treatments are recommended when there are persistent and disabling joint symptoms lasting over 3 months or in cases of severe disease or identified erosive joint damage. • **<u>Biologic agents:</u>** • Tumor necrosis factor (TNF) alpha blockers, of which there are several, have demonstrated high efficacy in treating a range of conditions, including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, skin lesions, other spondyloarthritides, and related enthesitis. They have also been reported to reduce the frequency of uveitis episodes when used to treat ankylosing spondylitis. • **<u>Rare treatments</u>** • **Pregnancy and breast feeding** • **HIV positive individuals** • **Follow up**
	Missing	2021 clinical practice guidelines for the diagnosis, treatment, and follow-up of patients with peripheral spondyloarthritis. Colombian	**Conventional DMARDs (cDMARDs)** • In adult patients with peripheral spondyloarthritis (pSpA), the recommended initial therapy is the use of conventional disease-modifying antirheumatic drugs (cDMARDs). (Conditional recommendation in favor of cDMARDs intervention. Certainty of the evidence low ⨁⨁ ○○) **Systemic glucocorticoids**

		Association of Rheumatology: Consensus statement (2021)[15]	• For patients with pSpA, it is advised to refrain from using systemic glucocorticoids. (Strong recommendation against treatment. Certainty of the evidence low ⨁⨁ ◯◯) **Therapy options after cDMARDs failure** • For patients with psoriatic spondyloarthritis (pSpA) who have not responded to therapy or cannot tolerate conventional disease-modifying antirheumatic drugs (cDMARDs), it is recommended to commence treatment with either an anti-TNFα or an anti-IL17A. (Strong recommendation in favor. Certainty of the evidence moderate ⨁⨁⨁◯) **Therapy options after bDMARDs failure** • In adult patients with peripheral spondyloarthritis (pSpA) who do not respond to their initial biologic disease-modifying antirheumatic drugs (bDMARD) therapy, the recommendation is to consider using another bDMARD as the next treatment option. This can involve either sticking with the same type of bDMARD or switching to one with a different mechanism of action. Another option is to consider a JAK inhibitor. (Conditional recommendation in favor of the intervention. Certainty of the evidence moderate ⨁⨁⨁◯) **Treatment of adult patients with pSpA and associated uveitis as an extra-articular manifestation, cDMARDs**

			• In adult patients with pSpA and anterior uveitis (associated as an extra-articular manifestation) the suggestion is to use methotrexate or sulfasalazine with a view to reducing flares. (Conditional recommendation in favor of the use of cDMARDs. Certainty of the evidence low ⨁⨁ ○○) **Treatment of adult patients with pSpA and associated uveitis as an extra-articular manifestation** • In adult patients with pSpA and concurrent uveitis (as an extra-articular symptom) who require bDMARD treatment, it is recommended to consider the use of an anti-TNFα medication to lower the occurrence of acute anterior uveitis. (Conditional recommendation in favor of the intervention. Certainty of the evidence very low ⨁ ○○○) **Treatment of adult patients with pSpA and associated inflammatory bowel disease** • For patients with pSpA who also have inflammatory bowel disease, it is recommended to begin treatment with conventional disease-modifying antirheumatic drugs (cDMARDs). (Conditional recommendation in favor of the intervention. Certainty of the evidence very low ⨁ ○○○)
	Missing	Current Clinical Microbiology Reports: Reactive Arthritis Article: Update (2020)[30]	**Clinical Manifestations** **Diagnosis of ReA** **Radiological Findings** **Therapeutic Approach** **Treatment of Acute ReA** • **<u>Non-steroidal Anti-inflammatory Drugs</u>**

			• Based on the experiences of healthcare providers, NSAIDs have demonstrated their clinical effectiveness in treating ReA, even though there have been only two limited prospective trials to formally assess their use. (••) - **Glucocorticoids** - In cases of acute ReA where patients exhibit an inadequate response to or cannot tolerate NSAIDs, it may be advisable to contemplate intra-articular glucocorticoid therapy. This approach can offer relief from symptoms and minimize the potential side effects associated with systemic steroids. • **Antibiotic** • Despite numerous studies examining antibiotics as a therapeutic option for ReA, there continues to be a discussion regarding their effectiveness. (••) **Treatment of Chronic ReA** - **Disease-Modifying Antirheumatic Drugs** - Radiographic damage observed in ReA shows similarities to that of other types of SpA, with PsA being a notable example. Consequently, conventional disease-modifying antirheumatic drugs (DMARDs) are frequently employed in the treatment of ReA. (••) - **Biological Agent** - Biological treatments have shown promise in managing treatment-resistant ReA, although the available studies are typically case reports and small-scale open clinical trials. Patients who underwent

			biological treatment experienced relief from symptoms and saw improvements in the inflammatory markers associated with arthritis (•) **Evolution and Prognosis**
	Missing	Enteropathic Spondyloarthritis: From Diagnosis to Treatment 2013 (Review article)[9]	**Definition** **Classification Criteria** **Pathogenesis** **Other Rheumatic and Extra-Articular Manifestations** **Cardiovascular Disease and EA** **Treatment** - Treatment often involves the use of corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and/or anti-TNFα medications, which not only help control intestinal inflammation but also typically result in a reduction of symptoms related to peripheral type I arthritis. These symptoms often respond well to rest, physiotherapy, and localized steroid injections. - Sulfasalazine and 5-aminosalicylic acid are frequently employed in the treatment of inflammatory bowel disease (IBD). Their effectiveness has also been verified in managing mild peripheral arthritis, especially in patients with ulcerative colitis (UC). However, their efficacy in treating Crohn's disease (CD) has not been definitively established. It's important to note that these medications do not influence the progression of joint damage to more severe forms of arthritis, and their utility in the axial subset is limited.

			Furthermore, they do not appear to prevent the potential development of intestinal inflammation in patients with spondyloarthritis (SpA). - Immunosuppressive medications like methotrexate, azathioprine, cyclosporine, and leflunomide have proven to be effective in certain patients who have peripheral arthritis and other extraintestinal manifestations. Recently, our research team has been investigating the effectiveness and tolerability of a 20 mg/week dose of methotrexate in individuals with peripheral arthritis associated with UC. Our findings have demonstrated a prompt and effective reduction of joint symptoms along with notable improvements in laboratory results and disease activity measures.
	Missing	Expert Review of Clinical Pharmacology: Management of patients with inflammatory bowel disease and spondyloarthritis (2017)[17]	**Classification of Spondyloarthritis** **Diagnosing SpA in IBD patients** **Treatment goals in SpA** **Treatment options** • Sulfasalazine is a viable option for the treatment of peripheral spondyloarthritis (SpA) due to its proven effectiveness in these individuals. • Administering localized steroid injections is a beneficial therapeutic choice specifically for patients with peripheral spondyloarthritis (SpA) who have oligoarthritis (involving four or fewer joints). In cases of a peripheral flare, systemic corticosteroids can also be employed, but it is essential to swiftly reduce the dosage.

			• Methotrexate has been established as an effective treatment approach for individuals with psoriatic arthritis and rheumatoid arthritis. Therefore, it can be contemplated as a potential therapy for patients with peripheral spondyloarthritis (SpA). • Anti-tumor necrosis factor (anti-TNF) agents, such as adalimumab, certolizumab, and etanercept, have shown their effectiveness in treating psoriatic arthritis. Additionally, adalimumab has displayed encouraging outcomes in two placebo-controlled studies involving patients with peripheral spondyloarthritis (SpA).
	Missing	Italian Expert Panel on the management of patients with coexisting spondyloarthritis and inflammatory bowel disease.[9]	**IBD-associated SpA: disease classification, diagnosis and manifestations** **IBD-associated SpA clinical presentation and diagnostic work-up** **IBD-associated SpA combined therapy: a patient-tailored approach** **Axial SpA and active luminal CD and UC** **Axial SpA and quiescent IBD** **Peripheral SpA (oligoarthritis and/or enthesitis and/or dactylitis) and active luminal CD and UC** **Polyarthritis (N4 joints) and active luminal UC and CD** **Peripheral SpA and IBD in remission**

Appendix C. MeSH Terms PubMed

C.1 Pubmed Search for other forms of spondyloarthritis

The following is the result of the PubMed search conducted for reactive arthritis guideline search:

Query	Filters	Search Details	Results
((((((((((((((Arthritis, Reactive[MeSH Terms]) OR (Reactive Arthritides[Title/Abstract])) OR (Reactive Arthritis[Title/Abstract])) OR (Arthritis, Post-Infectious[Title/Abstract])) OR (Arthritis, Post Infectious[Title/Abstract])) OR (Post-Infectious Arthritides[Title/Abstract])) OR (Post-Infectious Arthritis[Title/Abstract])) OR (Post Infectious Arthritis[Title/Abstract])) OR (Postinfectious Arthritis[Title/Abstract])) OR (Postinfectious Arthritides[Title/Abstract])) OR (Arthritis, Postinfectious[Title/Abstract])) OR (Reiter Syndrome[Title/Abstract])) OR (Reiter's Disease[Title/Abstract])) OR (Reiters Disease[Title/Abstract])) OR (Reiter's Syndrome[Title/Abstract])) OR (Reiters Syndrome[Title/Abstract])) OR (Reiter Disease[Title/Abstract])	Guideline, in the last 5 years	("arthritis, reactive"[MeSH Terms] OR "reactive arthritides"[Title/Abstract] OR "reactive arthritis"[Title/Abstract] OR "arthritis post infectious"[Title/Abstract] OR "arthritis post infectious"[Title/Abstract] OR "post infectious arthritides"[Title/Abstract] OR "post infectious arthritis"[Title/Abstract] OR "post infectious arthritis"[Title/Abstract] OR "postinfectious arthritis"[Title/Abstract] OR "postinfectious arthritides"[Title/Abstract] OR "arthritis postinfectious"[Title/Abstract] OR "reiter syndrome"[Title/Abstract] OR "reiter s disease"[Title/Abstract] OR "reiters disease"[Title/Abstract] OR "reiter s syndrome"[Title/Abstract] OR "reiters syndrome"[Title/Abstract] OR "reiter disease"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	1

There is no Mesh term for Enteropathic Spondyloarthritis.

Appendix D. Treatment Algorithms

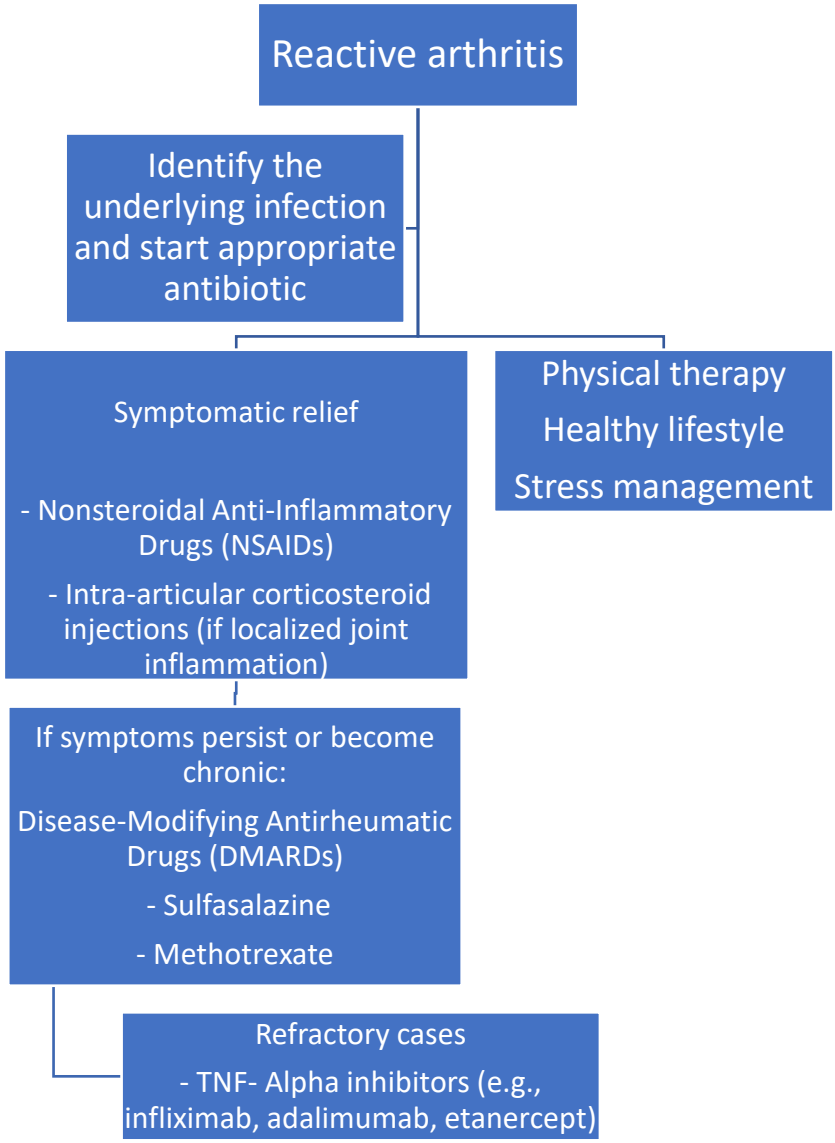

Figure 2. *Treatment algorithm for reactive arthritis*[11,12,30]

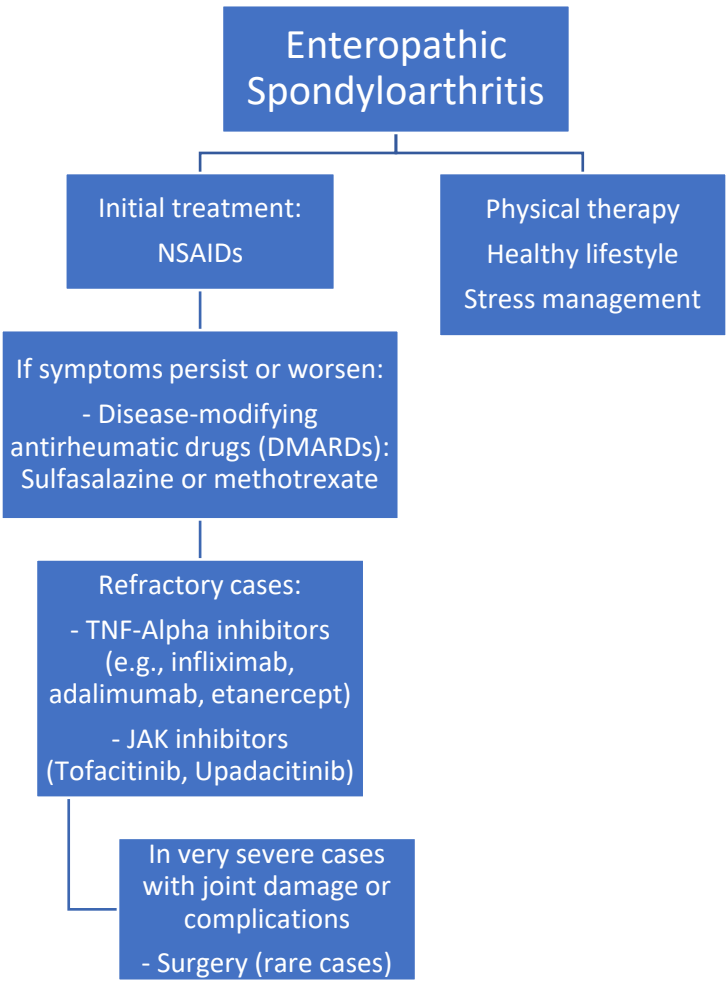

Figure 3. *Treatment algorithm for enteropathic spondyloarthritis*[9–11,13]