# Arthritis complicating inflammatory bowel disease – the future is now.

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## Summary

Fundamental advances are occurring across immune-mediated inflammatory diseases (IMIDs). Recent therapeutic developments include strategies to prevent rheumatoid arthritis (RA) in high-risk individuals, using baseline cellular immunophenotypes to predict biologic response in psoriatic arthritis (PsA), and employing biologicals in a ‘top-down’ approach in Crohn’s disease (CD). However, meaningful progress has not occurred in the management of patients with spondyloarthropathy (SpA) complicating inflammatory bowel disease (IBD). Currently, the pathophysiology of IBD-related SpA is poorly understood, moreover, there remain no accepted or disease-specific screening tools, diagnostic criteria, or licenced treatment(s). Furthermore, current approaches to clinical care from rheumatologists and gastroenterologists largely involve the extrapolation of SpA and IBD clinical guidelines respectively, despite increasing recognition of IBD-related SpA being its own entity, with a unique phenotype. There is an obvious contrast with the management of arthropathy complicating psoriasis, a disease area where defined diagnostic criteria and dedicated clinical trials allow clear management guidelines. We argue that the time has come for a parallel approach and dedicated focus of IBD-related SpA.

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## Introduction

Spondyloarthropathy (SpA) is the most common extraintestinal manifestation seen in IBD patients. The molecular, cellular and genetic pathogenesis of both separate diseases are increasingly well-established, leading to cutting-edge biomarker-based research, such as the METHYLOMICS trial

across IMIDs, as well as the PROFILE and OPTIMISE trials in Crohn's disease and psoriatic arthritis (PsA) respectively[1,2]. However, progress in IBD-related SpA lags behind significantly.

Currently, there is limited understanding of the pathophysiological relationship between joint and gut inflammation[3], contributing to a lack of consensus on screening, diagnosis , or management strategies for IBD-related SpA. Here, we discuss the current challenges and future directions in relation to screening strategies, classification criteria, and the management of IBD-related SpA.

We argue for the implementation of a coordinated, collaborative approach between gastroenterology and rheumatology, harnessing clinical practices, knowledge and research advances from across both specialties. This strategy will facilitate the development of unifying clinical guidance for IBD-related SpA, underpinned by results from dedicated IBD-related SpA clinical trials.

**Should we introduce screening for arthropathy complicating IBD; and for intestinal inflammation complicating arthritis as standard of care?**

**Current evidence for screening tools in IBD-related SpA**

Despite half of newly diagnosed IBD patients reporting musculoskeletal symptoms[4],there is no consensus as to whether or how patients should be screened for arthritis; nor how patients with arthropathy should be screened for IBD. In a recent study, SpA was diagnosed in 54/183 (29.5%) of IBD patients with musculoskeletal symptoms following rheumatological assessment, with over half of patients receiving new/altered DMARD therapy as a result[5].

To date, screening tools for arthropathy in IBD have shown promise, but these have not been widely incorporated into the care of IBD patients. The fourteen item IBd Identification of Spondyloarthritis Questionnaire (IBIS-Q) claimed a sensitivity of 0.93[6]. Elsewhere, with the six item DETection of Arthritis in Inflammatory bowel disease (DETAIL) questionnaire, for patients meeting at least three items, the post-test probability of being diagnosed with SpA was up to 81.90%.[7]. Across both screening tools, inflammatory back pain symptoms were one of the strongest and most consistent predictors of SpA. Interestingly, items relating to dactylitis and enthesitis symptoms also showed good performance in identifying patients affected by SpA. Nevertheless, studies investigating screening questionnaires for IBD-related SpA have shown relatively poor specificity, particularly in relation to inflammatory back pain items, and have predominantly involved patients with established, often well-controlled, IBD[6,7].

Attempts to screen for IBD in SpA patients have predominantly centred on endoscopic and histological investigation(s). In one single-centre study across SpA patients with no gastro-intestinal symptoms, 6/41 (14.6%) and 17/41 (41.5%) exhibited IBD-like changes at colonoscopy and pathology, respectively[8]. In another study involving 64 patients with SpA, capsule endoscopy revealed significant small bowel inflammation (SBI) consistent with Crohn's disease in 27/64 (42.2%), with

chronic gastrointestinal symptoms poorly correlating to the presence of SBI[9]. Whilst these studies reached differing conclusions on the utility of faecal calprotectin as a predictor of bowel inflammation, a unifying conclusion is that screening for IBD symptoms alone is likely to be insufficient for SpA patients.

**Future directions for the development and implementation of a screening tool in IBD-related SpA**

Several steps are required before screening can be successfully deployed. Firstly, given their limited specificity, potential screening questionnaires should be assessed in combination with other tools; for instance, HLA-B27 status and imaging in IBD patients, and calprotectin and endoscopy in SpA patients. These combined approaches to screening can help provide further clarity when differentiating IBD-related SpA from other clinically similar rheumatological conditions; notably, ultrasound (US) entheseal examination can help distinguish SpA from fibromyalgia in IBD patients[4].

Secondly, collaboration between gastroenterologists and rheumatologists is a pre-requisite for the implementation of unifying, practical and cross-specialty screening tool(s). To that end, a recent Delphi consensus panel, featuring interdisciplinary experts, reached a consensus that in clinical practice settings, IBD-related arthritis, should be initially recognized by both gastroenterologists and rheumatologists[10]. Although the panel concluded that clinical diagnosis for axial disease should be performed by a rheumatologist, these results reinforce the importance of a inter-speciality approach to developing and implementing a screening tool. Inspiration may be drawn from the DUET study in which using a simple clinical algorithm, ophthalmologists helped to identify 40% of patients presenting with acute anterior uveitis as having undiagnosed SpA, as later confirmed by rheumatology[11].

Moreover, there is a pressing need to develop classification criteria for IBD-related SpA. Rheumatologists increasingly favour the Assessment of SpondyloArthritis International Society (ASAS) criteria for categorizing IBD-related SpA into axial or peripheral disease. The gastroenterology literature has been strongly influenced by Orchard's studies defining type 1 (self limiting, mainly axial pauciarticular arthopathy involving , typically large joints) or type 2 (polyarticular arthropathy involving ≥5, typically peripheral joints) disease [12].

Currently, these classification systems, alongside others, have not been validated prospectively in IBD cohorts; indeed, this current lack of evidence base manifests in inconsistent approaches to diagnosis across both the current literature and clinical care of IBD-related SpA. A systematic review of study designs has shown that across studies investigating axial and peripheral joint disease in IBD, only 26/38 (68%) and 16/35 (46%) of studies used an established SpA classification criteria. Across the studies, investigated a variety of criteria, which have yet to be validated in IBD cohorts, were used (e.g. Modified New York, ASAS, ESSG or Amor)[13]. Thus, efforts to establish effective screening tools

for IBD-related SpA will be contingent on the development of criteria that can accurately distinguish and diagnose IBD-related SpA subtypes.

## The importance of a co-ordinated basic science and clinical approach for developing classification criteria

Given that rheumatologists increasingly view SpA as a continuous spectrum of disease, characterized by axial SpA, peripheral SpA, enthesitis, and dactylitis, a dichotomous classification system is unlikely to fully capture the spectrum of IBD-related SpA phenotypes. Going forwards, a two-fold approach, that dovetails basic science with clinical characterization of disease phenotypes, will likely underpin the development classification and diagnostic criteria.

Although an in-depth exploration of the pathophysiology of IBD-related SpA is beyond the scope of this article, several hypotheses linking gut and joint inflammation, encompassing numerous genetic variants, cellular processes and molecular signals have been proposed previously[18]. Whilst HLA-B27 is synonymous with ankylosing spondylitis and is a key tenet of ASAS criteria, its significance in IBD-related SpA is ambiguous. Evidence from animal models suggests that HLA-B27 misfolding in the gut can induce the IL23/IL17 axis, which can have pro-inflammatory effects on both intestinal and synovial tissue[16]. Accordingly, investigating variants in the genes involved in the IL23/IL17, alongside others, represent promising avenues for elucidating the genetic pathogenesis of IBD-related SpA[3]. Further characterization of the genes implicated in IBD-related SpA disease processes can help guide future diagnostic and classification criteria.

Whilst current attempts to characterize rheumatological extra-intestinal manifestations in IBD tend to centre on ASAS criteria, there is mounting evidence that this classification does not sufficiently capture and differentiate SpA presentations in IBD[17]. Thus, phenotypic characterization of SpA subtypes in large, prospective, multi-centre IBD cohorts will be crucial for validating current criteria and/or shaping a new classification system. Regarding inflammatory arthritis symptoms, it will be important to consider the pattern of joint involvement; the association between symptom(s) and IBD onset and activity; and ensure common differentials (e.g. osteoarthritis and fibromyalgia), which can be mistaken for SpA, are excluded[13].

Future work to inform classification criteria should encompass other SpA symptoms, such as dactylitis, tenosynovitis, and enthesitis.US imaging for rheumatological extra-intestinal manifestations is becoming increasingly used, with growing data to suggest that enthesitis in particular is an overlooked feature of IBD-related SpA; on examination, enthesitis is reportedly a more common finding than arthritis in IBD patients[17,18]. Patients with IBD-related SpA, compared to IBD without SpA, display greater rates of entheseal-related erosions and structural abnormalities on US. Nevertheless, the prevalence of power doppler ultrasonography enthesitis in patients not meeting ASAS criteria (i.e. characterized as subclinical US changes) is significant, ranging from 13-67%[4,17,19]

– mirroring the rates of subclinical enthesitis seen in psoriasis patients with no joint symptoms[20]. Interestingly, whilst ASAS criteria for axial SpA includes enthesitis only at the heel, according to ultrasound assessment, the most common entheseal site in IBD is reportedly the patellar tendon[21]. These findings have important implications for a potential IBD-related SpA classification system, and provide further evidence that current ASAS criteria may be insufficient. Going forwards, US-based assessment of enthesitis will likely play a significant role in attempts to classify IBD-related SpA, with a potential emphasis on the presence of erosive changes[19]. Whilst subclinical enthesitis in psoriasis predicts the later development of psoriatic arthritis (PsA)[20], its significance in disease pathophysiology and predictive value in IBD patients is unknown and warrants investigation in long-term follow up studies.

Future efforts to establish a validated screening and classification criteria should eventually facilitate consistency across future IBD-related SpA research, prompt and accurate diagnosis, as well as allowing treatment to be tailored to specific phenotypic presentations

**Shortcomings, and future steps, in the management of IBD-related SpA after diagnosis**

**Current available management options for IBD-related SpA**

There is a current lack of evidence to allow consensus regarding how to manage IBD-related SpA; currently there are no licensed or NICE-approved advanced therapies for IBD-related SpA. Typically rheumatologists extrapolate from treatment guidelines in PsA or axial spondyloarthritis; and gastroenterologists from parallel guidelines in CD and ulcerative colitis.Whilst ECCO guidelines, informed by cohort study data, recommend anti-TNF therapy for axial/non-axial SpA in IBD, no randomized control trials have been performed in IBD-related SpA. I

Inevitable inconsistences between IBD and SpA management remain (Table 1), both in early and advanced disease, For example, NSAIDs are a mainstay for early management in axial and peripheral SpA, however, their use in IBD is controversial. Whilst conventional NSAIDs can cause disease relapse in quiescent IBD, there is some albeit limited evidence that COX-2 selective NSAIDs (particularly etoricoxib and celecoxib) may have a better GI safety profile and tolerability in controlled IBD[22]. Elsewhere, aside from infliximab and adalimumab, there are a paucity of biologic therapies that are effective across IBD and SpA symptoms (Table 1); notably, IL17A inhibitors which are effective for both peripheral and axial SpA, are generally avoided in IBD due to the risk of exacerbating disease activity.

Whilst the emergence of small molecule inhibitors opens new therapeutic avenues across both rheumatology and gastroenterology (Table 1), there to date is limited evidence supporting their use in IBD-related SpA. Tofacitinib has been approved for both psoriatic arthritis, ankylosing spondylitis

and ulcerative colitis; however, post-hoc analysis of the OCTAVE Induction 1 and 2 trials showed that eight weeks of Tofacitinib did not reduce the proportion of UC patients with active arthritis[23]. However, the duration of therapy may have been sub-optimal: the majority of studies evaluating Tofacitinib therapy for IBD extra-intestinal manifestations span ≥12 weeks[24].

The limited options that are available for managing both SpA, particularly axial SpA, and IBD, highlight the need for longer-term observational studies and ideally dedicated clinical trials, especially those comparing advanced therapies, across different SpA phenotypes.

**Table 1: Drugs in the treatment of IBD and SpA that are currently licenced (shown in green), worsen disease activity (red), and drugs with promising early data/are currently in the advanced stages of clinical trials (amber). Adapted from Zioga et al. (2022)[25]**

| Drug target(s) | Example drug | Crohn's Disease | Ulcerative Colitis | Axial SpA | Peripheral SpA |
|---|---|---|---|---|---|
| | (Long-term) Conventional NSAIDs | | | | |
| Conventional DMARDs | Sulfasalazine | | | | |
| | Methotrexate | | | | |
| | Leflunomide | | | | |
| | Azathioprine | | | | |
| TNF-α | Infliximab/adalimumab | | | | |
| | Etanercept | | | | |
| | Golimumab | | | | |
| α4β7 | Vedolizumab | | | | |
| IL-17A | Secukinumab/Ixekizumab/Bimekizumab | | | | |
| IL-12/23 | Ustekinumab | | | | |
| IL-23 | Risankizumab | | | | |
| | Guselkumab | | | | |
| | Mirikizumab | | | | |
| JAK1 | Upadacitinib | | | | |
| | Filgotinib | | | | |
| JAK1/3 | Tofacitinib | | | | |
| S1P | Ozanimod | | | | |

Future avenues for IBD-SpA management

The time is now ripe for rheumatology and gastroenterology to collaborate, bringing together knowledge, experience and cutting-edge advances from each specialty, to develop research and improve the clinical care of IBD-related SpA. Harnessing personalised and intensive medical approaches for IBD-related SpA has the potential to generate further opportunities to alter disease

course and restitute normal gut and joint health. Early intervention for inflammatory arthritis has become standard in diseases like rheumatoid arthritis and psoriatic arthritis. Early intervention research is an growing area of interest in IBD. The recent PROFILE study, of patients with newly-diagnosed active CD, confirmed early data that intensive early "top-down" treatment (i.e. infliximab and immunomodulator) led to significantly higher rates of disease remission than conventional step-up treatment (79% vs 15% respectively, $p<0.0001$)[1]. Of great interest is the hope that very early intervention in at-risk individuals may allow disease prevention[26].

In this context, rheumatology has led the way in the clinical use of serological markers, allowing early diagnosis and intervention. This has been exemplified by the recent APPIPRA study: abatacept therapy for patients at high-risk of rheumatoid arthritis (RA), identified by positive rheumatoid factor and ACPA, reduced of progression to [26]. Gastroenterology, whilst at present lacking robust serological markers for diagnosis in clinical practice, is exploring this area; the specialty is leading the use of therapeutic drug monitoring (TDM), with strong evidence that higher biologic drug concentrations correlate with disease remission[27]. Using proactive, rather than reactive, TDM, with the aim of maintaining a target drug trough concentration for people with IBD, is gaining popularity. This strategy may in turn allow personalised therapeutics and represents a growing priority in rheumatology and gastroenterology clinical trials; notably there is great interest in the association between carriage of the super-allele HLA DQA1*05 in IMIDs and increased immunogenicity to TNF-α inhibitors, and its potential clinical application [28]

Whilst the biomarker used in the PROFILE study was not successful in treatment stratification, there continues to be intensive interest in personalizing care for immune-mediated diseases – this area is highlighted as a priority in IBD by the James Lind Alliance. In rheumatology, the ongoing biomarker-stratified OPTIMISE study is investigating whether baseline CD4+ T cell immunophenotyping can predict response to TNF-α or IL-17A inhibitors, with the aim of eventually using a precision medicine approach to biologic selection in PsA[2]. Across inflammatory diseases affecting gastro-intestinal tract, joints and skin, the METHYLOMIC studies will use DNA methylation biomarkers in peripheral blood to stratify patients for specific biological therapies[30.]

The expansion of personalised medicine to guide treatment selection and dose will be underpinned by advances in our understanding of IBD-related SpA molecular pathogenesis: such work will in parallel inform multi-omic analysis and shed light on diagnostic and therapeutic biomarkers.

**Table 2: A summary of the current issues and future directions of research and clinical practice in IBD-related SpA**

| | **Current challenges and unanswered questions** | **Next steps for future research and clinical practice** |
|---|---|---|
| **Screening** | - Lack of uptake of screening tools in clinical | - Ensuring inter-specialty approaches are taken to |

| | | |
|---|---|---|
| **tools for arthropathy in IBD** | care<br>- Current screening tools exhibit relatively poor specificity<br>- Current research into screening strategies has been predominantly limited to patients with long-standing and/or well-controlled IBD. | developing screening tools that are implementable for both rheumatology and gastroenterology<br>- Combining proposed screening tools with other clinical investigations (e.g. HLA-B27 and US imaging in IBD patients) to improve performance of screening strategies and help exclude differential diagnoses (e.g. osteoarthritis and fibromyalgia) |
| **Classification criteria** | - There are inconsistencies in both current clinical practice and literature, regarding which classification system is used<br>- Current classification criteria used by rheumatologists for IBD-related SpA (e.g. ASAS) lack validation in IBD-related SpA<br>- The Orchard classification criteria that is commonly used by gastroenterology, has not been validated prospectively in multi-centre cohorts | - A co-odinated basic science and clinical approach is important for developing a disease-specific classification criteria<br>- Incorporating clinical examination and US assessment of enthesitis and tenosynovitis should be a priority of future work to help characterise the different IBD-related SpA phenotypes |
| **Management** | - There are inconsistencies between both early and advanced management options in IBD and SpA (e.g. regarding conventional NSAIDs and IL-17A inhibitors)<br>- The lack of understanding of IBD-related SpA pathophysiology precludes the identification of potential prognostic and therapeutic biomarkers | - Assessing the efficacy of advanced therapies in future long-term observational studies and clinical trials specific to IBD-related SpA<br>- Developing our knowledge of disease pathophysiology will inform future therapeutic strategies, especially precision medicine approaches.<br>- Harnessing insights from recent efforts to deliver precision medicine and early disease intervention across gastroenterology and rheumatology (e.g. PROFILE, OPTIMISE, and APPIPRA studies |

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223 **Concluding remarks**

224 Focusing on patients with the combined challenges of arthritis and IBD is a priority area, with a series
225 of unmet needs to address (Table 2). Pre-requisites for optimising IBD-related SpA patient care
226 include marrying basic science approaches with characterisation of clinical phenotypes to inform a
227 scientifically-based classification system; developing a practical cross-specialty screening tool(s);
228 and inter-specialty collaboration to generate comprehensive, unified disease-specific management

guidelines (Table 2). These advances could underpin future personalised medicine-based research into early diagnosis, management and/or disease prevention of IBD-related SpA.

## Search strategy and selection criteria

We searched the PubMed database from inception up to May 1, 2024, using the keywords: “Inflammatory bowel disease”, “IBD”, “Ulcerative Colitis”, “UC, “Crohn’s disease”, “CD”, “Spondyloarthopathy”, “Spondyloarthritis”, “IBD-related arthritis”, “IBD-related SpA”, “IBD-related Spondyloarthopathy” and “IBD-related Spondyloarthritis”. Only papers published in English were reviewed. Relevant papers were also suggested by co-authors, whilst the reference list of key papers were also screened. Further references recommended by reviewers were included during redrafting of the manuscript.

## Contributions

All authors contributed to the conception of the article, first draft writing, critical revision and editing. All authors approved the final version and had final responsibility for the decision to submit for publication.

## Declaration of interests

JS reports grants or contracts from Crohn’s Colitis UK, Action Medical Research, ECCO, European Commission and Helmsley Trust; consulting fees from Janssen; support for attending meetings and/or travel from Janssen; pending patent applications for diagnostic biomarkers in paediatric IBD and development of non-immunogenic anti-TNF therapy; participation on a data safety monitoring or advisory board across the DSM TRIBUTE and MODULATE trials; leadership or fiduciary roles at UK IBD Registry, CCFA Precision Medicine Committee and CCUK; and is an advisor to NICE on precision medicine. LCC reports grants or contracts from AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Novartis, Pfizer and UCB; consulting fees from AbbVie, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Gilead, Galapagos, Janssen, Moonlake, Novartis, Pfizer and UCB; payment or honoraria from AbbVie, Amgen, Biogen, Celgene, Eli Lilly, Galapagos, Gilead, GSK, Janssen, Medac, Novartis, Pfizer and UCB; and is a board member for BritPACT charity (British PsA consortium). KS declares no competing interests.

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