



ECCO Scientific Workshop Paper

The Pathogenesis of Extraintestinal Manifestations: Implications for IBD Research, Diagnosis, and Therapy

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Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; TNF, tumour necrosis factor; PSC, primary sclerosing cholangitis.

Abstract

This article reports on the sixth scientific workshop of the European Crohn's and Colitis Organisation [ECCO] on the pathogenesis of extraintestinal manifestations [EIMs] in inflammatory bowel disease [IBD]. This paper has been drafted by 15 ECCO members and 6 external experts [in rheumatology, dermatology, ophthalmology, and immunology] from 10 European countries and the USA. Within the workshop, contributors formed subgroups to address specific areas. Following a comprehensive literature search, the supporting text was finalized under the leadership of the heads of the working groups before being integrated by the group consensus leaders.

Key Words: ECCO; inflammatory bowel disease; extra-intestinal manifestation; Crohn's disease; ulcerative colitis; spondyloarthritis; uveitis; erythema nodosum; pyoderma gangrenosum

1. Introduction

Up to 50% of IBD patients experience at least one extraintestinal manifestation [EIM].¹ The pathogenic mechanisms of EIM are not clearly defined. Unravelling these pathways has the potential to enhance our understanding of the pathogenesis not only of EIMs, but also of IBD overall. Defining pathogenic pathways in EIMs is challenging due to the lack of consistent criteria for diagnosis and the difficulty in distinguishing drug-induced extraintestinal pathologies from EIMs. Optimizing treatment may also be problematic. For many EIMs, commonly accepted definitions and high-quality evidence supporting different treatment strategies are lacking.² Therefore, there is a great need for both basic science studies and clinical trials to understand the pathogenesis and determine the optimal treatment for EIMs. The first ECCO European Evidence-based consensus on EIMs in IBD provided an authoritative guideline for the clinical management of EIMs.² The current article seeks to complement and extend the clinical guideline by identifying frontiers and opening questions for clinical research.

2. Definition

In order to standardize systematic inclusion of patients in scientific and clinical studies and align outcome measures to ensure clarity across the scientific literature, widely agreed-upon definitions of the pathology being studied are critical. In order to provide a frame of reference for scientific discourse, the expert panel suggests the following *mechanistic* definition of what constitutes an EIM:

“An inflammatory pathology in a patient with IBD that is located outside the gut and for which the pathogenesis is either dependent on extension/translocation of immune responses from the intestine, or is an independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD.”

A wide range of extraintestinal pathologies are associated with IBD; however, not all of these would be considered to be true EIMs according to the definition above. The panel proposes that current data supports the pathologies listed in the first column of [Table 1](#) as being true EIMs, with other pathologies classified as associated autoimmune conditions or complications of IBD and its treatment. The distinction between these categories can be imprecise, and overlap likely exists; it is probable that, with future new data, some pathologies will be reclassified. For the purpose of this review, the panel focused on true EIMs as described by the definition above.

3. Basic mechanisms of EIM

3.1. Immunological mechanisms

The potentially diverse immune mechanisms that underlie EIMs are poorly defined. We discuss two distinct theories that mechanistically link inflammation in the intestine and at other sites. First, EIMs arise from an extension of antigen-specific immune responses from the intestine to non-intestinal sites. Second, EIMs are independent inflammatory events initiated or perpetuated by the presence of IBD or by shared genetic or environmental risk factors in the host. These mechanisms are not mutually exclusive and may contribute to varying degrees in different EIMs [[Figure 1](#)].

3.2. Extension of immune responses from the intestine

3.2.1. Ectopic expression of gut-specific chemokines and adhesion molecules

Abnormal patterns of lymphocyte homing in IBD may contribute to EIMs.³ Expression of the vascular addressin MAdCAM-1 is normally restricted to intestinal tissue and, in the context of specific chemokine signals, enables gut tropic T cells that express $\alpha 4\beta 7$ integrin to traffic selectively to the intestinal mucosa. Additional tropism for the small intestine comes from the chemokine CCL25, attracting lymphocytes expressing its receptor CCR9. Ectopic expression of both chemokines and adhesion molecules can occur in IBD,⁴ and may facilitate trafficking of inflammatory T cells to extraintestinal sites. The best supporting evidence comes from IBD-associated primary sclerosing cholangitis [PSC]. Ectopic expression of both MAdCAM-1 and CCL25 has been demonstrated in the vascular endothelium of the portal tract.^{5,6} One-fifth of the infiltrating T cells co-express CCR9 and $\alpha 4\beta 7$, whereas the frequency of these cells is low in other forms of liver inflammation, indicating an important role for these molecules in recruitment of inflammatory lymphocytes in PSC.⁶ While it is attractive to propose ectopic expression of gut-associated addressins at extraintestinal sites as a logical mechanism for EIMs, evidence that this occurs in organs other than the liver is lacking. However, co-expression of $\alpha 4\beta 7$ with cutaneous leukocyte antigen [CLA], [implicated in homing to the skin], by some blood T cells from IBD patients,⁷ may indicate that gut-generated effector cells can acquire both gut and skin tropism.

3.2.2. T cell trafficking driven by non-specific adhesion molecules

Upregulation of inflammation-associated adhesion molecules and chemokines that lack tissue restriction may also enable capture of effector cells, facilitating their recruitment into non-intestinal sites.

Table 1. Suggested categorisation of extraintestinal conditions that occur in IBD patients, [list of extraintestinal conditions associated with IBD adapted from Harbord *et al.*²].

System	A. Extraintestinal manifestations [multifocal inflammation]	B. Complications of IBD and its treatment	C. Associated conditions with uncertain mechanism
Joints and bones	Spondyloarthritis	Metabolic bone disease/ osteoporosis—[drug or nutritionally induced]	Non-inflammatory arthralgia
Eye	Uveitis Episcleritis Scleritis	Drug-induced cataracts and other drug-induced and nutritional eye disease [see supplementary Figure 4]	
Oral, aural and nasal	Oral CD Orofacial granulomatosis Metastatic CD		Sensorineural hearing loss
Skin	Erythema nodosum Pyoderma gangrenosum Sweet syndrome Metastatic CD	Drug-induced skin disease [e.g. anti-TNF-induced psoriasis, DILE] Drug-induced skin cancer Drug hypersensitivity	Vitiligo Psoriasis Eczema Epidermolysis bullosa acquisita Cutaneous polyarteritis nodosa Hidradenitis suppurativa
Urogenital	Metastatic CD	Nephrolithiasis Amyloidosis Drug-induced tubulo-interstitial nephritis	
Hepato-pancreato-biliary	PSC	Portal vein thrombosis Hepatic amyloidosis DILI Drug-induced pancreatitis	Autoimmune hepatitis Granulomatous hepatitis Autoimmune pancreatitis
Neurological		Peripheral neuropathy [drug or nutritionally induced] Venous sinus thrombosis Stroke	Central demyelination
Cardiovascular		Ischaemic heart disease Cerebrovascular accident Mesenteric ischaemia	
Pulmonary		Drug-induced lung fibrosis	Inflammatory bronchial and parenchymal lung disease, including asthma, bronchiectasis, and interstitial pneumonias
Coagulopathy		Venous thromboembolism	
Endocrine		Drug-induced Cushing's and Addison syndromes Drug-induced diabetes	Type 1 diabetes Autoimmune thyroid disease
Infection		Infections including systemic and local secondary to immunosuppression; septic complications of IBD or surgery	

IBD: inflammatory bowel disease, CD: Crohn's disease, DILE: drug-induced lupus erythematosus, PSC: primary sclerosing cholangitis, DILI: drug-induced liver injury.

A. For several conditions, there is evidence for a mechanistic link between two pathologies, as described by the definition put forward in this paper of a 'true' extraintestinal manifestation [EIM] of IBD. We would propose that these conditions may also be considered multifocal inflammation.

B. Other conditions that occur in IBD patients are complications of the disease or its surgical or pharmacological management.

C. Several conditions occur more commonly in IBD patients, but there is lack of evidence for categorizing these as either complications or directly linking them mechanistically to IBD. It is likely that, as pathogenic mechanisms are better understood, it may be possible to re-classify some of these conditions as 'true' EIMs/ multifocal inflammation.

Gut leukocytes from IBD patients are able to bind to the synovial membrane, using a repertoire of adhesion molecules,⁸ but mainly using endothelial vascular adhesion protein 1 [VAP-1].⁹ VAP-1 also plays a role in transmigration of lymphocytes across the hepatic endothelium, and its expression is upregulated by inflammation.^{10,11} T cells from the intestinal mucosa of IBD patients express chemokine receptors, such as CXCR3 and CCR5,^{12,13} which may contribute to their ability to enter other tissues. Low-grade inflammation, injury, or mechanical stress at extraintestinal sites (as implicated in the pathogenesis of spondyloarthritis [SpA]¹⁴ and pyoderma gangrenosum, where this phenomenon is termed pathergy) may nucleate the

recruitment of gut-generated effector cells and further enhance the inflammatory process.

3.2.3. Microbial antigen translocation and/or cross-reactivity

Models of EIMs that invoke trafficking of gut effector T cells raise the question as to whether this process is dependent on antigen-specific reactivation at non-intestinal sites and, if so, what the antigen may be. Antigens derived from the gut microbiota are believed to be key targets for intestinal effector T cells in IBD, and transport of these antigens to the liver via the portal circulation may activate such cells localized here via $\alpha 4\beta 7$ -MAdCAM-1 interactions and other

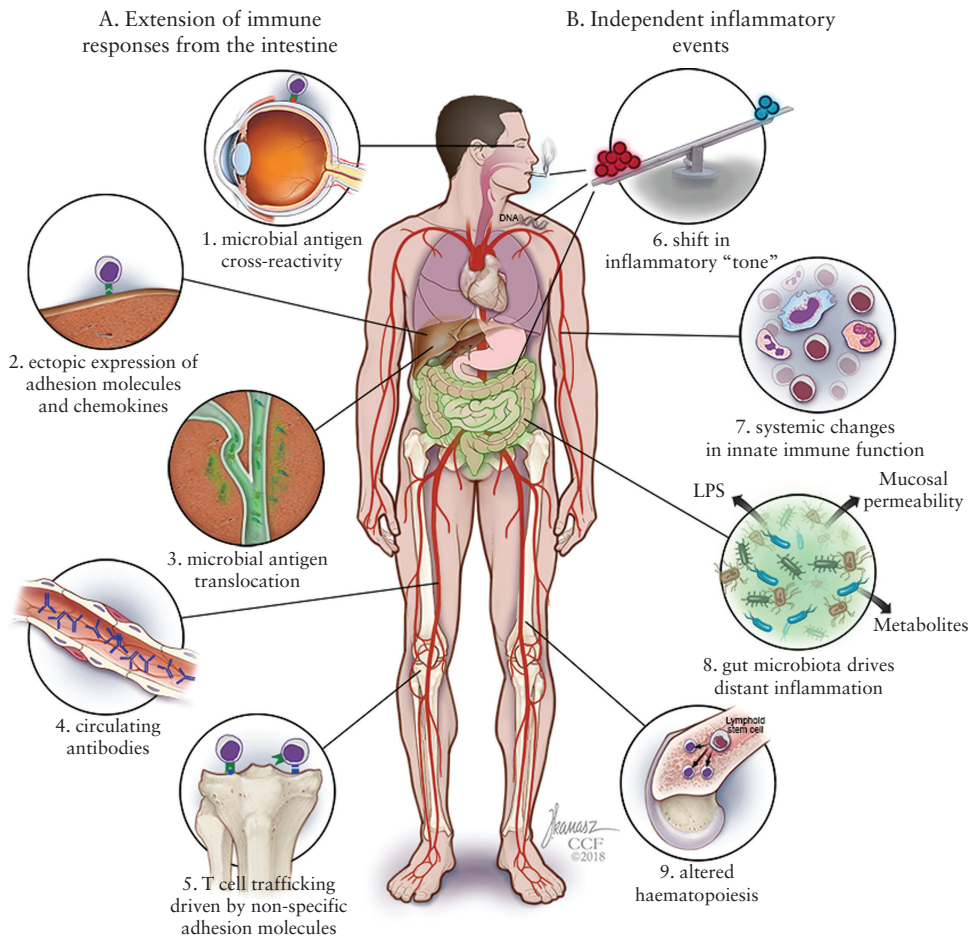


Figure 1. Potential mechanisms of EIMs. A. Extension of immune responses from the intestine: 1. Microbial antigen cross-reactivity *e.g.* molecular mimicry between enteric bacteria and self-antigen presented by host MHC molecules. 2. Ectopic expression of adhesion molecules and chemokines *e.g.* ectopic expression of MAdCAM-1 and CCL25 in the vascular endothelium of the portal tract. 3. Microbial antigen translocation *e.g.* via portal tracts. 4. Circulating antibodies that may bind epitopes shared between human colon and extraintestinal tissues. 5. T cell trafficking driven by non-specific adhesion molecules *e.g.* $\alpha 4\beta 7$ -independent binding of leukocytes to the synovial membrane using a repertoire of adhesion molecules. Non-specific interactions may be initiated after low-grade inflammation, injury, or mechanical stress. B. EIMs as independent inflammatory events: 6. Shift in inflammatory tone driven by genetic, environmental, or microbial factors or by a systemic increase in key inflammatory mediators. 7. Systemic changes in innate immune function *e.g.* neutrophil priming. 8. Gut microbiota drives distant inflammation via microbial products such as LPS, through changes in gut permeability and microbiota-derived metabolites. 9. Altered haematopoiesis driven by microbial products, intestinal inflammation, systemic inflammatory cytokines, increased gut permeability, changes in the composition or metabolic products of the microbiota.

pathways. The presence of distinct gut microbiota in IBD patients with PSC^{15–17} may suggest specific bacterial antigens. At other sites, cells may be reactivated by cross-reactive components of the resident microbiota or host antigens. Molecular mimicry, in the form of peptide sequences common between enteric bacteria and host MHC molecules has been reported,^{18,19} although the pathologic significance of this is unclear. In mice, retina-specific T cells that cause uveitis require activation in the gut by a microbiota-dependent signal, most likely a cross-reactive bacterial antigen,²⁰ providing evidence for a direct link between gut microbiota, recognition of self-antigens, and inflammation at a non-intestinal site. Indeed, leukocyte trafficking between the gut and the eye has been demonstrated in experimental models of autoimmune uveitis.²¹ However, the antigen specificity of T cells responsible for EIMs in humans has never been defined.

3.2.4. Circulating antibodies

Circulating antibodies could extend intestinal immune responses to additional sites, and immune complex-mediated inflammation has

been proposed to contribute to certain EIMs.²² Autoantibodies reactive to colonic proteins have been identified in patients with IBD,^{23,24} and [using monoclonal antibodies] epitopes shared between human colon and tissues such as eyes, joints, skin, and biliary epithelium have been identified.^{25–27} However, clear evidence of a causative role for antibodies or immune complexes in the pathogenesis of EIMs in IBD patients is lacking.

3.3. EIMs as independent inflammatory events

3.3.1. A shift in inflammatory tone favours the development of EIMs

An alternative explanation for EIMs would see them as independent inflammatory events sharing common genetic²⁸ or environmental²⁹ risk factors with IBD. The presence of intestinal inflammation and/or microbial dysbiosis in individuals with IBD might further increase the risk of developing extraintestinal inflammation through modulation of inflammatory ‘tone’, impacting on immune functions at other sites. Key inflammatory mediators, including IL-6, TNF α , IFN γ , and

VEGF,³⁰ are raised in the serum of IBD patients, as is bacterial LPS,³¹ which may promote cytokine production via activation of immune cells at non-intestinal sites. Systemic effects, including increases in epithelial permeability³² and upregulation of neutrophil extravasation ligands on vascular endothelium, may lower the threshold for immune activation at extraintestinal sites. IBD-associated cytokines, such as IL-23, which is produced at high levels in CD and UC, can activate immune cells resident within the synovial membrane and drive spondyloarthritis.³³

3.3.2. Systemic changes in innate immune function

Exposure of neutrophils to inflammatory cytokines or other signals can enhance their response upon subsequent activation, a phenomenon termed 'neutrophil priming'.³⁴ Circulating neutrophils show morphological evidence of activation in IBD³⁵ and are primed to produce increased levels of TNF α and IL-1 β .³⁶ In contrast, recruitment of neutrophils to the skin and clearance of subcutaneous bacteria is reduced in patients with CD.³⁷ Likewise, changes in circulating monocytes³⁸ and macrophages derived from blood monocytes³⁷ have been reported in IBD, with reduced inflammatory cytokine production in response to bacterial stimulation.

3.3.3. Altered haematopoiesis

Changes in circulating immune cells observed in IBD are likely to reflect altered haematopoiesis in the bone marrow. In mouse models, haematopoiesis is influenced by both microbial products^{39–43} and the presence of intestinal inflammation.^{44,45} In IBD, systemic inflammatory cytokines, increased permeability of the intestine to microbial products, or changes in the composition and metabolic products of the microbiota, could all influence the generation of innate immune cells.^{46,47}

3.3.4. Dysbiosis and gut microbiota

The long-established link between gut infections with enteric pathogens such as *Salmonella*, *Campylobacter*, *Yersinia*, and *Shigella* and reactive arthritis is a clear indication that potential pathogenic pathways between microbiota in the gut and extraintestinal inflammation exist. Specific EIMs are associated with gut dysbiosis: Patients with SpA have decreased faecal gut microbial diversity and increased abundance of *Ruminococcus gnavus* and the genus *Dialister*, which are positively correlated with disease activity.^{48,49} Patients with psoriatic arthritis also exhibit decreased faecal microbial diversity.⁵⁰ In addition, faecal *Saccharomyces cerevisiae* abundance is decreased in patients with psoriasis compared with healthy controls.⁵¹

Primary sclerosing cholangitis has also been associated with decreased faecal microbial diversity.^{15,52} One study has suggested that IBD patients have similar dysbiosis to IBD-PSC patients.¹⁷ However, a conflicting report⁵³ makes it difficult to judge whether the risk for developing PSC is driven by specific microbial factors.¹⁷ There is a paucity of studies determining gut dysbiosis in individuals with inflammatory eye disease, although one study demonstrated differences in gut microbiota between healthy individuals and those with age-related macular degeneration,⁵⁴ and preliminary data suggested the existence of an intraocular microbiota.⁵⁵

There is a range of potential mechanisms by which gut microbiota drive the pathogenesis of EIMs [Box 1]. The first four of these hypothesized mechanisms have been included in the discussion in the preceding section. However, gut microbiota may promote inflammation at extraintestinal sites through

1. Molecular mimicry: similarity between gut microbiota and non-microbial epitopes present at the extraintestinal site.
2. Microbial communities in the extraintestinal site: similarities with pro-inflammatory gut microbiota could drive extraintestinal inflammation.
3. Microbial translocation: Microbiota or their components are translocated from the gut to the extraintestinal site, [e.g. to the liver via the portal circulation].
4. Soluble microbial-derived factors, e.g. LPS, may be released into the circulation and promote inflammation at extraintestinal sites.
5. Disruption of gut barrier: Specific microbiota, such as mucin degraders, may disrupt the gut mucosal barrier, facilitating leakage of cellular or non-cellular factors into the circulation.
6. Microbiota-derived metabolites, e.g. from the metabolism of bile acids or the generation of short-chain fatty acids, both of which could alter immune signalling.
7. Acquisition of deleterious microbiota in early life could result in altered immune development, which in turn could generate a persistent pro-inflammatory immune 'tone'.

metabolic activities. *Ruminococcus*, which is altered in patients with arthritis, could initiate breach of the intestinal barrier through mucin degradation.⁵⁶ In rats, gut microbiota-dependent alterations in bile acid deconjugation are associated with altered bile acid profiles in extraintestinal sites, including kidney, heart, plasma, and liver, demonstrating that gut microbial metabolic functions have the potential to influence immune signalling at distant sites.⁵⁷ Short-chain fatty acids [SCFAs], produced by many gut bacteria, may have metabolic or immunomodulatory effects. In experimental autoimmune uveitis, oral administration of SCFAs attenuated uveitis severity and was associated with suppression of effector T cell induction.²¹ Furthermore, SCFAs have a potential role in modulating T cell trafficking to extraintestinal sites. Finally it has been hypothesized that IBD-linked dysbiosis may exert its pathogenic effect during immune development.⁵⁸ This is supported by animal models, with bacterial colonization of mice at age 3 weeks resulting in a persistent inflammatory tone, whereas colonization when aged 1 week did not.⁵⁹ Thus, disruption of the acquisition of gut microbiota early in life may generate persistent aberrant immune responses, manifested in the gut or extraintestinally or both. Indeed, factors that may influence the process of gut microbiota acquisition in early life, such as breastfeeding, have been shown to be protective against the occurrence of ankylosing spondylitis [AS].⁶⁰

Open questions:

1. Are the gut microbiota pathogenic in EIMs [via any of the mechanisms mentioned in the text] or are EIMs independent of gut microbiota?
2. If microbiota play a role, what is the mechanism?
3. If EIMs are driven by microbiota, are these the same as or different from those involved in IBD pathogenesis?
4. Are microbial communities in other parts of the body involved in IBD pathogenesis?

3.4. Genetic basis of extraintestinal manifestations

There is an extensive overlap in genetic risk loci for both IBD and EIMs, particularly AS.⁶¹ Association studies revealed a concordance in EIMs present in 70% of parent–child pairs and in 84% of sibling pairs, highlighting the role of genotype⁶² [or early life environmental factors]. In addition, the appearance of one EIM increases the probability of developing other EIMs.^{1,63} Further supporting the genetic underpinning of EIMs, the CD risk gene *NOD2*, encoding a pattern recognition receptor, has also been associated with sacroiliitis⁶⁴ and uveitis.⁶⁵ Several *HLA* genes and *HLA*-independent loci have been associated with the presence of EIMs, and a detailed description can be found in the Supplementary Data. The genetic contribution to the pathogenesis of EIMs and IBD comprises a combination of overlapping and independent loci, a situation that is consonant with the occurrence of EIMs in individuals both with and without evidence of gut inflammation. However, whether the involved loci all contribute to pathology in an EIM-specific fashion, or whether there are genes that liberate inflammatory responses from restriction to specific body compartments and thus give rise to EIMs in general, is not known.

Open questions:

1. Are the genes that predispose to specific EIMs in IBD patients the same as the genes that predispose towards the EIM pathology in non-IBD patients?
2. Are there genes common to all EIM patients and distinct from non-EIM IBD [immune mobility / promiscuity factors]?
3. Do IBD patients with no EIMs have protective factors, i.e. do they have the same genetic risk as EIM patients, but have additional [genetic or environmental] protective factors?

3.5. Animal models of EIMs

Animal models where inflammation is manifested at more than one anatomical site or bodily system [multifocal inflammation] provide experimental platforms for dissecting pathogenic pathways of EIMs and serve as tools for testing potential therapies. However, only a few models manifest multifocal inflammation, with colitis–arthritis models being the dominant phenotype available.

TNF^{ARE} mice carry a genetic deletion of TNF AU-rich elements [ARE], leading to overexpression of TNF.⁶⁶ The resulting phenotype is CD-like transmural and granulomatous chronic ileitis along with SpA-like sacroiliitis, Achilles tendon enthesitis, and peripheral arthritis. Paradoxically [given the importance of innate immune responses in human IBD], in this model ileitis appeared to be dependent on the presence of mature T and/or B cells, as mice with *TNF^{ARE}* in combination with a *RAG^{-/-}* background developed only arthritis.⁶⁶ Furthermore, mice with intestinal epithelial cell-specific TNF ARE deletion develop ileitis but not EIMs,⁶⁷ indicating that intestinal inflammation *per se* is not sufficient for induction of arthritis, which is therefore presumably dependent on local TNF production in the joint. Ileitis is abrogated in germ-free *TNF^{ARE68}* and *TNF^{ARE/β7^{-/-}}* mice,⁶⁹ but the effects of such manipulations on joint inflammation have not been reported yet. Taken together, in *TNF^{ARE}* mice, gut and joint inflammation likely represent independent phenomena mediated by a common pro-inflammatory factor.

HLA-B27 transgenic rats develop SpA and colitis, but also gastritis, psoriasis, and epididymitis.⁷⁰ In the intestinal mucosa, there is increased production of pro-inflammatory cytokines [IFN- γ , IL-2, IL-1 α , IL-1 β , TNF α , and MIP2], and in addition plasma concentrations of TNF α and IL-6 are raised. IL-23 and IL-17A may play

important roles, in association with HLA-B27 misfolding in the ER and activation of the unfolded protein response, leading to downstream inflammation.^{71,72} Interestingly, in this model, both colitis and arthritis [but not dermatitis or epididymitis] are dependent upon the presence of microbiota.⁷³ The HLA-B27 model is consistent with a common genetic origin of multi-organ inflammation, but also emphasizes the fact that some but not all EIMs are dependent on microbiota. However, when interpreting data from germ-free models, it is important to consider that conventionally reared mice are not only colonized with microbiota in the gut, but also in other organs such as skin, joints, and eye, which may also play a role in pathogenesis. More detailed experiments may be required to determine the contribution of extraintestinal microbiota communities in animal models of inflammation.

SKG mice that receive intraperitoneal injections of 1,3- β -glucan develop ileitis in association with enthesitis, arthritis, dactylitis, fasciitis, vertebral inflammation, and uveitis.⁷⁴ Treatment with anti-IL-23 mAbs or genetic deletion of the downstream cytokine IL-17A abrogate both ileitis and arthritis.⁷⁵ Time-course expression studies identified intestinal mucosa as the source of elevated IL-23 production.⁷⁵ Nevertheless, immunological pathways of joint and gut inflammation in this model are not identical, because IL-22 neutralization reduced the severity of enthesitis but exacerbated ileitis in 1,3- β -glucan-treated SKG mice.

Animal models: Open questions

1. Could further animal models with intestinal inflammation and extraintestinal involvement [including sites other than joints] be developed?
2. Which common pathways between mucosal and extraintestinal inflammation are implicated in animal models where both occur?
3. What is the role of microbiota [including faecal transplant] in the development of inflammation in animal models?
4. Can animal models be used to elucidate the temporal relationship between intestinal disease and development of EIMs?
5. How should animal models be used to investigate novel mechanisms and therapies such as neuroimmunomodulation?

3.6. Implications of the therapeutic effect of biologics and other treatments for EIMs

Emerging data for the efficacy of biologics for the treatment of EIMs may serve to expose underlying pathogenic mechanisms. Most evidence is available for anti-TNF α , with good response rates for cutaneous manifestations, arthritis, and ocular EIMs. This has implicated TNF α -dependent mechanisms in EIM pathophysiology.^{69–71,76} However, anti-TNF α drugs are increasingly recognized as causing drug-induced skin lesions, contributing to the burden of skin disease in IBD.^{77,78} The pathogenesis of these lesions remains unclear; blocking TNF α may result in an imbalance of cytokines [for example, increased IFN α release, which can cause psoriasis],^{79–81} and TNF α inhibition may lead to a reduced accumulation of Th1 and Th17 cells at the site of inflammation, but trigger a compensatory expansion at other locations.⁸² Female gender and family history of inflammatory skin disorders were identified as risk factors, which may also indicate a possible genetic predisposition for anti-TNF α -induced skin lesions.⁸³

The gut selective mechanism of the integrin $\alpha4\beta7$ antibody vedolizumab should restrict its activity to the gut, since its counterpart MADCAM1 is not expressed in the human skin.⁸⁴ The contribution of vedolizumab trials to understanding of EIM pathogenesis is complicated, since the evidence of its effect on EIMs appears to

be conflicting: One case series did not show any positive effect,⁸⁵ whereas a recent analysis from France suggested positive effects on EIMs in most cases, but also revealed new onset of arthritis and paradoxical skin lesions.⁸⁶ The pathogenic mechanisms behind these observations remain elusive.⁸⁵ It may be speculated that a compensatory expansion of T cells at locations other than the gut could explain this phenomenon [similar to anti-TNF α -induced lesions]. On the other hand, a beneficial effect of vedolizumab on the disease activity of EIMs could occur if lymphocytes require the $\alpha 4\beta 7$ -MAdCAM1 interaction to gain access to the gut, where they are activated, followed by non- $\alpha 4\beta 7$ -dependent entry to extraintestinal sites. There is also evidence in animal models that some regulatory T cells require $\alpha 4\beta 7$ -dependent entry into the gut to be educated before expressing their function elsewhere; vedolizumab could theoretically interfere with this.^{87,88} An alternative hypothesis is that $\alpha 4\beta 7$ is directly involved in homing to extraintestinal sites as outlined above. It remains likely that vedolizumab has the capacity to illuminate pathogenic pathways in EIMs.

Data on other biologic agents are limited. So far, no trial has been published evaluating the anti-IL12/23 antibody ustekinumab in the management of EIMs. Case series suggest it has efficacy in the treatment of anti-TNF α -induced skin lesions^{89,90}; however, development of pustular psoriasis has been described.⁹¹ Whether ustekinumab is effective in the treatment of non-drug-induced EIMs has yet to be determined. In contrast to anti-IL12/23 and despite the pathogenic role of Th17 cells in the development of colitis, trials with anti-IL-17A have failed in IBD with even higher adverse rates than placebo.⁹² Moreover, in contrast to its efficacy in other inflammatory disorders, anti-IL-17A can even exacerbate IBD activity,⁹³ which highlights a distinct involvement of the IL-17A pathway in these entities. No data on JAK inhibitors is available so far, but upregulation of STAT3 in erythema nodosum and pyoderma gangrenosum⁸⁴ makes a response to JAK inhibitors reasonable to predict and sheds light on the possible involvement of the JAK-STAT pathway in cutaneous EIMs.

Taken together, it is important that clinical trials and observational studies of biologic agents are designed to optimize the capture of data on effects on inflammation in multiple sites, not just in the disease defined in the primary outcome.

Open questions:

1. How does vedolizumab affect EIMs? Does it have the same effect on all EIMs?
2. What is the implication of the overexpression of STAT for the prospect of using JAK-inhibitors for treating PG and EN?
3. How will EIM respond to IL12/23 treatment?

4. Clinical Research

Despite the presence of a wide range of EIMs associated with IBD, standardized criteria for diagnosis, documentation or monitoring are lacking. Thus far, only one randomized controlled trial including IBD patients with EIMs has been conducted.⁹⁴ Here we discuss the currently available paradigms and tools for clinical research in three of them: Skin, joint, and eye EIMs.

4.1. Diagnosis and monitoring of EIMs

Because the diagnostic and monitoring tools for EIMs have been developed within the organ-based specialities, this section is presented according to an organ-based structure.

4.1.1. Clinical criteria, indexes, and scales

Joint manifestations

IBD-associated joint symptoms may be subdivided into inflammatory and non-inflammatory joint pain, [arthritis and arthralgia, respectively].^{95,96} Inflammatory arthropathies in IBD are the most common EIM and belong to the SpA group, with a prevalence of 20–50% for axial inflammation,^{97–99} and 5–20% for peripheral arthritis.^{100,101} The Assessment of SpondyloArthritis international Society [ASAS] developed classification criteria for both inflammatory axial and peripheral joint disease. These criteria are the current standard for clinical trials research and have good performance, as tested against the rheumatologist's diagnosis [Supplementary Figures 1 and 2].^{102–104} However, limited data evaluate ASAS criteria specifically in IBD patients. In IBD patients with inflammatory back pain, ASAS criteria have an equivalent sensitivity but lower specificity compared with non-IBD patients.¹⁰⁵ This lower specificity may be due to the inclusion of IBD as one of the ASAS criteria of axial SpA. Alternative classification tools such as the Amor classification¹⁰⁶ and the European Spondyloarthropathy Study Group [ESSG] criteria¹⁰⁷ also include IBD as a criterion, whereas the older Modified New York classification do not.¹⁰⁸ Nevertheless, in order to ensure applicability of research data to clinical practice, it is advantageous that the definition of patient groups in clinical trials and research is consistent with that used in rheumatology [i.e. ASAS criteria]. Therefore, validation of these currently used tools in IBD patients should be carried out.

Monitoring tools for determining response to treatment and disease outcomes have also been developed by ASAS. The current gold standard tool for axial SpA is the Ankylosing Spondylitis Disease Activity Score [ASDAS],¹⁰⁹ providing both a measurement of disease activity that may be followed over time, as well as cut-offs to allow grouping of patients into different disease activity states [Supplementary Figure 3]. ASDAS includes back pain as one of the criteria. Hence, it is not well-adapted for use in the 5–20% of IBD patients with peripheral arthritis. In response to the lack of validated outcome measures in peripheral SpA the authors of one randomized controlled trial of adalimumab in patients with non-psoriatic peripheral SpA developed a new outcome measure, the Peripheral SpA Response Criteria [PSpARC40] measured after 12 weeks of treatment.¹¹⁰ However, this outcome measure has not been widely applied, and there is a need to validate the use of these tools in patients with multifocal inflammation.

Eye manifestations

The most common eye EIMs are episcleritis and anterior uveitis. Scleritis and posterior or intermediate uveitis are rarer, but pose a greater potential risk to sight. Supplementary Figure 4 summarizes some of the more common types of inflammatory eye disease, as well as some of the ocular complications of IBD and its treatment. Episcleritis is usually treated topically with corticosteroids or non-steroidals. Uveitis may pose a greater diagnostic and therapeutic challenge. The SUN [Standardisation of Uveitis Nomenclature] classification is internationally acknowledged, and as such research and clinical trials in uveitis in IBD patients should follow this system [Supplementary Tables 2–7].^{111,112} SUN classification may be used both for diagnosis and classification of uveitis at presentation, as well as for monitoring disease progression. However, it is relevant to consider that the SUN classification may have limitations, especially for judging the significance of the outcome of clinical interventions. The FDA defines a significant clinical response as a two-step change in parameters of the SUN classification, but many successful therapies do not meet the required two-step improvement [especially in vitreous haze]. Furthermore, the SUN classification describes

anterior chamber cells as in unequal steps [0, +0.5, +1, +2, and +3], estimated subjectively by the consulting ophthalmologist, which is therefore not optimal for quantitative research.

Skin manifestations

Cutaneous manifestations are common in IBD patients¹¹³ and include ectopic cutaneous IBD in addition to the other categories of pathologies as set out in [Table 1](#). The diagnosis of cutaneous manifestations is principally based on clinical examination of the patient due to the inherently accessible nature of the skin. In atypical cases, a skin biopsy is helpful.¹¹⁴ In skin disorders, such as psoriasis and eczema, specific indexes to objectively measure skin disease extent and activity have been developed (e.g. the Psoriasis Area Severity Index [PASI]^{115–117} and the Eczema Area and Severity Index [EASI]).¹¹⁸ However similar standardized assessment techniques for cutaneous EIMs of IBD, such as EN and PG, are lacking. The only randomized controlled trial of therapy for an EIM in IBD patients [infliximab for PG] employed a primary end point of clinical improvement at Week 2, as determined by the clinician and patient's global assessment of reduction in ulcer size and depth and the degree of undermining of the ulcer edge.⁹⁴ Infliximab was shown to be superior to placebo, particularly in patients with disease duration of ≤ 3 months. Standardisation of assessment methods, such as that employed in this trial, will enhance reproducibility in clinical research as well as facilitating meta-analysis of EIM research.

In summary, current tools for the diagnosis of EIM have for the most part been developed in patients with unifocal inflammation. Studies to validate the use of these tools in patients with multifocal inflammation, including IBD patients, are needed. Even better would be a system of diagnosis and monitoring that reflects common pathogenic mechanisms that could then be applied to diseases generated by that common mechanism but manifesting in diverse clinical phenotypes.

Open questions:

1. Are tools for monitoring of unifocal inflammation valid for use in patients with multifocal inflammation?
2. If one of the criteria in an algorithm for diagnosing inflammatory pathology at an extraintestinal site is that the patient has IBD, will such an algorithm provide adequate diagnostic discrimination when applied to a population of IBD patients?
3. Is a single multidimensional scale for diagnosis and monitoring of inflammation at multiple sites possible? Is it desirable?

4.1.2. Biomarkers

There are no specific biomarkers for EIM activity in IBD, with acute-phase proteins ESR and CRP, leucocytosis, thrombocytosis, and anaemia being non-specific and, in addition, ESR and CRP having low sensitivity being elevated in only 40–50% of patients with axial SpA. Conversely, faecal calprotectin is only validated in the diagnosis and monitoring of gut inflammation and does not reflect disease activity at other sites.

Genetic markers for SpA

Genetic factors may be utilized as biomarkers in the diagnosis of inflammatory pathology.^{119,120} Combining clinical factors with genetic data has been shown to be superior in predicting the development of EIMs compared with either alone. HLA-B27-positive IBD patients are at increased risk of developing AS.² Apart

from HLA-B27, over 41 genes have been identified predisposing to AS.^{121,122} However, most of these have not been associated with increased risk for extra-articular inflammation. Currently there are neither reliable genetic biomarkers for peripheral SpA,^{119,123,124} nor for cutaneous or ocular EIMs.

Imaging biomarkers for spondyloarthritis

Traditional X-rays are of value in diagnosing axial SpA, but only demonstrate changes in advanced cases. Magnetic resonance imaging usually demonstrates the first radiological changes in axial SpA and is—despite moderate sensitivity and specificity¹²⁵—the imaging test of choice for detection of early disease,^{126–128} as well as the best objective technique for assessing inflammatory disease activity.^{129–134} This assessment has been standardized with the use of the Bath Ankylosing Spondylitis Radiology Index [BASRI].¹³⁵ In peripheral arthritis, which is generally non-erosive, joint radiography is usually normal, so ultrasonography is often employed to confirm the diagnosis. In addition, there is no evidence to confirm or refute the assumption that radiological findings in inflammatory arthropathy differ between patients with only arthritis and those who also have inflammation at distal sites.

Antimicrobial antibodies

IBD is associated with the presence of antibodies to a variety of microorganisms, such as anti-*Saccharomyces cerevisiae* antibodies [ASCA], antineutrophil cytoplasmic antibodies [ANCA], anti-I2 [associated with anti-*Pseudomonas* activity], anti-*Escherichia coli* outer membrane porin C [anti-OmpC], and anti-flagellin antibodies [anti-CBir1]. Subclinical intestinal inflammation has been reported to be present in a significant proportion of patients with radiographic axial SpA.^{136,137} The data on the presence of these antimicrobial antibodies in patients with both IBD and SpA are inconsistent and mostly relate to axial SpA. Anti-I2 antibodies have been associated with the combination of AS and intestinal inflammation,¹³⁷ as have antibodies against ASCA, anti-OmpC, and anti-CBir1.¹³⁸

Open questions:

1. Should patients presenting with inflammatory pathologies be screened for multifocal inflammation?
2. Which biomarkers would be most appropriate for screening and in which populations?
3. Would biomarkers be useful for guiding therapeutic decisions, even in patients with unifocal inflammation [to reveal underlying mechanisms]?

4.2. Predictors and treatment of EIMs

4.2.1. Predictors of EIMs

The identification of patients at risk of EIMs is desirable, because this raises the possibility not only of treatment initiation prior to permanent tissue destruction, but even the potential for disease prevention. Moreover, patients in whom a propensity to develop inflammatory disease has already declared itself in one system may provide a unique opportunity for targeted screening in order to detect inflammation at distant anatomical sites. Several studies have investigated factors influencing the risk of developing EIMs, but with inconsistent results. This is likely caused by differences across studies regarding definitions and assessment of EIMs as well as patient populations, since only very few population-based studies exist. Furthermore, the occurrence and risk factors for EIMs may also vary geographically.^{139–141}

On the simplest level, demographic and clinical factors may be used to detect risk. For example, female sex,^{29,63,113,142–146} CD rather than UC,^{113,142,143,147,148} increasing age,^{29,143,149} long disease duration,^{142,143} colonic location in CD,^{100,143} extensive UC compared with proctitis,^{142,147} indicators of severe disease including the need for steroids,¹⁴⁶ azathioprine,¹⁴⁶ biologic therapy,²⁹ or surgery,^{100,144,148} and smoking both in CD^{29,148} and UC^{29,150} have all been associated with an increased risk for EIMs. However, these associations are not reported consistently and are not replicated in all population-based studies^{147–149} and, as such, this approach may have limited applicability in clinical practice. Genetic factors play an important role in determining the presence of EIMs,^{119,120} especially genes in the *HLA* region on chromosome 6, as described above.^{151–153} Combining clinical factors with genetic data has been shown to be superior for predicting the development of EIMs compared with either alone.^{119,124} Furthermore, specific features of the clinical presentation may alert the clinician to the potential for future EIMs. For example, IBD is in the differential of any patient with ocular inflammation, especially in the ‘typical’ constellation of bilateral anterior/intermediate granulomatous uveitis. Conversely, it is wise to monitor liver function tests, especially in the IBD patient presenting with the clinical picture of mild, extensive colitis with rectal sparing and backwash ileitis, often associated with PSC.

Screening for IBD in patients with AS has been studied with some success, although the low rate of development of IBD in this group made the usefulness of screening somewhat questionable.¹⁵⁴ EIMs are often tested for based on clinical suspicion; however, screening for secondary diagnoses in patients with inflammatory pathologies has not yet proved to be a fruitful strategy.

Open questions:

1. Can accurate predictors of EIMs be developed?
2. Once predictors are available: Can early intervention alter the future development of EIMs?

4.2.2. Treatment

A recent systematic review by Peyrin-Biroulet *et al.* based on nine interventional studies, seven open-label studies, and thirteen non-interventional studies found a good clinical efficacy of adalimumab and infliximab for the treatment of musculoskeletal, cutaneous, and ocular manifestations, and some beneficial effect in metabolic bone disease and haematological or vascular EIMs in IBD patients.¹⁵⁵ In contrast, no or limited efficacy of other biologic drugs, including certolizumab pegol, golimumab, vedolizumab, or natalizumab was identified. In this review, however, different ranges of pathology get grouped together, which may obscure the therapeutic effect for specific types of EIMs that share a common mechanism.

Paradoxically, drug-induced EIMs are well documented and hint at the complex effects that interference with immune function may have. This complexity is potentially compounded in patients with multifocal inflammation. The effect of vedolizumab, [which blocks $\alpha 4\beta 7$ -dependent migration of lymphocytes into the gut] on EIMs has been difficult to predict, as discussed above. Potentially vedolizumab may have no effect on extraintestinal inflammation due to its gut-selective nature; alternatively if lymphocytes causing extraintestinal inflammation require activation in the gut before migration to the distant site, then vedolizumab would be predicted to improve EIMs. Finally, if prevention of migration to the gut resulted in accumulation of lymphocytes at extraintestinal sites, then vedolizumab could cause exacerbation of EIMs. Of course, it may be that each of these mechanisms

is present in different patients. Another treatment strategy that may be examined in the future is combination therapy with biologics with different molecular targets, for example, combined anti-integrin/anti-TNF α therapy for IBD patients with EIMs has shown some efficacy.¹⁵⁶

It has been hypothesized that the extent of inflammation [e.g. the size of ulcerations in PG] may determine optimal drug dosing, with larger ulcers requiring higher doses of the drug.⁹⁴ However no dose–response studies and no RCTs have been presented in IBD-EIM patients during the induction phase of anti-TNF α treatment to determine optimal trough levels.¹⁵⁷ The concept of relating drug dose to total inflammatory burden has instinctive validity and could potentially be of great relevance to patients with EIMs. However, this concept remains speculative at present and requires validation in clinical trials.¹⁵⁸

Open questions:

1. Is there a dose–response relationship between anti-TNF α therapy and EIM treatment response?
2. Are all anti-TNF α antibodies equally effective for the treatment of EIMs?
3. Is there an additive effect of combined immunosuppression in IBD patients with EIM?
4. Are optimal anti-TNF α trough levels for IBD patients with EIMs different from those for IBD patients without EIM?

4.3. Treat to target and patient-reported outcome measures in EIMs

A ‘treat to target’ strategy has been developed in many areas of medicine, in which treatment outcomes are defined by specific objective end points. The concept driving this strategy is that traditional outcome measures fail to reflect subclinical, yet active disease, permitting the accumulation of tissue damage over time. With a treat-to-target strategy therapy is intensified until the relevant evidence-based treatment target is in the desired range, which is associated with a reduction in end-organ destruction. For example in rheumatoid arthritis, scores such as the Disease Activity Score Calculator for Rheumatoid Arthritis [DAS-28] have been established.¹⁵⁹ This approach has also been used successfully in endocrinology, especially in diabetes management.^{160–162} Ongoing studies are developing this strategy in IBD.¹⁶³ Whether the same treatment targets developed for unifocal inflammation, can be applied [individually or perhaps in combination] in IBD-EIMs, or whether different targets should be developed, is unclear.

Another current advancement in the care of patients with chronic conditions is the development of Patient-Reported Outcome Measures [PROMs], which may themselves function as a treatment target. PROMs are defined by the FDA as “any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else.”¹⁶⁴ PROMs may be disease specific, such as the Inflammatory Bowel Disease Questionnaire [IBDQ-32],¹⁶⁵ the Inflammatory Bowel Disease Quality of Life Questionnaire [IBDQOL],¹⁶⁶ or the Work Productivity and Activity Impairment: Crohn’s Disease [WPAI: CD].¹⁶⁷ The use of PROMs designed for the assessment of unifocal inflammation in patients with multifocal inflammation presents obvious drawbacks, potentially missing significant aspects of the patient’s experience. However, non-disease-specific instruments have been developed, such as the Short-Form

Health Survey¹⁶⁸ and the EQ-5D,¹⁶⁹ which may be more applicable in multifocal inflammation.

Open questions:

1. What are appropriate treatment targets for patients with multifocal inflammation?
2. Can established treatment targets from patients with joint, skin, or eye disease be employed for patients with EIMs in IBD?
3. Would there be a difference in how PROMs and treat-to-target strategies function in patients with EIM activity that is synchronous with the IBD activity, compared with patients with asynchronous disease activity?

5. Conclusion

Determining the mechanisms that cause inflammation to manifest unifocally or multifocally in different patients remains an enticing conundrum in immunology. Solving this conundrum may illuminate novel mechanisms and reveal a broader range of therapeutic targets. In the context of the availability of a greater number of drugs targeted toward this broadening range of molecular targets, the previous organ-based approach to inflammatory disease may be inadequate. A holistic approach to the diagnosis and monitoring of inflammatory disease will allow a personalized therapeutic strategy. New tools for monitoring multifocal inflammation are needed in order to better capture the experience of the patient. This holistic approach to inflammatory disease requires greater cooperation between specialities and across research disciplines.

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Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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