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Expert consensus: practical algorithms for management of inflammatory bowel disease patients presenting with back pain or peripheral arthropathies

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Summary

Background: Spondyloarthritis is the most frequent extra-intestinal manifestation of IBD.

Aim: To present simple strategies to identify and differentiate inflammatory joint pain in IBD patients.

Methods: A panel of Belgian gastroenterologists and rheumatologists developed seven algorithms for IBD patients with joint symptoms based on a Delphi exercise conducted between April and December 2016. Here, we focus on referral strategies for patients with chronic back pain (evidence-based strategy), large joint monoarthritis, oligo- or polyarticular arthritis or arthralgia (based on expert opinion). We also present management tools for IBD patients with acute back pain and small joint monoarthritis (Supplementary file).

Results: The reported algorithm for IBD patients with chronic back pain uses basic clinical criteria to identify which patients should be referred to the emergency room (spondylodiscitis), physical medicine and rehabilitation (mechanical back pain) or rheumatologist (spondyloarthritis). IBD patients with large joint monoarthritis should be referred to emergency room if septic arthritis is suspected; in other patients, blood analyses and referral to a rheumatologist for articular puncture with evacuation of synovial fluid are recommended. The analysis of synovial fluid allows for identification of non-inflammatory (e.g., osteoarthritis) and inflammatory (e.g., [pseudo]-gout, peripheral spondyloarthritis and *Borrelia burgdorferi* arthritis) conditions. In patients with inflammatory oligoarticular or polyarticular arthralgia, erythrocyte sedimentation rate, concomitant therapies, anti-nuclear factor and anti-double-stranded DNA antibody levels should be evaluated; in anti-tumour necrosis factor-treated patients, a drug-induced lupus-like syndrome should be considered.

Conclusion: We propose straightforward strategies for IBD patients with joint symptoms, which are specific enough to select initial treatment and referral pattern.

Dirk Elewaut and Martine De Vos contributed equally to the manuscript.

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1 | INTRODUCTION

IBD, including Crohn's disease and ulcerative colitis, affects not only the gut but also extra-intestinal sites in approximately one-third of patients, predominantly the skin and the joints.[1,2] The most frequent extra-intestinal manifestation of IBD is spondyloarthritis,[1] a group of articular chronic inflammatory diseases, including ankylosing spondylitis, psoriatic arthritis, reactive arthritis, IBD-related spondyloarthritis, and undifferentiated spondyloarthritis.[3] IBD and spondyloarthritis are associated in genetic background, and in clinical and imaging features.[4-6]

Depending on the predominant manifestation, spondyloarthritis is divided into axial spondyloarthritis and peripheral spondyloarthritis.[7] The early diagnosis of spondyloarthritis may be a major challenge for physicians due to the lack of objective disease markers.[8,9] Moreover, joint symptoms usually occur in patients treated with immunomodulatory drugs, masking clinical presentation.[7] In axial spondyloarthritis, the main symptom is chronic (low) back pain induced by inflammation of the sacroiliac joints (sacroiliitis) or spine (spondylitis). In some patients, axial spondyloarthritis evolves into ankylosing spondylitis, a more severe disease stage with structural damage of the sacroiliac joints and/or spine visible on X-ray.[10,11] The main symptoms of peripheral spondyloarthritis are arthritis, enthesitis and dactylitis.[12]

A recent meta-analysis has shown that up to 13% of IBD patients are diagnosed with peripheral arthritis, whereas prevalence estimates for sacroiliitis and ankylosing spondylitis are 10% and 3%, respectively.[12] Joint flares usually, but not exclusively, accompany gut flares.[13,14] Although sacroiliitis can be seen on X-ray and computed tomography of the abdomen in IBD patients,[15-17] recent studies have shown that magnetic resonance imaging is superior to detect inflammatory sacroiliitis and allows an earlier diagnosis of axial spondyloarthritis, before the occurrence of structural changes.[18,19] However, the abnormalities of the sacroiliac joints present on magnetic resonance enterography were not associated with inflammatory back pain (IBP).[19] Therefore, imaging findings should be interpreted cautiously in asymptomatic patients. Indeed, the significance of subclinical sacroiliitis is unknown and research has mainly focused on the diagnosis and treatment of symptomatic patients.

Considering the high prevalence of rheumatic diseases in IBD patients, the difficult diagnosis of spondyloarthritis and the shortage of rheumatologists, there is a need for feasible and simple referral strategies, sensitive and specific enough to select patients with rheumatic conditions suggestive of spondyloarthritis.

2 | MATERIALS AND METHODS

This paper has been developed based on a Delphi exercise amongst a panel of experts in the field of spondyloarthritis and/or IBD between April and December 2016.

First, the development of referral algorithms for IBD patients with joint symptoms was initiated by experts from the University of Ghent, who drafted initial referral proposals based on expert opinions, scientific literature and clinical experience. The relevant literature was selected through a thorough PubMed search, based on the following terms and their combinations: “inflammatory bowel disease”, “arthritis”, “sacroiliitis”, “arthralgia”, “referral”, “spondyloarthritis” and “ankylosing spondylitis”.

Secondly, a panel of eight interuniversity specialists in the field of IBD and spondyloarthritis, including Belgian gastroenterologists and rheumatologists from the Universities of Ghent, Leuven and Liège, were selected to attend a consensus meeting on May 2, 2016. Pairs of gastroenterologists and rheumatologists from the three universities discussed the proposed referral algorithms for common joint symptoms in IBD patients, such as acute back pain, chronic back pain, large joint monoarthritis, small joint monoarthritis, oligo- or polyarthritis, monoarticular arthralgia and oligo- or polyarticular arthralgia. Based on the critical appraisal of the experts, the referral algorithms were revised. Updated proposals were shared with all experts who could provide additional feedback via email. Finally, the proposed referral algorithms were presented and tested for feasibility and applicability in a national meeting with nonselected gastroenterologists on December 2, 2016, leaving room for additional remarks from the audience.

Here, we focus on referral algorithms for IBD patients with chronic back pain, large joint monoarthritis and arthralgia, which are the most frequently encountered topics in clinical practice.

3 | RESULTS AND DISCUSSION

3.1 | Axial spondyloarthritis

Although axial spondyloarthritis is a common cause of chronic low back pain in IBD patients, its early diagnosis remains challenging. The proposed evidence-based referral algorithms for IBD patients with back pain are largely based on an existing algorithm developed for the overall population, but have been adapted to IBD patients taking into account their treatment.[8]

3.1.1 | Exclusion of spondylodiscitis

In IBD patients taking immunosuppressants, infectious spondylodiscitis must be excluded in case of new-onset back pain. In case of fever, high inflammatory parameters, infectious focus or neurological symptoms, immediate referral to the emergency room with a diagnostic work-up is advised. Magnetic resonance imaging of the spine is recommended. Potential causative pathogens should be identified by blood culture or biopsy before initiation of treatment with antibiotics.[20] An extensive review of treatment options for spondylodiscitis is beyond the scope of this article.

3.1.2 | Acute vs chronic back pain

Acute back pain is defined as back pain with a duration of less than 6 weeks.[21] Although lumbalgia and ischialgia are common in the

setting of strain or trauma, acute back pain can have inflammatory features resembling inflammatory back pain. However, unlike strain and trauma, sacroiliitis or spondylitis will usually not result in antalgic posture or limping. Likewise, neurologic symptoms are more indicative of degenerative disc disease, spinal canal stenosis or pain originating from facet joints. A referral strategy for IBD patients with acute back pain can be found in Figure S1. Overall, acute back pain is rarely caused by rheumatologic conditions, and patients should be referred to other musculoskeletal specialists.

Chronic back pain is generally defined as back pain with a duration of at least 6-12 weeks. [21] Although back pain is often the main complaint in axial spondyloarthritis, only 5% of patients with chronic back pain have underlying axial spondyloarthritis.[22,23] However, the prevalence of axial spondyloarthritis is higher in patients with chronic back pain and a closely related disease, such as IBD.[12]

3.1.3 | Referral strategy for IBD patients with chronic back pain

Based on an algorithm previously developed to assist in the early diagnosis of axial spondyloarthritis in all patients with chronic back pain,[8] we designed an adapted referral algorithm for IBD patients. Our decision tree was supported by calculations of post-test probabilities by applying formulas based on Bayes' theorem, as described in the original article.[8]

The previously developed algorithm utilises average representative sensitivities and specificities of several spondyloarthritis features, which were collected from the literature. As recognition of some of the spondyloarthritis features may be difficult for physicians who are less familiar with rheumatic disease, we simplified the algorithm to include inflammatory back pain, response to nonsteroidal anti-inflammatory drugs (NSAIDs) and human leucocyte antigen (HLA)-B27 status, which are important and well-known spondyloarthritis characteristics. C-reactive protein (CRP) elevation was not included because IBD may account for elevated CRP levels regardless of concomitant spondyloarthritis. As our tool will be used for screening, sensitivity was prioritised.

The cardinal symptom in axial spondyloarthritis is inflammatory back pain, which is present in most patients (Figure 1).[24] Different sets of criteria used in clinical practice were proposed to identify patients with inflammatory back pain. Age at onset is an important differentiating factor in back pain. However, immunosuppressants, including anti-tumour necrosis factor (anti-TNF), may in some cases suppress inflammation and therefore postpone incipient

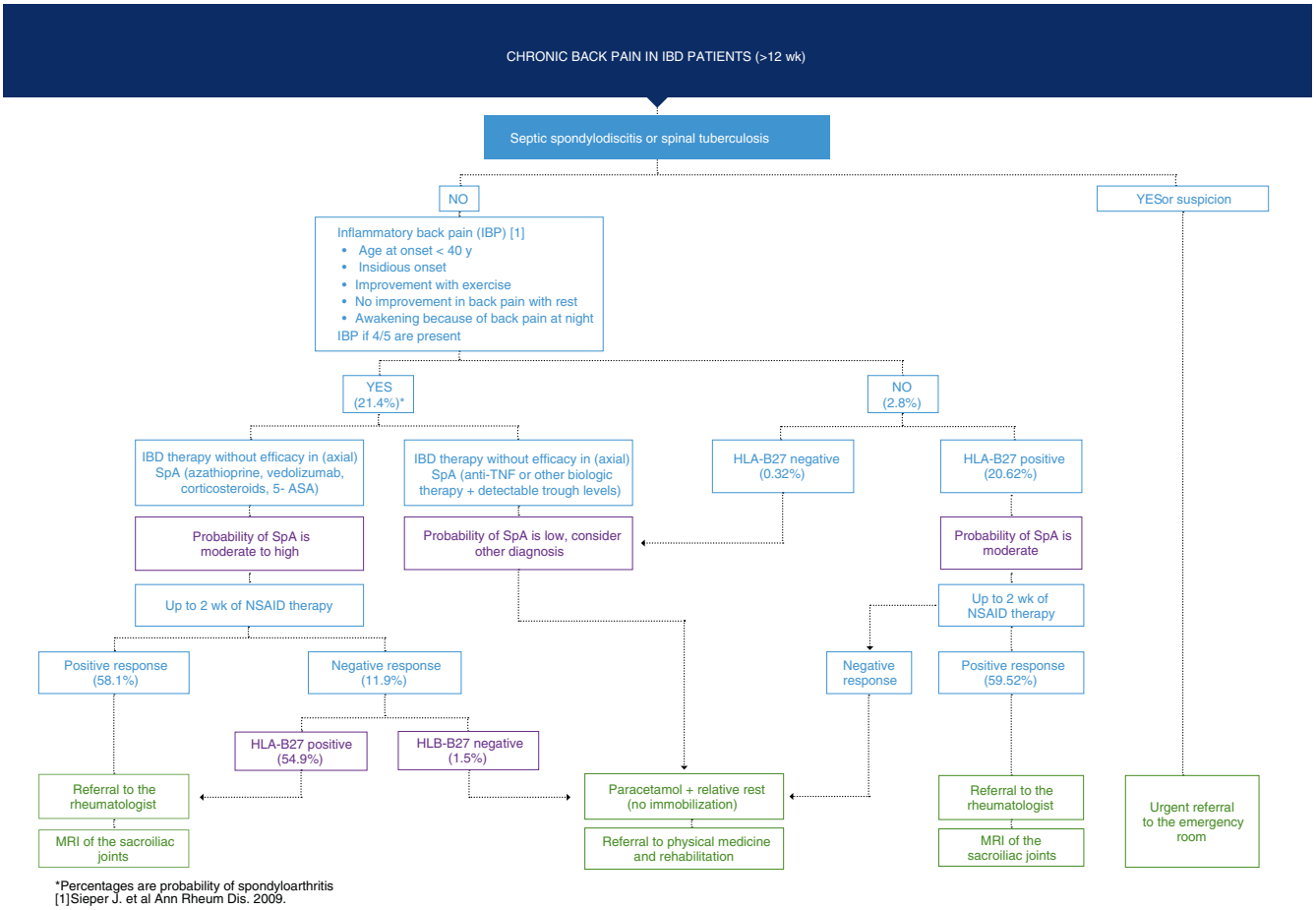

FIGURE 1 Referral pattern for IBD patients with chronic back pain. Abbreviations: anti-TNF, anti-tumour necrosis factor; HLA, human leucocyte antigen; IBD, inflammatory bowel disease; IBP, inflammatory back pain; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; SpA, spondyloarthritis. Percentages indicate post-test probabilities[33]

symptoms.[25] To be recognised as having inflammatory back pain, patients had to present with four out of five of the following criteria: age at onset <40 years, insidious onset, improvement with exercise, no improvement in back pain with rest or awakening because of back pain at night.[25]

Axial spondyloarthritis prevalence in IBD patients was estimated at 8%, which is the prevalence of symptomatic sacroiliitis in these patients. Asymptomatic sacroiliitis cannot be considered as axial spondyloarthritis and was therefore not included. When IBD patients who present with inflammatory back pain, receive anti-TNF therapy or other biologics with proven efficacy against axial spondyloarthritis and have detectable serum trough levels, onset of axial spondyloarthritis is improbable, although not impossible. In these patients, degenerative changes or fibromyalgia should be considered. Importantly, although ustekinumab showed efficacy in a small open-label study, larger randomised controlled trials have failed to validate these results.[26-29] In patients receiving IBD treatments not considered as protective against spondyloarthritis (eg azathioprine, corticosteroids or vedolizumab), the probability of axial spondyloarthritis is moderate to high.[30-32] In these patients, NSAID therapy should be considered. Although all NSAIDs are equally effective in treating axial spondyloarthritis, the optimal dose per product is necessary (Table 1).[33] Even though IBD flares in patients using NSAIDs were reported in case reports and observational studies, randomised controlled trials and cohort studies have produced reassuring data regarding the short-term use of Cox-selective NSAIDs.[34-36] Nevertheless, in patients with uncontrolled IBD, NSAIDs should be used cautiously.

Based on the estimated axial spondyloarthritis prevalence in IBD patients (pre-test probability) and the sensitivity and specificity of inflammatory back pain criteria, IBD patients with chronic inflammatory back pain have a probability of 21.4% of having axial spondyloarthritis. Good response to NSAIDs results in a rise in the axial spondyloarthritis probability to 58.1%. Lack of response to NSAIDs results in a decrease in the axial spondyloarthritis probability to 11.9%; in these patients, determining the HLA-B27 status can provide an alternative route if suspicion remains high, with positive tests resulting in the axial spondyloarthritis probability of 54.9%. Indeed, in patients with chronic low back pain, both HLA-B27 status and inflammatory back pain have proven to be good referral criteria.[37] If inflammatory back pain is not present, the axial spondyloarthritis probability decreases to 2.8%. Even if patients without inflammatory back pain are positive for HLA-B27, this probability only rises to 20.6%. If these patients also have a good response to NSAIDs, a reasonable probability of 59.5% can be reached.

TABLE 1 Comparable efficacy of each NSAID with 150 mg of diclofenac, adapted from Dougados et al[33]

NSAID	Daily dose (mg)
Diclofenac	150
Naproxen	1000
Aceclofenac	200
Celecoxib	400
Etodolac	600
Etoricoxib	90
Flurbiprofen	200
Ibuprofen	2400
Indometacin	150
Ketoprofen	200
Meloxicam	15
Nimesulide	200
Phenylbutazone	400
Piroxicam	20
Tenoxicam	20

The sensitivities and specificities used in this paper are based on a high number of estimates from several large studies in IBD. Nevertheless, applying different sensitivities and specificities may lead to different probabilities. The post-test probabilities should be regarded as estimates and the validity of these algorithms should be tested in real-life setting. Additionally, convergence was limited by the inclusion of independent variables in the algorithm.

The referral algorithm presented here can be used to evaluate IBD patients presenting with chronic back pain and to identify which patients should be referred to specialists based on basic clinical criteria and one objective laboratory test. Because of the need of specific expertise in interpretation of imaging, the opinion of the committee was that imaging is not necessary before referral. Indeed, X-rays of sacroiliac joints may give false-negative results in early disease stages and pelvic X-ray interpretation has proven unreliable and reader-dependent.[38] Additionally, magnetic resonance imaging is expensive, in high demand and only reliably interpretable in patients with high suspicion of spondyloarthritis. Different types of mechanical stress, including physiological changes induced by pregnancy, may mimic sacroiliitis. These imaging techniques should only be requested and interpreted by experienced readers with full knowledge of the clinical background.

In conclusion, chronic back pain is a prevalent and multi-layered complaint which may be influenced by therapy. This algorithm provides a clinical tool to differentiate whether referral is needed by the use of pain pattern, the patient's IBD therapy, response to NSAID and the HLA-B27 status. Imaging is not essential in the initial work-up of any patient, as imaging quality and expertise may be required.

3.2 | Peripheral arthritis

Peripheral arthritis prevalence in IBD patients has been estimated at 13%, being highest (25%) in 20-30-year-old patients.[12] Arthritis is characterised by swelling and pain, but redness and warmth are also frequent. Before diagnostic investigation, it is critical to collect the patient's medical history—including concomitant symptoms and previous joint flares—and to perform a complete clinical examination with attention to age, skin and distribution of affected joints.[39] Symptoms of preceding enteric or genitourinary infection

with pathogens such as *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Clostridium* or *Chlamydia trachomatis* should be inquired for.

Typically, peripheral spondyloarthritis has an oligoarticular distribution with a preferential localisation in large joints of lower limbs in young patients.[40] In contrast, rheumatoid arthritis (RA) and (drug-induced) systemic lupus erythematosus (SLE) display a more symmetrical distribution, generally localised on small joints of hands and feet.[41]

3.2.1 | Monoarthritis in IBD patients

Monoarthritis of a joint is a common clinical presentation in any population. However, the differential diagnosis is broad, and about half of patients with acute monoarthritis do not have a definitive diagnosis within 2 years.[42]

In the case of monoarthritis in IBD patients, exclusion of trauma and/or septic arthritis is essential. The latter can lead to joint destruction and sepsis with multiple organ failure, especially in patients treated with immunosuppressants or having other risk factors (eg, older age, diabetes mellitus, surgery or prosthetic joint).[43] Patients with clinical indications of possible septic arthritis, such as fever, skin infection or entry wound, should be referred to the emergency room for blood analysis, evacuation of purulent material, puncture and blood culture before initiation of antibiotics. A white blood cell (WBC) count of >50 000 cells/μl with ≥90% neutrophils in the puncture fluid may be indicative of septic arthritis.[43] Moreover, the sensitivity of a positive synovial culture is 75%-95% for septic arthritis.[43] Other blood analyses are commonly performed for diagnosis purposes (WBC count, CRP, sedimentation, uric acid, rheumatoid factor [RF] and anti-cyclic citrullined peptide [anti-CCP] levels).

Large joint monoarthritis

Since there are no established referral strategies for peripheral arthritis, the development of the decision tree for IBD patients with large joint monoarthritis was based on expert opinion, literature and experience (Figure 2).

Patients with large joint monoarthritis (knee, ankle, hip, shoulder, elbow or wrist) should be referred to a rheumatologist for articular puncture with synovial fluid evacuation (Figure 2). The purpose of this procedure is both therapeutic and diagnostic (cell count, culture and/or characterisation of crystals). Treatments, such as oral corticosteroids, disease-modifying anti-rheumatic drugs and antibiotics, should not be initiated before the puncture, as they may mask distribution, systemic inflammation and in some cases auto-immune serology, thereby complicating prompt diagnosis.

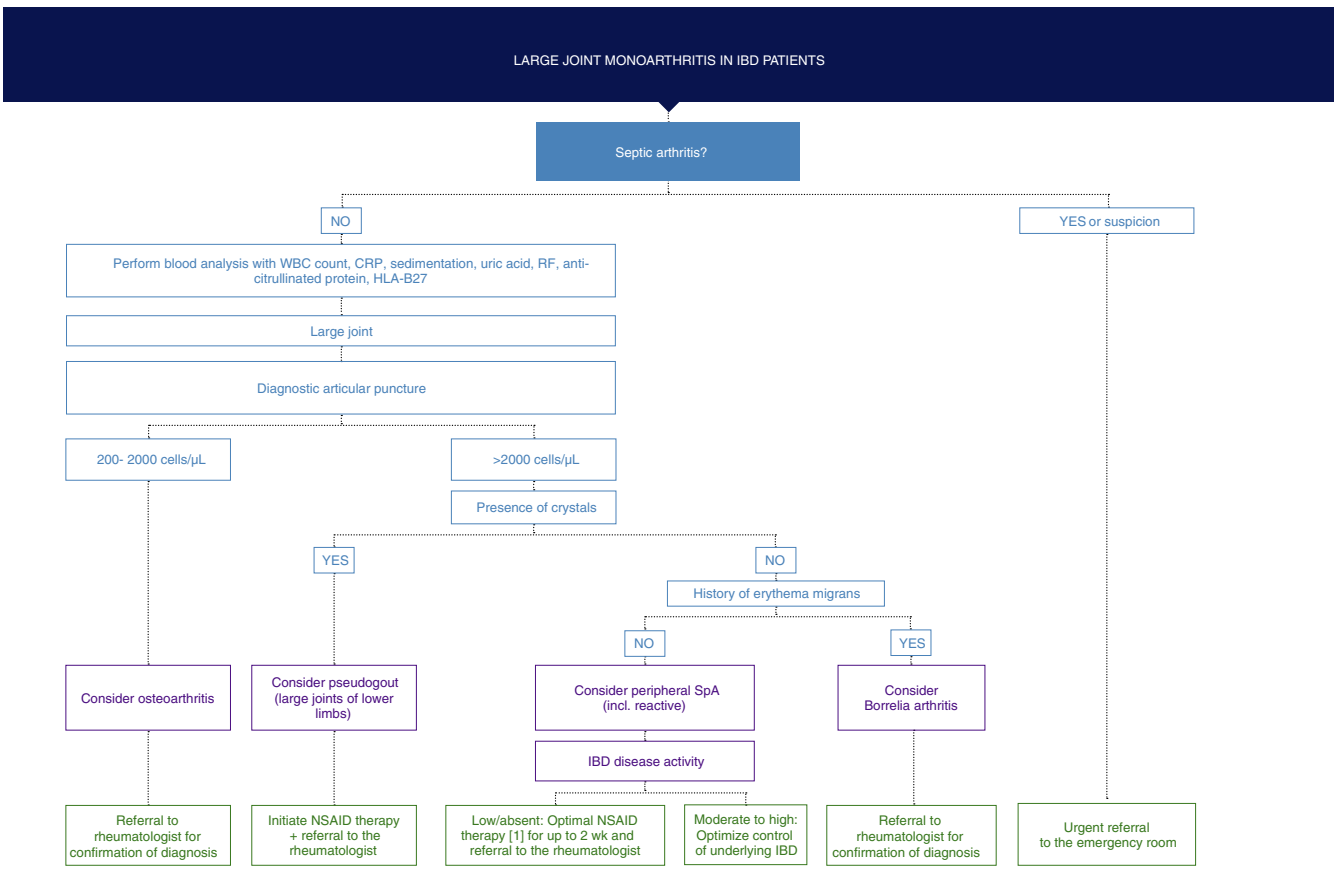

FIGURE 2 Referral pattern for IBD patients with large joint monoarthritis. Abbrevations: CRP, C-reactive protein; IBD, inflammatory bowel disease; NSAIDs, nonsteroidal anti-inflammatory drugs; RF, rheumatoid factor; SpA, spondyloarthritis; WBC, white blood cell[33]

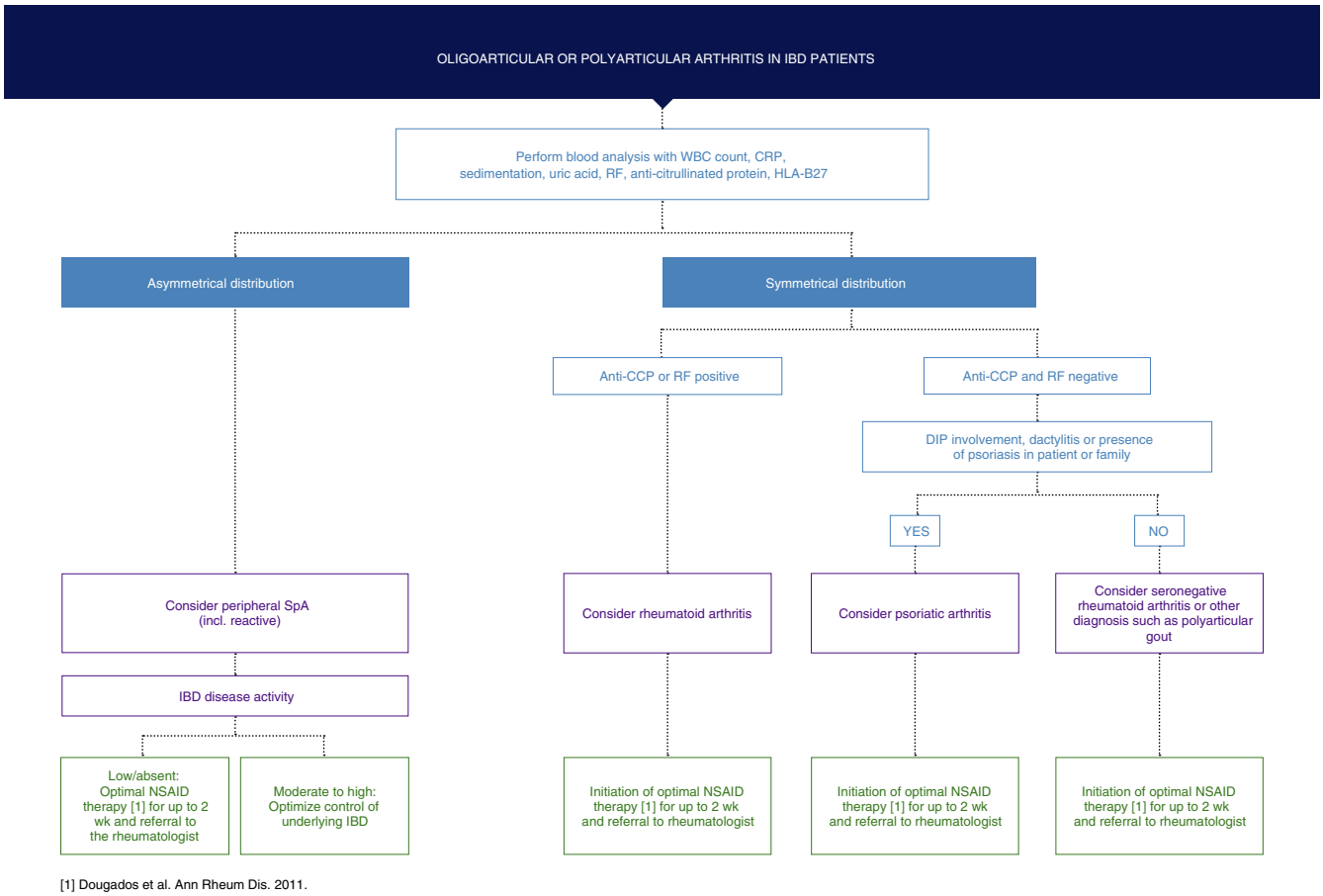

FIGURE 3 Referral pattern for IBD patients with oligo- or polyarticular arthritis. Abbreviations: CCP, cyclic citrullined peptide; CRP, C-reactive protein; DIP, distal interphalangeal; IBD, inflammatory bowel disease; NSAIDs, nonsteroidal anti-inflammatory drugs; RA, rheumatoid arthritis; RF, rheumatoid factor; SpA, spondyloarthritis; WBC, white blood cell[33]

Synovial fluid containing >2000 WBC/μl and >75% polymorphonuclear cells is indicative of inflammatory joint disease, whereas synovial fluid containing <2000 WBC/μl is usually indicative of mechanical joint disease/osteoarthritis.[44,45] In case of inflammatory joint disease, polarisation microscopy should be used to detect the presence of monosodium urate or calcium pyrophosphate dihydrate crystals, indicative of gout and pseudogout, respectively.[46] If crystals are present, (pseudo)-gout should be considered, local corticosteroid infiltration administered, and NSAID or colchicine therapy initiated. Referral to a rheumatologist is recommended. If no crystals are detected, *B burgdorferi* arthritis should be suspected in patients with current or previous erythema migrans or documented tick bites as a late manifestation of Lyme disease. *B burgdorferi* serology should not be done in every patient as the screening assay has high sensitivity at the expense of specificity.[47] The suspicion of *B burgdorferi* will be influenced by the local incidence rate of Lyme's disease. When in doubt, the presence of DNA in the synovial fluid can be tested using polymerase chain reaction. In the absence of erythema migrans history, peripheral spondyloarthritis should be considered and optimal NSAID therapy or low-dose corticosteroids should be initiated. Referral to a rheumatologist is recommended. An extensive review of treatment of peripheral spondyloarthritis is beyond the scope of this article. Nevertheless, methotrexate, leflunomide and sulphasalazine are slow-acting agents, which are useless for immediate symptom control but may have an evaluable clinical benefit only after 8-12 weeks.

Small joint monoarthritis

The approach in case of small joint monoarthritis is more difficult, as diagnostic puncture is rarely an option. The differential diagnosis is mainly based on serology (Figure S2). In RF- or anti-CCP-positive patients, early RA diagnosis is possible, although the most frequent initial presentation of RA is symmetrical polyarthritis.[48] In RF- and anti-CCP-negative patients, osteoarthritis, peripheral spondyloarthritis or gout are potential diagnoses. Nevertheless, a small portion of patients exhibit seronegative RA.

In case of single arthritis at the level of the hands in combination with bony changes of other proximal interphalangeal and distal interphalangeal joints, erosive hand osteoarthritis should be considered in middle-aged or elderly patients.[49] The presence of tophi or the typical localisation at the first toe metatarsophalangeal joint can advocate in favour of gout, even in the absence of high serum uric acid in the acute phase. Importantly, monoarthritis

in IBD patients can be the first symptom of systemic disease and subsequently spread towards other joints or the axial skeleton.

3.2.2 | Oligo- or polyarthritis in IBD patients

When several joints are involved, both distribution and auto-immune serology are crucial. If articular puncture of a large joint is possible, the latter should be performed to refine diagnosis (Figure 3).

3.2.3 | Arthralgia in IBD patients

Arthralgia is the presence of one or more painful joints without objective signs of inflammation, such as swelling, redness or warmth. An inflammatory cause should be suspected if pain is worst during the night and in the morning, the patient has morning stiffness and feels better with exercise. A mechanical cause should be suspected if pain is worsening throughout the day, the patient has pain upon weight bearing and feels better with rest. In case of mechanical pain, a "wait and see" approach with paracetamol for pain relief is recommended (Figure 4 and Figure S3).

Monoarticular arthralgia

In patients with persistent monoarticular arthralgia caused by mechanical pain and in patients with inflammatory arthralgia, the presence of inflammatory activity should be assessed using ultrasound. In the absence of systemic inflammation, arthralgia related to overuse or osteoarthritis should be considered. In the case of positive ultrasound results, monoarthritis should be considered, and treatment with NSAIDs should be initiated. In both cases, referral to a rheumatologist is recommended (Figure S3).

Oligoarticular and polyarticular arthralgia

In patients with persistent oligoarticular and polyarticular arthralgia caused by mechanical pain, osteoarthritis and fibromyalgia should be considered (Figure 3).

In patients with inflammatory oligoarticular and polyarticular arthralgia, erythrocyte sedimentation rates should be evaluated (Figure 3). In patients with normal sedimentation, arthralgia is often related to treatment or discontinuation of therapy in absence of systemic inflammation. Arthralgia and/or myalgia have been reported in 14% of azathioprine-treated patients, of whom

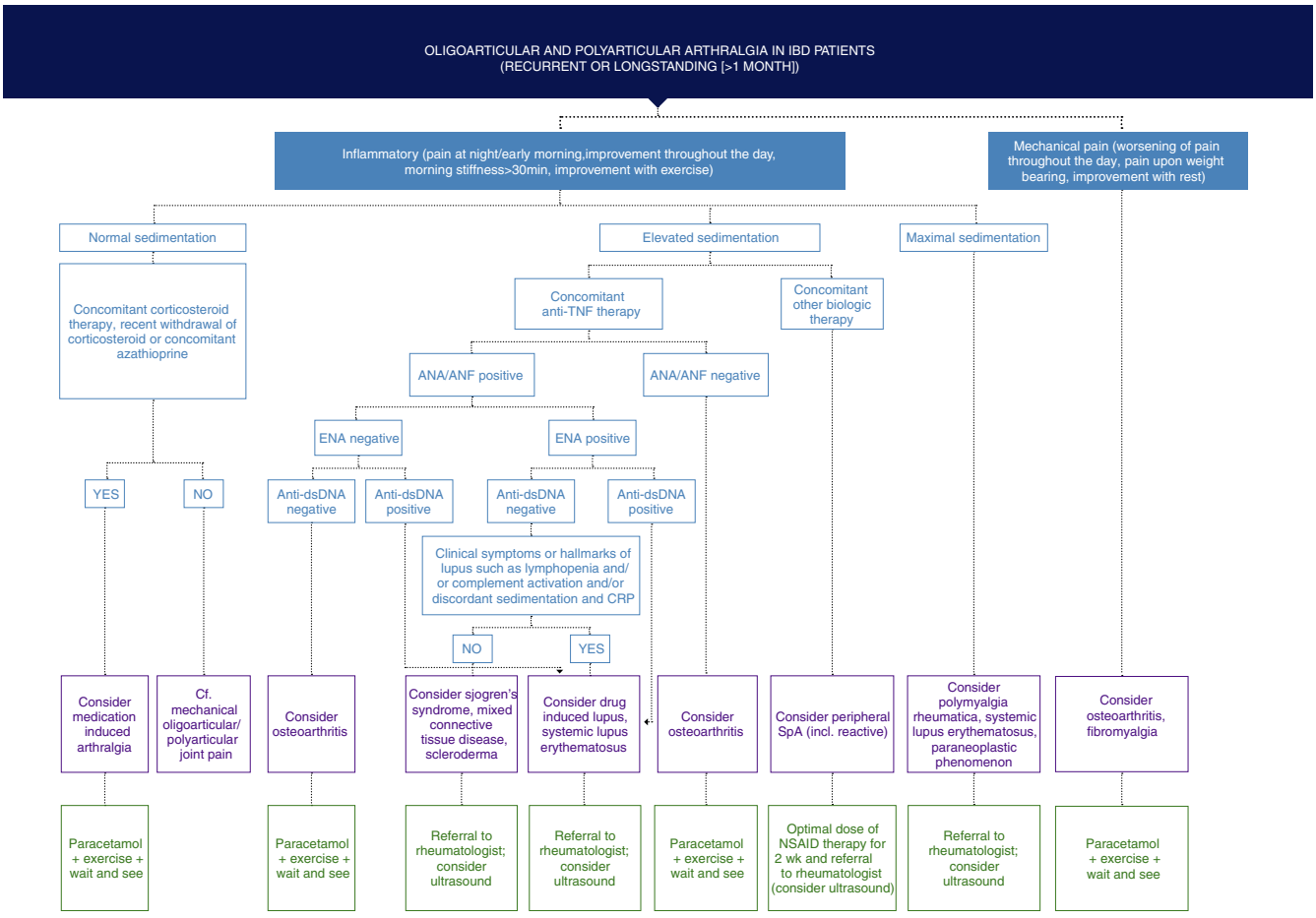

FIGURE 4 Referral pattern for IBD patients with oligoarticular and polyarticular arthralgia. Abbreviations: ANA, antinuclear antibody; ANF, antinuclear factor; anti-dsDNA, anti-double-stranded DNA; Cf., confer; CRP, C-reactive protein; DD, differential diagnosis; ENA, extractable nuclear antigens; IBD, inflammatory bowel disease; NSAIDs, nonsteroidal anti-inflammatory drugs; SpA, spondyloarthritis; TNF, tumour necrosis factor; WBC, white blood cell

68% tolerated a switch to mercaptopurine.[50] Likewise, the introduction of infliximab entails a risk of transitory arthralgia,[51] and the withdrawal of corticosteroids may involve a temporary increase of musculoskeletal symptoms.[52] In patients with elevated sedimentation, possible culprits may be sulphasalazine or anti-TNF therapies.[53,54] Although immunogenicity has been described with all anti-TNFs, infliximab seems to be the most immunogenic.[55,56] Importantly, anti-TNF therapy primarily induces immunoglobulin (Ig) M, rather than IgG antibodies. Therefore, isolated antinuclear factor (ANF) elevation is of limited significance in absence of clinical symptoms. Moreover, while ANF induction is common, drug-induced SLE is rare.[55] Drug-induced SLE should be considered in patients with arthralgia who were treated with anti-TNF and present with anti-double-stranded deoxyribonucleic acid (anti-dsDNA) IgGs, hypocomplementaemia, lymphopenia, discrepant sedimentation and CRP or clinical signs of SLE. However, even in patients receiving anti-TNF therapies, idiopathic SLE might have been present before drug initiation. Although clinical symptoms may disappear rapidly after discontinuation of the culprit drug, laboratory abnormalities may remain for some time. In patients with elevated sedimentation receiving other biologics, the response to NSAIDs or low-dose corticosteroids should be evaluated prior to referral to a rheumatologist. The rheumatologist may consider ultrasound to assess the presence of inflammatory activity. In patients exhibiting very high sedimentation, an infectious locus should be considered. However, in the presence of concomitant proximal muscle weakness, prompt referral to a rheumatologist is recommended because these symptoms may be indicative of polymyalgia rheumatica or other systemic auto-immune disease.

4 | CONCLUSION

In this paper, we presented straightforward referral algorithms for IBD patients with spondyloarthritis symptoms, developed by a panel of Belgian gastroenterologists and rheumatologists. The main focus was on IBD patients with chronic back pain, large joint monoarthritis and arthralgia. The proposed strategies allow a clear evaluation for referral based on basic clinical criteria in combination with laboratory tests to identify which patients should be referred to emergency room, physical medicine or rheumatologist. The proposed strategies are specific enough to evaluate IBD patients with joint symptoms without overloading rheumatologists with unnecessary referrals.

A limitation of this study is the use of different terminologies in gastroenterology and rheumatology regarding axial spondyloarthritis, leading to a potential underestimation of the axial spondyloarthritis prevalence. Moreover, we developed referral strategies based on expert opinion because the absence of scientific literature regarding the referral of IBD patients with peripheral arthritis is striking. Overall, the proposed algorithms may help gastroenterologists to make a broad clinical differential diagnosis and to adequately select patients for referral.

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AUTHORSHIP

Guarantor of the article: Gaëlle Varkas, Dirk Elewaut and Martine De Vos.

Author contributions: GV, CR, EL, FVDB, RL, SV, DE, MDV were involved in the study concept and design (Delphi exercise). GV, FVDB, DE, MDV acquired the data. GV, CR, EL, FVDB, RL, SV, DE, MDV analysed and interpreted the data. GV, DE, MDV collaborated with Claire Verbelen and prepared the manuscript. GV, CR, EL, FVDB, RL, SV, DE, MDV revised the manuscript. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section at the end of the article.

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