Taylor & Francis
Taylor & Francis Group

Expert Review of Gastroenterology & Hepatology

ISSN: 1747-4124 (Print) 1747-4132 (Online) Journal homepage: www.tandfonline.com/journals/ierh20

Extra-intestinal manifestations in inflammatory bowel disease: a comparative review of pediatric and adult-onset disease

Chiara Viganò, Alice Laffusa, Lorena Pirola, Laura Cristoferi, Giovanna Zuin, Naire Sansotta, Daphne D'Amato, Stefania Orlando, Francesco Medici, Alberto Scirè Carlo & Pietro Invernizzi

To cite this article: Chiara Viganò, Alice Laffusa, Lorena Pirola, Laura Cristoferi, Giovanna Zuin, Naire Sansotta, Daphne D'Amato, Stefania Orlando, Francesco Medici, Alberto Scirè Carlo & Pietro Invernizzi (2025) Extra-intestinal manifestations in inflammatory bowel disease: a comparative review of pediatric and adult-onset disease, Expert Review of Gastroenterology & Hepatology, 19:10, 1133-1147, DOI: 10.1080/17474124.2025.2550518

To link to this article: https://doi.org/10.1080/17474124.2025.2550518

© 2025 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.

Published online: 29 Aug 2025.

Submit your article to this journal

Article views: 547

View related articles

View Crossmark data

Citing articles: 1 View citing articles

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=ierh20

EXPERT REVIEW OF GASTROENTEROLOGY & HEPATOLOGY
2025, VOL. 19, NO. 10, 1133–1147
https://doi.org/10.1080/17474124.2025.2550518

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

Extra-intestinal manifestations in inflammatory bowel disease: a comparative review of pediatric and adult-onset disease

Chiara Viganò[a], Alice Laffusa[b], Lorena Pirola[a], Laura Cristoferi[a], Giovanna Zuin[c], Naire Sansotta[d], Daphne D'Amato[a,e], Stefania Orlando[b], Francesco Medici [f], Alberto Scirè Carlo[g,h] and Pietro Invernizzi[i,j]

[a]Gastroenterology, Fondazione IRCCS San Gerardo Dei Tintori, Monza, Italy; [b]Gastroenterology and Endoscopy Unit, Papa Giovanni XXIII Hospital, Bergamo, Italy; [c]Pediatrics, Fondazione IRCCS San Gerardo Dei Tintori, Monza, Italy; [d]Pediatric Hepatology Gastroenterology and Transplantation Unit, ASST Papa Giovanni XXIII, Bergamo, Italy; [e]Gastroenterology Residency, University of Turin, Turin, Italy; [f]Pediatric Residency, University of Milano Bicocca, Monza, Italy; [g]Rheumatology Unit, Fondazione IRCCS San Gerardo Dei Tintori, Monza, Italy; [h]School of Medicine, University of Milano-Bicocca, Milan, Italy; [i]Division of Gastroenterology, Center for Autoimmune Liver Diseases, European Reference Network on Hepatological Diseases (ERN RARE-LIVER), IRCCS Fondazione San Gerardo Dei Tintori, Monza, Italy; [j]Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

ABSTRACT

Introduction: Inflammatory Bowel Diseases (IBD) are chronic immune-mediated disorders diagnosed in both adult and pediatric populations. In recent years, there has been a significant global increase in pediatric-onset IBD, not only in Western countries but also in newly industrialized regions. Age of onset plays a crucial role in disease behavior and prognosis, with pediatric onset often associated with a more extensive and aggressive disease. As a systemic inflammatory condition, IBD can involve multiple organ systems beyond the gastrointestinal tract, thus resulting in extraintestinal manifestations (EIMs) of variable severity. These manifestations (musculoskeletal, dermatological, oral, ocular, and hepatobiliary) may significantly impact patients' quality of life, sometimes even more than intestinal symptoms. To support this review, a PubMed search was conducted using the terms inflammatory bowel disease, Crohn's disease, ulcerative colitis, pediatric inflammatory bowel disease, extraintestinal manifestations, focusing on the most relevant papers with no time restrictions.

Areas covered: This review aims to provide a comprehensive revision and comparison of the presentation, course, and management of EIMs in pediatric- versus adult-onset IBD.

Expert opinion: A deeper understanding of EIMs in different age groups is essential for timely diagnosis and holistic care, ultimately improving the overall quality of clinical management of patients with IBD.

ARTICLE HISTORY
Received 21 May 2025
Accepted 18 August 2025

KEYWORDS
Crohn's disease; extraintestinal manifestations; inflammatory bowel diseases; ulcerative colitis; pediatric inflammatory bowel disease; spondyloarthritis; erythema nodosum; uveitis

1. Introduction

Inflammatory bowel diseases (IBD) are chronic inflammatory disorders of the gut, comprising Crohn's disease (CD) and ulcerative colitis (UC). While gastrointestinal symptoms are often the most prominent, IBD is a systemic disorder as virtually every organ can be involved in the inflammatory process. In fact, up to 50% of IBD patients will develop at least one extraintestinal manifestation (EIM) [1]. IBD primarily affects young adults, though it can occur at any age, and as many as 25% of patients experience onset before the age of 18 [2]. Adult and pediatric-onset IBD exhibit many differences. Children and adolescents are more likely to have CD than UC. The disease in pediatric patients tends to be more severe ad extensive and is more likely to progress to more extensive anatomical involvement even in the first two years after diagnosis [3]. Concerning EIMs, they are reported as particularly common among pediatric IBD patients, with nearly 30% of them showing signs before an official IBD diagnosis is made [4,5]. The scope of this review is to unravel the differences between pediatric-onset IBD and adult IBD concerning classical EIMs in general and of each in particular.

For this purpose, a PubMed search was conducted using the terms inflammatory bowel disease, Crohn's disease, ulcerative colitis, pediatric inflammatory bowel disease, extraintestinal manifestations, focusing on the most relevant papers with no time restrictions.

2. Classification of EIMs and differences in pediatric-onset IBD compared to adult-onset IBD

The systemic nature of IBD highlights the diverse manifestations that extend beyond the gastrointestinal tract, and the definition of EIM is not unambiguous. It may indeed range from more stringent to wider definitions, which include diseases that are rather associations or complications of IBD [6]. The definition of classical EIMs encompasses manifestations that arise from the inflammatory process at distant sites, for which the pathogenesis is either dependent on the extension of the immune response of the intestine or is an independent event yet perpetuated by the IBD [7] (Table 1).

Beyond classical EIMs, there are associations with other immune-mediated disorders and complications of systemic

CONTACT Chiara Viganò chiara.vigano@irccs-sangerardo.it Gastroenterology, Fondazione IRCCS San Gerardo Dei Tintori, Via Gian Battista Pergolesi, 33, Monza 20900, Italy

© 2025 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way. The terms on which this article has been published allow the posting of the Accepted Manuscript in a repository by the author(s) or with their consent.

Article highlights

- **Extraintestinal manifestations (EIMs) affects up to 50% of IBD patients** and seem to be very common in pediatric-onset IBD, where they often appear earlier in the disease course and may precede intestinal symptoms.
- **Musculoskeletal EIMs are very common and significantly contribute to disease burden**. They have been extensively studied in adult cohorts, and similar prevalence has been reported in pediatric cohorts.
- **Cutaneous, oral and ocular EIMs** show distinct prevalence and patterns between pediatric and adult populations, though data are limited.
- **Primary sclerosing cholangitis is the most relevant hepatobiliary EIM**, frequently associated with ulcerative colitis, and markedly increasing the risk of colorectal cancer, especially in pediatric patients.
- **Improved recognition and timely diagnosis of EIMs**, particularly in pediatric populations, are crucial to reduce diagnostic delays and guide holistic, multidisciplinary management and to limit long-term morbidity.

inflammation and treatment. These may involve many other organs and systems, including the lung, the heart and vascular system, the pancreas, and the kidneys.

Airways inflammation with bronchiectasis is the most common lung involvement, while IBD-related interstitial lung diseases are rare and should always raise suspicion of infection or adverse drug reactions [8]. Several systemic inflammatory conditions are associated with a significant increase in cardiovascular risk, but this has not been completely confirmed for IBD. Myocarditis represents an associated inflammatory condition, while pericarditis is usually a treatment-related complication. On the other hand, patients with IBD have a well-established increased risk of venous thromboembolism [9,10]. Renal manifestations in IBD are reportedly rare; they can involve both the glomeruli and/or the tubular structure and the pathogenesis is poorly understood [11]. On the contrary, pancreatic involvement in IBD is frequent, with acute pancreatitis due to gallstones and drugs being the most frequent manifestation. However, autoimmune pancreatitis is a rare disorder with a strong association with IBD, particularly type 2 pancreatitis and UC [12].

Regarding classical EIMs, the pathophysiology is not completely elucidated, and two possible mechanistic interpretations have been proposed. On the one hand, EIMs can develop as a direct extension of the intestinal immune response, manifesting as an altered T cell trafficking due to abnormal patterns of lymphocyte homing or to upregulated expression of nonspecific adhesion molecules, either determined or not by an antigen-specific reactivation at non-intestinal sites. Alternatively, EIMs can represent an independent inflammatory process that is linked in its pathogenesis to the underlying IBD by sharing common genetic or environmental risk factors. In this case the proposed mechanisms could be a shift in the inflammatory tone, a systemic change in innate immune function or a common alteration of the gut microbiota [7] (Figure 1).

Classical EIMs vary widely, spanning dermatologic, musculoskeletal, ocular, oral and hepatobiliary systems, and they are usually classified according to the organ and system affected. Moreover, it is possible to classify EIMs according to the disease course in relation to the IBD itself. In particular there are EIMs which are typically associated with intestinal disease activity, such as erythema nodosum or episcleritis, as well as others that do not associate with IBD activity, like axial arthropathy. In some cases either course has been reported (Table 2).

The reported prevalence of EIMs in adult patients ranges from 6 to 50% [13,14], with most studies indicating a prevalence of 35–40%. The highly variable frequencies reported are likely due to different definitions of EIMs and variable study designs and inclusion criteria.

In pediatric patients some reports suggest that EIMs are even more frequent, though data are actually limited. The prevalence reportedly ranges from 12 up to 70% of patients, mainly depending on study design and duration of follow up [5,15]. However, in the majority of studies the reported prevalence lies between 30 and 50% [4,16–18]. Of note, only a few studies have directly compared pediatric and adult IBD, with regards to EIMs manifestation. In a study by Guariso et al, the presence of EIMs in the pediatric-onset group during follow up reached 50%, which was significantly higher than in the adult-onset population (34%) [4]. On the other hand, the Pediatric Swiss IBD Study, a nationwide substudy of the Swiss IBD cohort study with enrollment started in 2008, reported a much lower cumulative prevalence of 16.7% in pediatric-onset IBD [5]. This difference could be related to a more stringent definition of EIMs in the Swiss study and the different enrollment period, with the study by Guariso et al. conducted in the pre-biologic era.

Concerning the time of onset of EIMs, it has been reported that in up to 30% of pediatric patients EIMs manifest before the IBD diagnosis [5], which is rather similar to what reported in the adult population [1]. However, in most pediatric studies, EIMs are diagnosed prior to IBD in 6 to 14% of patients [4,5,16,17]. On the other hand, direct comparative studies demonstrated an earlier onset of EIM in pediatric patients

Table 1. Classification of extra-intestinal manifestations in inflammatory bowel disease (IBD).

EIMs in IBD	Manifestations
Classical (inflammatory process at distant site)	Uveitis, Scleritis, Episcleritis, Oral manifestations, Spondyloarthropathy (axial/non-axial), Primary Sclerosing Cholangitis (PSC), Autoimmune Hepatitis (AIH), Pyoderma gangrenosum, Erythema nodosum, Sweet syndrome
Associated with other Immune-disease	Multiple Sclerosis (MS), Interstitial Lung Disease (ILD), Bronchiectasis, Myocarditis
Complications of systemic inflammation	Cerebrovascular Accident (CVA), Ischemic Heart Disease (IHD), Venous thromboembolism (VTE), Fatigue, Anemia
Treatment related	Psoriasiform rash, Pericarditis, Pancreatitis, Osteoporosis

Abbreviations: EIMs, Extra-intestinal manifestations. IBD, Inflammatory bowel disease.

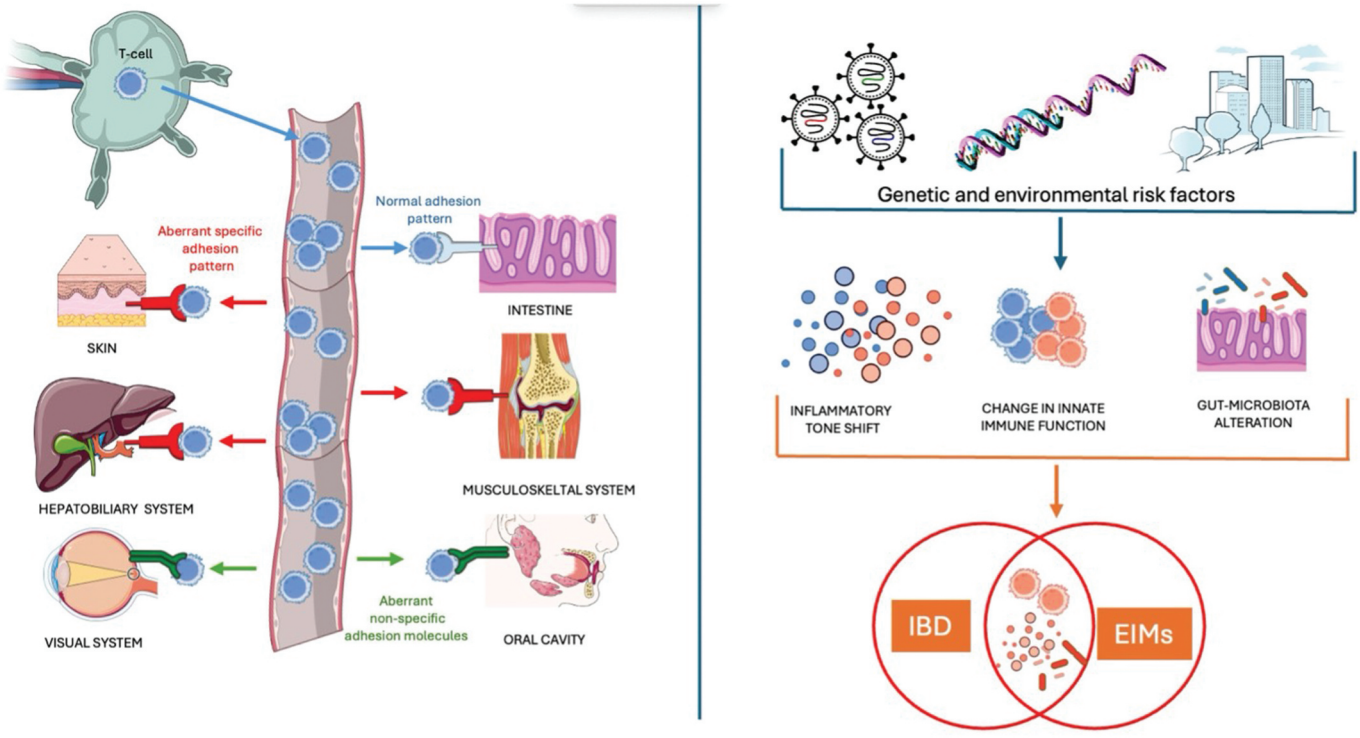

Figure 1. Pathogenesis of extra-intestinal manifestations in IBD.
The pathogenesis of EIMs in IBD can be explained by two possible mechanisms. EIMs may be a direct extension of the intestinal immune response, through an altered T cell trafficking, either due to abnormal patterns of lymphocyte homing or to upregulated expression of nonspecific adhesion molecules (left side of the figure). Alternatively, EIMs are independent inflammatory processes, that share genetic or environmental risk factors with the intestinal disease, via a a shift in the inflammatory tone, a systemic change in innate immune function, or a common alteration of the gut microbiota (right side of the figure).

Abbreviations: IBD: Inflammatory bowel disease. EIMs: Extra-intestinal manifestations.

Table 2. Classification of EIMs based on association of activity with intestinal disease course.

Related to IBD activity	Unrelated to IBD activity	Unclear correlation with IBD activity
Musculoskeletal	**Musculoskeletal**	**Ocular**
– Non axial spondyloarthropathy (oligoarticular)	– Non axial spondyloarthropathy (polyarticular)	– Scleritis
	– Axial Spondyloarthropathy	
Cutaneous	**Cutaneous**	**Oral**
– Erythema nodosum	– Pyoderma gangrenosum	– Mucosal cobblestoning
– Sweet syndrome	**Ocular**	
Oral	– Uveitis	
– Aphthous stomatitis		
– Periodontitis		
– Pyostomatitis vegetans		
– CD-specific oral conditions		
Ocular		
– Episcleritis		
Hepatobiliary		
– Primary Sclerosing Cholangitis		

Abbreviations: EIMs: Extra-intestinal manifestations. IBD: Inflammatory bowel disease. CD: Crohn's disease.

vs. adult patient. In the study by Guariso et al. EIM development before IBD diagnosis occurred in 14% of pediatric patients compared to 7% of adult patients, and in the Pediatric Swiss IBD Study in 8.5% vs 5% respectively [4,5]. On the contrary, in the ENEIDA pediatric cohort, the prevalence of EIMs at diagnosis was not different in pediatric IBD patients compared to adults (12% vs 13.8 respectively, p = NS) [19].

In any case, in the pediatric population EIMs seem to develop early in the disease course. In the Pediatric Swiss IBD Study, median time between IBD diagnosis and occurrence of first EIM was one month (range −37.5–149.0) [5], whereas in the adult Swiss IBD Cohort Study Group, the median time before IBD diagnosis was 5 months (range 0–25) [1]. Dotson et al. reported that 87% of EIM occurred within the first year of diagnosis in the Pediatric IBD Collaborative Research Group Registry [18].

Regarding the association with specific disease type, EIMs are usually more common in CD, with the notable exception of primary sclerosing cholangitis [20,21]. The same applies to

the pediatric population, in the Swiss study EIMs occurred in 22.5% of CD patients compared to 10.3% of UC/IBD unclassified patients ($p < 0.05$) [14]. Similar data were reported by the comparative study from Guariso et al. [4].

In adult patients, the presence of one EIM increases the risk of developing subsequent EIMs, in accordance with the hypothesis of a common pathogenetic pathway. Additionally a family history of IBD also increases the risk of EIM occurrence in adult CD patients, thus probably supporting a shared genetic susceptibility between IBD and EIMs [20].

Limited data are available about the risk factors associated with the development of EIMs in the pediatric population. Dotson et al. reported that increased disease severity at baseline was significantly associated with EIMs [18]. This data was confirmed by Cohen and coauthors, which also reported extensive CD, lower albumin level and higher C-reactive protein level as risk factors for EIMs development in pediatric patients [16].

The presence of EIMs at diagnosis was associated with an increased risk of colectomy in a population-based study of pediatric-onset UC [22].

3. Musculoskeletal EIMs

Enteropathic arthritis (EA) represents a distinct clinical entity within the spectrum of spondyloarthritis (SpA), characterized by the co-occurrence of inflammatory joint disease and IBD. It is the most prevalent EIM in IBD patients and presents with different musculoskeletal clinical manifestations (Table 3). The diagnosis requires integrated clinical, laboratory, and imaging assessments. The coexistence of EA with IBD has significant implications for the treatment plan, requiring joint management by rheumatologists and gastroenterologists.

3.1. Pathophysiology

The pathophysiology of EA arthritis represents a complex interplay between genetic predisposition, environmental factors, and dysregulated immune responses affecting both the intestinal mucosa and joint structures. While the precise mechanisms underlying the link between gut inflammation and joint disease remain incompletely understood, significant advances have been made in elucidating the shared pathways that connect these seemingly disparate organ systems [23,24]. The gut-joint axis in EA may involve the aberrant expression of homing receptors and adhesion molecules, allowing gut-derived immune cells to migrate to joint tissues. This concept is supported by the observation that a significant proportion of patients with spondyloarthritis exhibit subclinical gut inflammation, even in the absence of overt IBD symptoms [25].

The traditional classification of EA distinguishes between type I (mono-oligoarticular) arthropathy and type II (polyarticular). The first usually affects fewer than five joints, primarily large joints of the lower limbs, is typically acute and self-limiting, and often coincides with intestinal inflammation flares. Type II (polyarticular) arthropathy affects five or more joints, including small joints of the upper limbs, tends to be persistent, and follows a course independent of IBD activity [26]. More recently, EA has been classified within the broader framework of spondyloarthritis using the Assessment in Spondyloarthritis international Society (ASAS) criteria, which categorize SpA into peripheral (p-SpA) and axial forms (ax-SpA) [27,28]. Axial-SpA with evidence of damage at conventional radiography of the spine or sacroiliac joint is called radiographic ax-SpA (r-ax-SpA), while ax-SpA with only Magnetic Resonance Imaging (MRI) findings is called non-radiographic ax-SpA (nr-ax-SpA). While the ASAS criteria have been widely adopted in research and clinical practice, it is

Table 3. Prevalence of extraintestinal manifestations in adult and pediatric IBD patients.

EIMs	Prevalence in adults IBD patients (%)	Prevalence in pediatrics IBD patients (%)
Musculoskeletal	**1–46**	**2.4–18.5**
- Non axial spondyloarthropathy	16	2–50
- Axial Spondyloarthropathy	5	2.8
Cutaneous	**5–15**	**2.1–3.1**
- Erythema nodosum	5–15	2.8
- Pyoderma gangrenosum	0–5–2.6	0.3–0.6
- Sweet syndrome	**	**
Oral	**0.7–37**	**7–23**
- Aphthous stomatitis and periodontitis	0.7–20*	3.2–41*
- Mucosal cobblestoning	6–20*	6–20 *
- CD-specific oral conditions	20–50*	5–15 *
- Pyostomatitis vegetans	**	**
- Orofacial granulomatosis	**	**
Ocular	**4–12**	**0.62–1.8**
- Episcleritis	2–4*	**
- Uveitis	1.7–5*	**
- Scleritis	**	**
Primary Sclerosing cholangitis	**8**	**0.6 (CD)** **9.9 (UC)**

*Heterogeneous data from studies with different reported prevalence.
**Prevalence not available due to limited data (rare conditions).
Abbreviations: IBD: Inflammatory Bowel Disease. UC: ulcerative colitis. CD: Crohn's disease.

important to note that they were not specifically developed for nor validated in patients with IBD. This has led to still unresolved challenges in the classification and diagnosis of EA, and considerable heterogeneity remains in the diagnostic criteria used in both clinical practice and research [29].

3.2. Clinical manifestations

EA presents diverse musculoskeletal clinical manifestations. Axial involvement includes sacroiliitis and spondylitis, and it is characterized by early onset inflammatory back pain that improves with exercise, worsens with rest, and is often associated with morning stiffness. As the disease progresses, patients may develop limitations of spinal mobility. The course of axial disease in EA is typically independent of intestinal disease activity, with axial symptoms often persisting or progressing despite quiescence of IBD.

Peripheral arthritis (synovitis) may be present in the two classical phenotypes: type I (oligoarticular) and type II (polyarticular). The clinical presentation of type I arthropathy typically includes: acute onset of joint pain, swelling, and stiffness; asymmetric distribution; migratory pattern, with different joints affected over time; self-limiting course, usually resolving within 2–3 months; and temporal relationship with IBD flares. Conversely, the clinical features of type II arthropathy include symmetric or asymmetric involvement of multiple joints; predilection for small joints of the upper extremities; persistent symptoms, often lasting for months to years; course independent of IBD activity; potential for erosive joint damage and deformity. Synovitis is not limited to synovial joints but also includes tendon sheaths and bursae, leading to tenosynovitis and bursitis. Peripheral involvement may also target enthesis: enthesitis, an inflammation at insertion sites of tendons, ligaments, and joint capsules, clinically affects the Achilles tendon, plantar fascia, and the common extensor tendon (lateral epicondyle). Clinically, enthesitis presents as localized pain, tenderness, and sometimes swelling at the affected sites. The pain is typically exacerbated by movement or pressure and may be associated with stiffness, particularly after periods of inactivity. In severe cases, enthesitis can lead to significant functional impairment and disability. Another typical, though less frequent, peripheral manifestation is called dactylitis, often referred to as 'sausage digit,' which is characterized by diffuse swelling of an entire digit (finger or toe) due to inflammation of the digital tendons, joints, and surrounding tissues. It is a distinctive clinical feature of SpA and can occur in patients with EA.

3.3. Diagnosis

Diagnosis of EA relies on a comprehensive evaluation that integrates clinical, laboratory, and imaging assessments. The ASAS classification criteria for axial and peripheral spondyloarthritis provide a standardized framework applicable to patients with IBD-associated joint disease [27,28]. Imaging plays a crucial role in the diagnosis of EA. Conventional radiography remains the initial imaging modality for evaluating joint and spine involvement in patients with suspected EA. Key radiographic findings include signs of sacroiliitis (sclerosis, erosions, bone bridges and ankylosis); or spondylitis (squaring of vertebral bodies, erosions at the corners of vertebral bodies, syndesmophyte formation). Radiographic changes in peripheral joints may include periarticular osteopenia, joint space narrowing, erosions, and periosteal new bone formation.

MRI has revolutionized the early diagnosis of axial SpA by enabling the detection of active inflammation before structural damage occurs. Active sacroiliitis on MRI is characterized by bone marrow edema (BME) in the subchondral bone of the sacrum or ilium. Similarly active spondylitis on MRI is characterized by BME at the corners of vertebral bodies, in the vertebral bodies, at the sites of attachment of the annulus fibrosus to the vertebral bodies or in the posterior elements of the spine. MRI can detect enthesitis as increased signal intensity at ethereal sites on T2-weighted or short inversion recovery (STIR) sequences, often accompanied by adjacent BME. Ultrasound is a valuable imaging modality for evaluating peripheral joints, tendons, and entheses in patients with EA, particularly to detect synovitis, tenosynovitis, bursitis, enthesitis and dactylitis (Figure 2).

In addition to ensuring diagnostic accuracy, early diagnosis is crucial in inflammatory arthritis, including SpA, to prevent long-term joint damage. Several screening tools have been developed to help identify patients with IBD who either have coexisting SpA or are at risk of developing it. These tools can facilitate early recognition and appropriate referral to rheumatology services. Among them, the Detection of Arthritis in Inflammatory Bowel Disease (DETAIL) and the IBD Identification of Spondyloarthritis Questionnaire (IBIS-Q) are validated screening tools for SpA in IBD patients [30,31].

3.4. Epidemiology

The frequency of EA is highly variable across studies, due to different study samples and applied definitions. In IBD, the prevalence of axSpA ranges from 1% to 46% (median 5%) and for pSpA from 1% to 43% (median 16%), respectively [32]. Recent estimates have provided more precise prevalence data of SpA symptoms in IBD patients. Using screening tools in IBD, Hong et al. found that 35% of patients with IBD screened positive for SpA symptoms, identifying risk factors including female sex, older age, smoking history, and prior biologic therapy [33]. Similarly, Ermann et al. reported that 41% of IBD patients screened positive for SpA symptoms, with 69% of screen-positive patients having neither a documented inflammatory rheumatic disease diagnosis nor a rheumatologist visit within the past year, suggesting substantial underdiagnosis [34].

In pediatric patients, joint involvement occurs with prevalence rates ranging from 2.4% to 18.5%, and it is more commonly observed in patients with CD compared to those with UC. Moreover, in 30–40% of cases, arthritis can precede the diagnosis of IBD, potentially leading to delays in diagnosis, as the initial presentation may be mistaken for juvenile idiopathic arthritis (JIA) rather than IBD [5,18,35,36]. Both previous extensive studies, such as the one by Jose et al. [17], which examined a cohort of 1649 pediatric IBD cases, and a more recent research conducted by the Italian Society of Pediatric Gastroenterology Hepatology and Nutrition (SIGENP) [37]

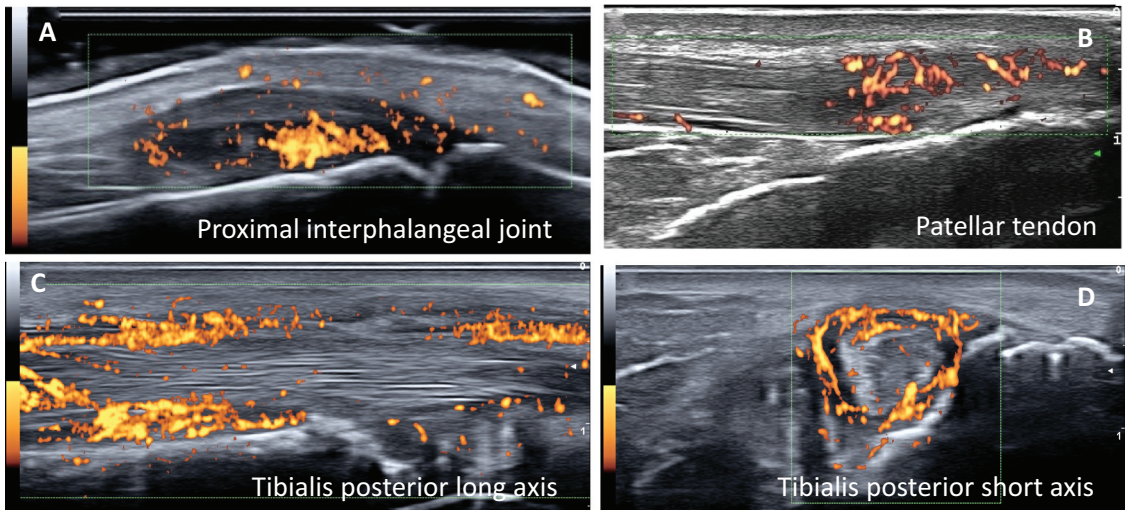

Figure 2. The role of ultrasound for evaluating peripheral joints, tendons, and entheses in patients with enteropathic arthritis, showing thickening and hypoechoic appearance of tissues with power doppler sign: A) synovitis; B) enthesitis; C and D) tenosynovitis.

with 3061 pediatric patients, confirm an arthritis prevalence rate of 4.3% and 4.9%, respectively, with a higher prevalence in patients with CD than those with UC/IBD Unclassified (7.6% vs 2.9%, $p < 0.01$). The SIGENP study also found that arthritis occurred before the IBD diagnosis in 26% of patients, concurrently in 34%, and after the IBD diagnosis in 40% [37]. A systematic review examining the prevalence of axial SpA in adult patients with IBD found sacroiliitis in 10% of patients and ankylosing spondylitis in 3% [38]. This manifestation is more common in patients with CD [39].

Regarding pediatric patients, the SIGENP study showed a prevalence of axial SpA in 2.8% of patients, with a higher frequency in those with CD (4.4%) compared to those with UC/IBDU (1.6%). Additionally, there were no significant differences in the prevalence of axial SpA between patients with active and those with quiescent IBD [37].

Concomitant axial and peripheral joints disease can occur in 3–6% of adult patients [40].

Peripheral spondyloarthritis is the most common form of articular manifestation in IBD (Table 3). Population studies showed a prevalence of peripheral arthropathies of 5–10% in adult patients with UC and 10–20% in CD (23). Pediatric studies have reported a prevalence of peripheral arthritis ranging from 4–49% in CD and 2–50% in UC [26]. This was further confirmed by Jose et al. who reported a 4.2% 10-year cumulative incidence of peripheral arthritis in pediatric IBD [17], and the SIGENP study, which found an overall prevalence of 4.1%, higher in CD patients (6.5%) than in those with UC/IBDU (2.3%) [37].

Enthesopathies and dactylitis have been studied less extensively in IBD. Data on the epidemiology of enthesitis in the pediatric population are even more limited. In an old small cross-sectional study, enthesis involvement was unexpectedly high, observed in 21% of 43 pediatric IBD patients [41]. On the other hand, in the SIGENP study [37] and the study conducted by Derfalvi et al. [42], the prevalence of this articular phenotype was significantly lower, with rates of 0.5% and 1.2%, respectively.

Moreover the SIGENP study was the first to report the prevalence of dactylitis in pediatric IBD patients, which was present in 0,4% of the population examined [37].

3.5. Treatment

Therapeutic strategies must address both articular and intestinal components of the disease [17]. NSAIDs are commonly used to manage joint symptoms, though their use in IBD is tempered by concerns over gastrointestinal toxicity, making COX-2 inhibitors a preferred option in selected patients. Corticosteroids, while effective for acute flares, are unsuitable for long-term use. Conventional DMARDs such as sulfasalazine and methotrexate are beneficial for peripheral arthritis, particularly when gut inflammation is also present. Biologic therapies have transformed the management landscape, with tumor necrosis factor (TNF) inhibitors demonstrating efficacy in both joint and intestinal domains. Agents targeting IL-23, offer additional options, particularly in patients with refractory disease or patients with associated psoriatic disease. On the other hand, caution is warranted with interleukin (IL)-17 inhibitors due to the potential exacerbation of IBD. Janus kinase (JAK) inhibitors represent a newer class of therapy with promise in both SpA and IBD.

Non-pharmacological approaches also contribute to comprehensive care. Physical therapy and exercise are essential to maintain function and prevent disability. The emerging paradigm of trans-disciplinary care advocates for joint management by rheumatologists and gastroenterologists, enabling a holistic and personalized approach.

4. Cutaneous EIMs

In patients with IBD, the skin is frequently involved in the inflammatory process, presenting with different clinical manifestations [43]. Dermatological involvement has been reported in approximately 5–15% of adult IBD patients (Table 3).

Among the most common cutaneous manifestations are pyoderma gangrenosum (PG) and erythema nodosum (EN) [44]. In a large adult IBD cohort, nearly 10% of patients exhibited at least one skin manifestation, with EN observed in 7.4% and PG in 2.3% [44]. In pediatric patients cutaneous manifestations appear to be less prevalent. Dotson et al. studied EIMs in a registry of 1009 pediatric IBD patients, finding that 3.1% developed cutaneous EIMs during follow-up [18]. A similar study by Greuter et al. reported an even lower prevalence of 2.1% [5]. The presence of cutaneous EIMs significantly contributes to the overall morbidity and, in some cases, mortality associated with IBD [43].

4.1. Erythema nodosum

EN is the most common cutaneous EIM of IBD, with a reported prevalence ranging from 5 to 15% in patients with CD and 2 to 10% in those with UC. EN is more frequently observed in females and typically affects individuals between the ages of 20 and 30 years [1,5]. In the pediatric population, EN is less common [40]. In a large study by Dotson et al. EN was reported in 2.8% of pediatric IBD patients (3.6% of those with CD and 0.71% of those with UC) [18]. Greuter et al. found an even lower overall prevalence of 1.5% in a similar pediatric cohort [5]. EN most often develops after the diagnosis of the intestinal disease, with fewer than 15% of cases preceding IBD onset [1]. Although EN is known to parallel intestinal disease activity, its severity does not always correlate with the degree of intestinal inflammation [1]. Notably, EN often coexists with other EIMs, including ocular and joint involvement, pyoderma gangrenosum, and isolated colonic disease [45].

Clinically, EN presents as tender, erythematous to violaceous, non-ulcerative subcutaneous nodules measuring 1–5 cm in diameter [46]. Lesions are usually symmetrical and located on the extensor surfaces of the lower limbs, especially the anterior tibial area. Less frequently, they may occur on the thighs and the forearms, and only rarely on the face, trunk and upper extremities (Figure 4).

The pathogenesis of EN remains complex and not fully understood; it is thought to involve immune-mediated mechanisms, particularly type IV hypersensitivity reaction. Histologically, EN corresponds to a septal panniculitis without vasculitis [46,47].

The diagnosis is established based on clinical judgment; skin biopsies are generally not necessary. EN is typically self-limiting, with lesions resolving spontaneously within 2–8- weeks, without ulceration, scarring, or atrophy. In patients with IBD-associated EN, effective treatment of the underlying intestinal inflammation usually leads to resolution of the cutaneous lesions [47]. Mild cases may be managed conservatively with leg elevation, use of analgesics, potassium iodine, and compression stockings [48]. In more severe or refractory cases, alternative etiologies, such as infections (e.g. *Streptococcus spp*., *Yersinia pseudotuberculosis, Yersinia enterocolitica, syphilis*), Bechet's disease, sarcoidosis, or medication-related EN (e.g. oral contraceptives) should be excluded. Systemic corticosteroids are often considered the first-line therapy in such cases [1,47,49]. For patients with concomitant active IBD, anti-TNF agents have demonstrated efficacy and may serve as a rescue therapy [50]. More recently, monoclonal antibodies targeting the IL-12/23p40 subunit have shown potential therapeutic benefit for EN [51].

4.2. Pyoderma gangrenosum

Pyoderma Gangrenosum (PG) is the second most common cutaneous manifestation of IBD, with an estimated prevalence of 0.5–2.6% among adult patients[1]. Similar to EN, PG seems to be less frequently observed in pediatric populations, with reported rates ranging from of 0.3 to 0.6% [5,18].

PG is more frequently associated with UC than CD [45,52], and tends to occur more commonly in older adults (around the age of 50) and in females. Additional risk factors include a Black African descent, a family history of UC, severe IBD, colonic involvement, presence of a permanent stoma, ocular manifestations, and concurrent EN [53]. Conversely, up to 50% of patients diagnosed with PG have underlying IBD, which may precede the onset of skin lesions and lead to the eventual diagnosis of IBD [54]. PG lesions are often triggered by minor trauma, even years prior to the lesion onset, in a phenomenon known as *pathergy effect* [20]. The disease typically begins as an erythematous pustule or nodule that rapidly evolves into a painful, deep ulcer with irregular, violaceous undermined borders and necrotic or purulent base, which is typically sterile on culture [55]. Ulcers may be solitary or multiple, unilateral or bilateral, and can vary widely in size from a few centimeters to involving an entire limb (Figure 3). Common locations include the extensor surfaces of the legs and areas adjacent to postsurgical stomas; however, lesions can occur anywhere, including the genital region. Peristomal PG is occasionally seen as a complication in patients with IBD [56]. There are also case reports of PG arising from preexisting EN lesions [57]. The pathogenesis of PG remains unclear, though it is generally considered an immune-related autoinflammatory disorder involving both innate and adaptive immune response. Diagnosis is primarily clinical; wound cultures and skin biopsy are often performed to rule out infectious or neoplastic causes. Histopathological findings are nonspecific, typically showing diffuse neutrophilic infiltration and dermal destruction.

PG often follows a severe, unpredictable, and debilitating clinical course [1]. Notably, there is usually no correlation between the cutaneous activity of PG and the clinical activity of the underlying IBD. PG may persist despite adequate control of intestinal disease.

Prompt recognition and intervention are crucial to prevent complications and minimize tissue damage. Mild cases may respond to local treatment, including topical agents (e.g. sodium cromoglycate 1–2% solution), intralesional corticosteroid injections, and hydroactive dressings [47,55,58]. Systemic agents, such as sulfasalazine, dapsone, corticosteroids, and immunomodulators (e.g. azathioprine, cyclophosphamide, cyclosporine, methotrexate, tacrolimus, and mycophenolate mofetil) have shown varying degrees of effectiveness [58,59]. Nonetheless, many patients exhibit a refractory disease course. Several case reports and series

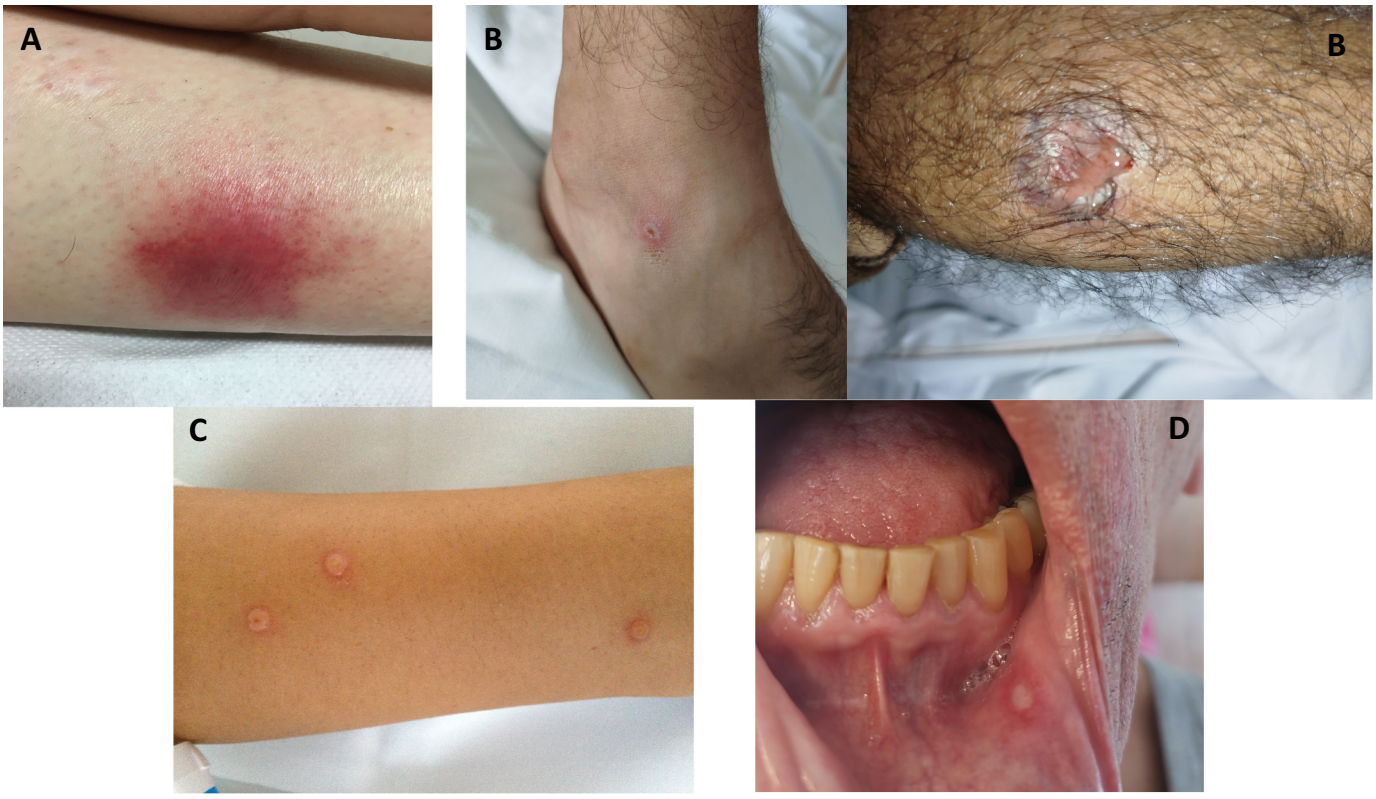

Figure 3. Mucocutaneous EIMs in IBD.
(A) Erythema nodosum of the lower limb in a young female patient with active colonic CD.
(B) Two small lesions of pyoderma gangrenosum of the ankle and calf in a 21-year-old male patient presenting with new onset acute severe UC, treated with infliximab as a rescue therapy with complete resolution of the lesions.
(C) Sweet's syndrome in a 27-year-old female patient diagnosed with acute severe UC and associated also with erythema nodosum of the lower limb and bilateral anterior uveitis. The patient was treated with infliximab as a rescue therapy with complete resolution of all EIMs and clinical remission of UC.
(D) A 22 year-old male patient with CD and previous subtotal colectomy presenting with metastatic CD of the glans with histologically visible granuloma.
(E) Oral aphthous ulcer in a 65 year-old male patient with active left-sided UC.
EIMs, Extra-intestinal manifestations. IBD, Inflammatory bowel disease. CD, Crohn's disease. Ulcerative Colitis (UC).
Informed patient consent was provided for the publication of these images.

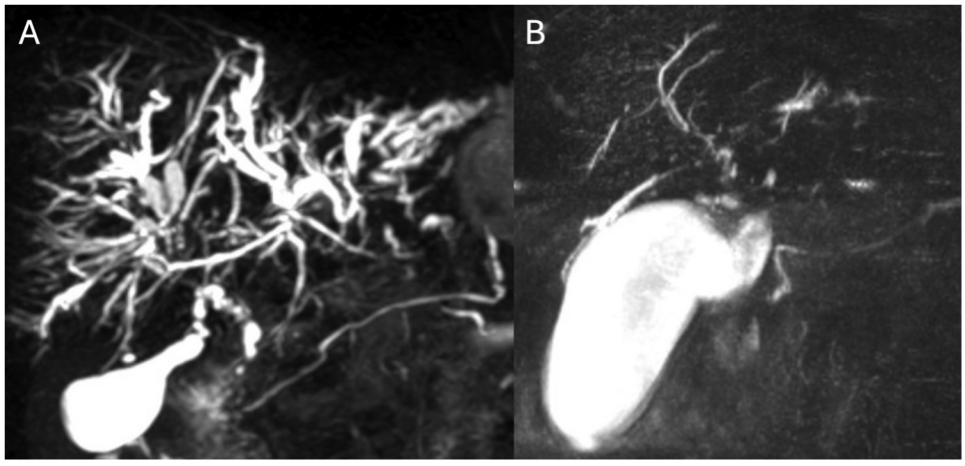

Figure 4. Typical MRI features of primary sclerosing cholangitis (PSC) include intrahepatic and extrahepatic biliary tree abnormalities, characterized by multifocal strictures and segmental dilatations, which may be severe (A) or moderate (B). A distended gallbladder (B) is also a common finding in patients with PSC.

have demonstrated the effectiveness of anti-TNF agents in severe PG. IL-12/23 inhibitors also represent a theoretically promising options [60]. Of note, although PG is initially sometimes treated by surgical debridement, surgical intervention typically exacerbates the condition. If PG is suspected, surgical procedure should be avoided, until the diagnosis is definitively excluded.

4.3. Sweet's syndrome

Sweet's syndrome is a rare dermatologic manifestation observed in both CD and UC. It is classified as an acute febrile neutrophilic dermatosis and it is characterized by the abrupt onset of painful and erythematous skin lesions associated with fever. In addition to IBD, Sweet's syndrome has been associated with a variety of systemic conditions, including malignancies [61]. Clinically it presents with a polymorphic skin eruption that may include small papules (bumps) or vesicles (blisters), flat patches, nodules, tender or papulosquamous lesions, or anular plaques (Figure 3). Lesions may range from isolated to widespread, and typically persist for several days to weeks. They most commonly affect the face, neck and upper extremities. Histopathological examination reveals neutrophilic infiltrate. Systemic symptoms frequently associated with Sweet's syndrome include fever, arthritis, and ocular manifestations, such as conjunctivitis. Its occurrence in the context of IBD usually correlates with intestinal disease activity but can occasionally precede the diagnosis of IBD. Notably, there has been a reported case linking the development of Sweet's syndrome to azathioprine treatment in a IBD patient [62]. The majority of cases respond well to topical or systemic corticosteroids, often resolving without residual scarring. In isolated reports, other treatments such as metronidazole have also shown effectiveness.

4.4. Metastatic Crohn's disease

Cutaneous metastatic CD is a rare manifestation, posing significant diagnostic and therapeutic challenges. Fewer than 100 cases have been described in the literature. It is characterized by granulomatous dermatitis affecting skin site anatomically distant from the gastrointestinal tract and separated by unaffected tissue (Figure 3). This distinguishes it from other cutaneous manifestations of CD, such as perianal or peristomal lesions, which result from direct contiguous extension of the intestinal inflammation to the skin [63].

Metastatic CD may precede the diagnosis of CD by months or even years. Notably, pediatric patients are more likely to present with cutaneous lesions in the absence of overt gastrointestinal symptoms [64]. Treatment remains largely unsatisfactory. A variety of therapeutic agents have been employed with variable success, including oral metronidazole, topical and systemic corticosteroids, azathioprine, cyclosporine, sulfasalazine, tetracyclines, topical or systemic tacrolimus, and biologic agents such as infliximab or adalimumab. Surgical treatment and oral zinc sulfate have also been reported as part of the available treatment options [65].

5. Oral EIMs

Oral manifestations are the second most common EIMs in IBD, with reported prevalence ranging from 0.7% to 37% in adults and from 7% to 23% in children, and reaching 41% in pediatric CD patients [66] (Table 3). Among patients presenting with EIMs as the first sign of IBD, 27.8% have oral involvement [40]. However, the reported prevalence of oral EIMs is highly variable, widely due to physician inexperience in recognizing these lesions, study heterogeneity, and lack of standardized classification [66]. Given the accessibility of the oral cavity for examination and biopsy, some authors recommend routine oral inspection in suspected IBD cases [67]. Oral lesions in IBD should be distinguished from primary gastrointestinal tract involvement, such as continuous CD [40]. According to the latest ECCO guidelines, they are classified as orofacial manifestations (oral aphthous ulcers, periodontitis, pyostomatitis vegetans, mucosal cobblestoning, and orofacial granulomatosis), and CD-specific oral conditions [6].

5.1. Orofacial manifestations

Oral aphthous ulcers, the most common of the oral manifestations in IBD (0.7–20% in adults and 3.2–41% in children) [66,68], present as small, painful ulcers with an erythematous halo, and require biopsy for diagnosis as they appear exactly like regular mouth aphthae [69] (Figure 3). Periodontitis, a chronic inflammatory condition, is highly prevalent in both adults and children, and may lead to bone and soft tissue destruction, and even tooth loss [40]. Both conditions are linked to active bowel disease and can occur either isolated or in the context of recurrent stomatitis, which may impair nutrition and growth in children [66]. They typically improve with systemic IBD treatment, with topical therapies (antiseptic mouthwashes and local steroids) as needed [40,69].

Pyostomatitis vegetans, a rare condition mainly seen in male adult and pediatric UC patients, presents with pustules on erythematous mucosa that necrotize and rupture, causing painful swallowing and difficult eating. Diagnosis is histological, showing acanthosis and intraepithelial and subepithelial abscesses [66]. It is related to active bowel disease and typically improves with IBD treatment, although local steroid treatment may be needed [67].

Mucosal cobblestoning is characterized by deep transverse and longitudinal ulcers separating intact mucosa; it occurs in 6–20% of pediatric and adult IBD patients [66] and topical steroids are recommended for treatment.

Orofacial granulomatosis (OFG), most commonly associated with CD, manifests as recurrent buccal swelling, angular cheilitis, gingival enlargements, oral ulcers, and occasionally facial paralysis and cervical lymphadenopathy, without systemic involvement. Cheilitis granulomatosa may precede CD diagnosis, particularly in pediatric patients with a family history of IBD [66,68]. Histological confirmation requires non-caseating granulomatous inflammation, and differential diagnosis includes sarcoidosis, tuberculosis and allergic conditions. Patients with OFG should be screened for IBD [66]. Treatment is nonspecific and includes corticosteroids, thiopurines, and anti-TNF alfa agents; cheiloplasty can be considered in severe cases.

5.2. CD-specific oral conditions

CD-specific oral conditions are specific lesions in which histology reflects gastrointestinal inflammation. They affect 5–15% of pediatric and 20–50% of adult CD patients, presenting with cheilitis, oral cobblestoning (different from that associated with UC, both histologically and in terms of correlation with disease activity), mucogengivitis, deep ulcers, mucosal tags, fissures, and stomatitis. The diagnosis requires biopsy: as

stated, histology reflects gastrointestinal inflammation. These lesions are related to intestinal disease activity and usually resolve with IBD control, although corticosteroids may be necessary for painful ulcers [67,69].

6. Ocular EIMs

Several studies have examined the prevalence and characteristics of ocular EIMs in IBD patients with different prevalence rates, depending on study methodology and population [70]. The reported prevalence ranges between 4 and 12% in adult IBD patients [71]. There are few data about pediatric patients. Ottaviano et al. conducted a meta-analysis of pediatric patients, reporting an ocular EIMs prevalence of 0.62% – 1.8%, which is therefore inferior to that reported in adults [72]. However, in pediatric IBD patients prevalence of asymptomatic uveitis detected by routine screening was up to 23% in one study [73]; pediatric patients with asymptomatic uveitis were more commonly adolescent males with CD and with colonic involvement [72]. The lower prevalence in the pediatric population could therefore be explained by the possibility of asymptomatic uveitis and the short duration of intestinal disease. On the contrary, a recent study offering ophthalmologic evaluation as a routine screening in a pediatric IBD center, reported a significantly lower prevalence of 1% [74].

Ocular EIMs are more frequent in CD than UC, although some studies in adult patients show conflicting results [70]. This trend has also been reported for pediatric uveitis [72].

Ocular EIMs may precede or follow the diagnosis of IBD. Ben-Tov et al. analyzed a pediatric IBD cohort and found that 3% of children developed ocular EIMs, with 31% experiencing ocular symptoms prior to IBD diagnosis, suggesting that ocular involvement may be used as an early clinical sign of IBD in pediatric patients [75]. It is well-established that ocular manifestations are more likely to coexist with other EIMs, particularly with arthritis and EN [76].

The most common ocular involvements include episcleritis, uveitis and scleritis, although rarer manifestations such as keratopathy, peripheral ulcerative keratitis, retinitis, retinal vasculitis, and orbital inflammation may also occur [77]. Pediatric patients primarily present uveitis [72], while in adult patients episcleritis and uveitis are the most frequent manifestations, with prevalence rates respectively of 2–4% and 1.7–5% [78].

Episcleritis usually is a mild condition, characterized by inflammation of the episcleral vascular layer between the sclera and the conjunctiva. It is usually associated with active IBD, and there is no difference of frequency in CD e UC [79]. Symptoms include mild-to-moderate discomfort in one or both eyes, painless episcleral injection that blanches with topical application of phenylephrine, without loss of vision.

Uveitis is the inflammation of the middle layer of the eye, including the ciliary body, choroid, and iris. It is more frequent in CD than UC and usually occurs independently of bowel inflammation [79]. The most common manifestation is anterior uveitis (iritis) [80], characterized by pain, eye redness, photophobia, and blurred vision.

Scleritis, an inflammation of the sclera, is a rare condition affecting less than 1% of IBD patients [81]. Early recognition is crucial as it can lead to vision loss and serious complications. Symptoms include redness of the sclera, tenderness, blurred vision and severe pain, particularly at night.

The treatment of ocular manifestations is primarily guided by the severity of ocular inflammation. Mild manifestations such as episcleritis are usually treated with artificial tears, topical NSAIDs or topical corticosteroids, and IBD activity control. Scleritis necessitates an immediate treatment with oral NSAIDs and oral corticosteroids to prevent complications; steroid-sparing agents, including immunosuppressant or biologics, may be used in refractory cases or when corticosteroid response is incomplete [82].

Uveitis, especially in severe cases, requires systemic steroids, immunosuppressant (e.g. methotrexate, azathioprine) or biological therapies. If advanced treatment is needed, a multidisciplinary discussion between a gastroenterologist and an ophthalmologist is crucial to develop a personalized management of both conditions. Biological agents such as TNF alfa inhibitors (adalimumab, infliximab) are highly effective to treat ocular manifestations [83]. There are emerging data for agents with different mechanisms of action including Ustekinumab and JAK inhibitors in refractory cases, but data are limited [84]. The diagnosis of ocular EIMs requires multidisciplinary management as ophthalmological complications in IBD could be underrecognized. However, there are currently no sufficient data to recommend an ophthalmological screening protocol. In patients with IBD, particularly those with CD, ocular symptoms should not be underestimated and IBD patients should be encouraged to report them. Given the possibility of these symptoms being either an EIM or a side effect of ongoing therapy, referral to an ophthalmologist is warranted.

7. Hepatobiliary EIMs

Many hepatobiliary manifestations have been linked to IBD, including primary sclerosing cholangitis (PSC), hepatitis, cirrhosis, cholelithiasis, and fatty liver. Among them, a preeminent position is occupied by PSC, due to its high prevalence and impact on prognosis.

PSC is a rare disease but has a strong association with IBD, most often UC. It has a dramatic impact on morbidity and mortality and to date the only curative therapy is liver transplantation (LT).

The pediatric form of PSC is less frequent, tends to manifest a more inflammatory phenotype that may respond to immunosuppressants, and exhibits a more favorable course.

7.1. PSC pathogenesis and epidemiology

PSC is a rare and multifactorial chronic liver disease characterized by progressive inflammation and fibrosis of the intra and extrahepatic bile ducts. This pathological process leads to bile duct strictures, impaired bile flow, and ultimately liver damage [85]. The disease develops in patients with a genetic predisposition to autoimmune conditions, although the precise environmental or immunological triggers responsible for initiating and sustaining the disease remain largely unidentified.

A particularly notable aspect of PSC is its strong and well-documented link to IBD [86]. The interplay between the gut and liver is increasingly recognized as central to the disease pathogenesis. From a hepatological viewpoint, approximately

80% of individuals diagnosed with PSC also suffer from IBD, most often UC. Conversely, from a gastroenterological standpoint, PSC represents the most frequent hepatobiliary complication in IBD patients, affecting roughly 8% of this population. Prevalence of PSC varies from 0.1 to 16 per 100.000 in adults, and 0.1–0.2 in pediatric individuals respectively; incidence varies between 0.4 and 2 and around 0.2 per 100.000 inhabitants per year in adults and pediatric patients respectively [87–89].

PSC typically manifests in young adults, with a median age at diagnosis of 30 years. The most common form of coexisting IBD is UC, in 80–90% of cases [87,90] which often exhibits distinctive features in PSC patients. These include rectal sparing, predominant inflammation in the right colon, and the presence of backwash ileitis, findings that deviate from the classical presentation of UC in the general population [91].

7.2. PSC clinical picture

Clinically, PSC presentation is widely heterogeneous. Many patients exhibit varying degrees of cholestasis, which can manifest through elevated liver enzymes, jaundice, and in some cases, pruritus, which can be severe and significantly impacts quality of life. Hepatitis-like features may also be present, contributing to the overall hepatic dysfunction seen in these patients.

The diagnostic gold standard for PSC is Magnetic Resonance Cholangiopancreatography (MRCP), which allows noninvasive visualization of the biliary tree [92]. The hallmark radiological findings include multifocal strictures and segmental dilatations of the intrahepatic and/or extrahepatic bile ducts, producing a characteristic 'beaded' appearance (Figure 4).

Establishing a diagnosis of PSC carries significant prognostic implications, particularly in the context of concomitant IBD. Patients with PSC-IBD have a 5 to 10-fold increased risk of colorectal cancer (CRC) compared to patients with IBD alone [85,88]; risk for hepatobiliary cancers (HBC) is also increased, with the diagnosis of cholangiocarcinoma (CCA) in up to 10% of PSC patients [90].

Consequently, evidence-based surveillance strategies have been implemented. Current guidelines recommend annual colonoscopy for CRC screening and annual abdominal ultrasound to monitor for gallbladder polyps or other lesions, which may harbor malignant potential [92]. Although MRCP has not proven effective as a screening tool for CCA [93], it remains the gold standard for initial diagnosis and longitudinal monitoring of disease progression in PSC patients.

To date, no pharmacological treatments have received regulatory approval for PSC, and LT remains the only definitive curative option for 5–15% of PSC patients [94]. LT is indicated in cases of advanced biliary fibrosis leading to cirrhosis and portal hypertension related complications, or in patients experiencing recurrent cholangitis unresponsive to medical, endoscopic, or interventional radiological therapies. However, disease recurrence after transplantation (rPSC) is a notable concern, occurring in 16 up to 30% of patients within five years post-transplant [92,94]. Of note, the active IBD in the peri-transplant setting is a risk factor for rPSC. Given the complexity and high-risk nature of the disease, it is essential that patients with PSC are referred to specialized centers. These centers can offer access to clinical trials, advanced diagnostics, and off-label treatment options, with the goal of enhancing disease management, and, importantly, generating evidence to support the development and approval of new treatments.

7.3. Pediatric-onset PSC

Although PSC is predominantly diagnosed in adults, a small proportion of cases occur in pediatric patients, offering valuable insights into the natural history and developmental trajectory of the disease [95]. The pediatric form of PSC differs significantly from the adult presentation. As in adults, PSC often coexists with IBD in children; but when hepatic involvement is observed, the disease tends to exhibit a more inflammatory phenotype that may respond to immunosuppressive treatments, rather than the fibrotic characteristics commonly seen in adults. As a result, diagnoses of PSC with overlapping features of autoimmune hepatitis (AIH) are more frequently made in the pediatric population with a reported prevalence of 25–72% compared to 7–14% in adults [96,97]. This overlapping presentation has led to the description of a distinct clinical entity known as autoimmune sclerosing cholangitis (ASC), which was considered the pediatric counterpart of adult-onset PSC. However, emerging pathogenetic theories suggest that ASC and PSC may not represent fundamentally different diseases, but rather age-related variations of the same underlying condition [98]. In this view, the inflammatory phenotype seen in children may evolve over time into the more fibrotic, progressive form characteristic of adult PSC [98,99].

Prognostically, pediatric patients generally experience a favorable disease course, with a reported transplant-free survival rate of approximately 91% at 10 years following diagnosis of PSC [100] and children with IBD-PSC have better clinical outcomes than have been reported previously, particularly if diagnosed early [97].

Despite this encouraging outcome, children with PSC-IBD face a significantly elevated cumulative risk of developing CRC, considering that pediatric UC patients have a 35-fold-increased lifetime risk compared to the general population [101], with PSC being the highest risk factor for early death in pediatric patients with IBD [102]. This underscores the importance of early and rigorous surveillance strategies in pediatric patients to mitigate long-term oncologic complications.

8. Conclusion

EIMs are a frequent manifestation of IBD, occurring in up to 50% of IBD patients. They can manifest either before or after the IBD diagnosis and they add a significant burden in terms of morbidity and long-term disability.

In pediatric patients, EIMs seem to be even more common, though data are quite limited. Their patterns and progression in some reports show marked differences compared to adult-onset IBD. In particular EIMs seem to manifest earlier in the disease course compared to the adult-

onset population, thus underscoring their diagnostic significance. On the other hand, very few data are available concerning the course of EIMs in pediatric patients.

Increased awareness and recognition of EIMs can help clinicians in reducing the diagnostic delay of IBD and improving comprehensive treatment, thus decreasing the disease burden both in terms of morbidity and mortality.

9. Expert Opinion

This narrative review emphasizes that extraintestinal manifestations (EIMs) are commonly observed in both adult and pediatric patients with inflammatory bowel disease (IBD). The clinical significance of EIMs lies in their considerable impact on patients' quality of life, functional capacity, and long-term disability.

While some EIMs have been extensively studied and characterized in adult cohorts, there are limited data available for other EIMs, particularly in the pediatric population. Nonetheless, the reported pooled prevalence varies significantly among studies, primarily due to different definitions of EIMs and varying study designs.

In recent years, it has become clear that the term 'classical EIMs' should be used to describe inflammatory processes that arise distant from the gut but share a common pathological pathway with the intestinal disease. Clarifying a correct definition of EIMs is crucial for generating accurate and interpretable evidence.

Educating clinicians to actively screen for the presence of EIMs and enhance their recognition capabilities is of paramount importance. EIMs may precede, coincide with, or follow the onset of the intestinal disease, creating diagnostic challenges and often leading to delayed recognition and treatment. Increased awareness of EIMs can also assist in diagnosing IBD itself when they manifest before intestinal symptoms, and this is particularly true for pediatric patients.

Given these premises, future research should aim to refine the estimation of both pooled and specific prevalence of EIMs, through the application of standardized and rigorous definition, especially within pediatric cohorts, where current data remain limited. Another key area of investigation should be the characterization of clinical patterns and disease course of EIMs, including their association with distinct IBD phenotypes and their potential prognostic implication.

From a therapeutic perspective, it is well recognized that the presence of EIMs makes the management of IBD even more challenging, requiring a multidisciplinary approach. EIMs exemplify the challenges and opportunities of managing complex, multisystemic diseases. Increased awareness of EIMs would facilitate timely and comprehensive treatment of both intestinal and extra-intestinal diseases.

Recent advances in understanding pathophysiological mechanisms have paved the way for novel therapeutic approaches targeting specific molecular pathways involved in both intestinal and extra-intestinal inflammation, thus offering the opportunity for a tailored therapeutic approach. However, there remains a substantial lack of evidence regarding the efficacy and effectiveness of medical therapies for IBD on EIMs. Indeed, despite the rapid increase in the therapeutic armamentarium for IBD, very few trials report data on EIMs and most evidence is generated from small retrospective studies. This should definitely be an area of future research.

Moreover, it is not unusual that EIMs show a treatment response which is at least in part divergent from that of the intestinal disease. Therefore, future research should also focus on the development of integrated multisystemic activity measure allowing a comprehensive treatment response assessment and the application of precision medicine.

It should also be investigated whether the widespread use of newer targeted therapies could potentially intercept or modify the onset or clinical presentation of IBD and EIMs.

Prioritizing collaborative research and fostering partnerships among gastroenterologists, pediatric specialists, and other relevant disciplines will be essential to bridge current knowledge gaps and to promote the development of multidisciplinary care models. Such integrated approaches are key to improving clinical outcomes and the overall quality of care for individuals affected by EIMs.

Funding

This paper was not funded.

Declaration of interest

C. Viganò received consultancy and lecture fees from: AbbVie, Galapagos, Janssen-Cilag, Johnson & Johnson, Pfizer, Takeda, Celltrion, Alfasigma, Eli Lilly, and research grant from Celltrion and Pfizer. L. Pirola received consultancy fee from Abbvie and lecture fees from Takeda, Janssen-Cilag, and Pfizer. S. Orlando received consultancy fees from Abbvie and Janssen-Cilag. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

All listed authors fully adhere to the authorship criteria established by the International Committee of Medical Journal Editors (ICMJE). Each author has made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data; has participated in drafting or critically revising the manuscript for important intellectual content; has given final approval of the version to be published; and agrees to be accountable for all aspects of the work in ensuring its accuracy and integrity.

AI-based tools and technologies declaration

During the preparation of this work the authors used ChatGPT version 3 in order to ensure adherence to English standards and the guidelines of the journal. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

ORCID

Francesco Medici http://orcid.org/0000-0001-9865-5088

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Vavricka SR, Schoepfer A, Scharl M, et al. Extraintestinal manifestations of inflammatory bowel disease. Inflamm Bowel Dis. 2015;21(8):1982–1992. doi: 10.1097/MIB.0000000000000392
2. Rosen MJ, Dhawan A, Saeed SA. Inflammatory bowel disease in children and adolescents. JAMA Pediatr. 2015;169(11):1053–1060. doi: 10.1001/jamapediatrics.2015.1982
3. Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology. 2008;135(4):1114–1122. doi: 10.1053/j.gastro.2008.06.081
4. Guariso G, Gasparetto M, Visonà Dalla Pozza L, et al. Inflammatory bowel disease developing in paediatric and adult age. J Pediatr Gastroenterol Nutr. 2010;51(6):698–707. doi: 10.1097/MPG.0b013e3181da1db8
   - **A comparative study of pediatric and adult-onset IBD, focusing also on EIMs.**
5. Greuter T, Bertoldo F, Rechner R, et al. Extraintestinal manifestations of pediatric inflammatory bowel disease: prevalence, presentation, and anti-TNF treatment. J Pediatr Gastroenterol Nutr. 2017;65(2):200–206. doi: 10.1097/MPG.0000000000001455
6. Gordon H, Burisch J, Ellul P, et al. Ecco guidelines on extraintestinal manifestations in inflammatory bowel disease. J Crohns Colitis. 2024;18(1):1–37. doi: 10.1093/ecco-jcc/jjad108
   - **An excellent and comprehensive overview of the current state of the art regarding the various EIMs associated with IBD.**
7. Hedin CRH, Vavricka SR, Stagg AJ, et al. The pathogenesis of extraintestinal manifestations: implications for IBD research, diagnosis, and therapy. J Crohns Colitis. 2019;13(5):541–554. doi: 10.1093/ecco-jcc/jjy191
8. Cavalli CAM, Gabbiadini R, Dal Buono A, et al. Lung involvement in inflammatory bowel diseases: shared pathways and unwanted connections. J Clin Med. 2023;12(19):6419. doi: 10.3390/jcm12196419
9. Bigeh A, Sanchez A, Maestas C, et al. Inflammatory bowel disease and the risk for cardiovascular disease: does all inflammation lead to heart disease? Trends Cardiovasc Med. 2020;30(8):463–469. doi: 10.1016/j.tcm.2019.10.001
10. Massironi S, Mulinacci G, Gallo C, et al. The oft-overlooked cardiovascular complications of inflammatory bowel disease. Expert Rev Clin Immunol. 2023;19(4):375–391. doi: 10.1080/1744666X.2023.2174971
11. van Hoeve K, Hoffman I. Renal manifestations in inflammatory bowel disease: a systematic review. J Gastroenterol. 2022;57(9):619–629. doi: 10.1007/s00535-022-01903-6
12. Massironi S, Fanetti I, Viganò C, et al. Systematic review-pancreatic involvement in inflammatory bowel disease. Aliment Pharmacol Ther. 2022;55(12):1478–1491. doi: 10.1111/apt.16949
13. Bernstein CN, Blanchard JF, Rawsthorne P, et al. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. Am J Gastroenterol. 2001;96(4):1116–1122. doi: 10.1111/j.1572-0241.2001.03756.x
14. Vavricka SR, Gubler M, Gantenbein C, et al. Anti-TNF treatment for extraintestinal manifestations of inflammatory bowel disease in the Swiss IBD cohort study. Inflamm Bowel Dis. 2017;23(7):1174–1181. doi: 10.1097/MIB.0000000000001109
15. Grossman BJ, DeBenedetti CD. Extraintestinal manifestations of chronic inflammatory bowel disease in children. Proc Inst Med Chic. 1970;28(3):119.
16. Cohen S, Padlipsky J, Yerushalmy-Feler A. Risk factors associated with extraintestinal manifestations in children with inflammatory bowel disease. Eur J Clin Nutr. 2020;74(5):691–697. doi: 10.1038/s41430-019-0490-1
17. Jose FA, Garnett EA, Vittinghoff E, et al. Development of extraintestinal manifestations in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis. 2009;15(1):63–68. doi: 10.1002/ibd.20604
   - **An interesting study on pediatric EIMs based on a large registry.**
18. Dotson JL, Hyams JS, Markowitz J, et al. Extraintestinal manifestations of pediatric inflammatory bowel disease and their relation to disease type and severity. J Pediatr Gastroenterol Nutr. 2010;51(2):140–145. doi: 10.1097/MPG.0b013e3181ca4db4
   - **An interesting study on pediatric EIMs based on a large registry.**
19. Chaparro M, Garre A, Ricart E, et al. Differences between childhood- and adulthood-onset inflammatory bowel disease: the CAROUSEL study from GETECCU. Aliment Pharmacol Ther. 2019;49(4):419–428. doi: 10.1111/apt.15114
20. Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol. 2011;106(1):110–119. doi: 10.1038/ajg.2010.343
21. Isene R, Bernklev T, Høie O, et al. Extraintestinal manifestations in Crohn's disease and ulcerative colitis: results from a prospective, population-based European inception cohort. Scand J Gastroenterol. 2015;50(3):300–305. doi: 10.3109/00365521.2014.991752
22. Gower-Rousseau C, Dauchet L, Vernier-Massouille G, et al. The natural history of pediatric ulcerative colitis: a population-based cohort study. Am J Gastroenterol. 2009;104(8):2080–2088. doi: 10.1038/ajg.2009.177
23. Fragoulis GE, Liava C, Daoussis D, et al. Inflammatory bowel diseases and spondyloarthropathies: from pathogenesis to treatment. World J Gastroenterol. 2019;25(18):2162–2176. doi: 10.3748/wjg.v25.i18.2162
24. Gracey E, Vereecke L, McGovern D, et al. Revisiting the gut-joint axis: links between gut inflammation and spondyloarthritis. Nat Rev Rheumatol. 2020;16(8):415–433. doi: 10.1038/s41584-020-0454-9
   - **A clear explanation of the complexity of the gut-joint axis, including its clinical implications, and treatment options.**
25. Cypers H, Varkas G, Beeckman S, et al. Elevated calprotectin levels reveal bowel inflammation in spondyloarthritis. Ann Rheum Dis. 2016;75(7):1357–1362. doi: 10.1136/annrheumdis-2015-208025
26. Orchard TR, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. Gut. 1998;42(3):387–391. doi: 10.1136/gut.42.3.387
27. Rudwaleit M, van der Heijde D, Landewé R, et al. The development of assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68(6):777–783. doi: 10.1136/ard.2009.108233
28. Rudwaleit M, van der Heijde D, Landewé R, et al. The assessment of SpondyloArthritis international Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011;70(1):25–31. doi: 10.1136/ard.2010.133645
29. Falloon K, Dossaji Z, Mude P, et al. Diagnosis of inflammatory bowel disease-associated peripheral arthritis: a systematic review. Inflamm Bowel Dis. 2025;31(3):812–842. doi: 10.1093/ibd/izae114
30. Di Carlo M, Luchetti MM, Benfaremo D, et al. The detection of arthritis in inflammatory bowel diseases (DETAIL) questionnaire: development and preliminary testing of a new tool to screen patients with inflammatory bowel disease for the presence of spondyloarthritis. Clin Rheumatol. 2018;37(4):1037–1044. doi: 10.1007/s10067-017-3937-6
31. Variola A, Zanolin ME, Cipriano G, et al. The IBIS-Q [IBd identification of spondyloarthritis questionnaire]: a novel tool to detect both axial and peripheral arthritis in inflammatory bowel disease patients. J Crohns Colitis. 2020;14(12):1680–1686. doi: 10.1093/ecco-jcc/jjaa096

32. Schwartzman M, Ermann J, Kuhn KA, et al. Spondyloarthritis in inflammatory bowel disease cohorts: systematic literature review and critical appraisal of study designs. RMD Open. 2022;8(1):e001777. doi: 10.1136/rmdopen-2021-001777
33. Hong SJ, Dalal RS, Kuhn KA, et al. Prevalence and risk factors of spondyloarthritis symptoms in a US-based multicenter cohort of patients with inflammatory bowel disease. Am J Gastroenterol. 2025. doi: 10.14309/ajg.0000000000003292
34. Ermann J, Hong SJ, Stahly A, et al. Frequency of spondyloarthritis symptoms among US patients with inflammatory bowel disease: a cross-sectional multi-center study. Arthritis Care Res (Hoboken). 2025;77(6):777–784. doi: 10.1002/acr.25493
35. Cardile S, Romano C. Current issues in pediatric inflammatory bowel disease-associated arthropathies. World J Gastroenterol. 2014;20(1):45–52. doi: 10.3748/wjg.v20.i1.45
36. McErlane F, Gillon C, Irvine T, et al. Arthropathy in paediatric inflammatory bowel disease: a cross-sectional observational study. Rheumatology (Oxford). 2008;47(8):1251–1252. doi: 10.1093/rheumatology/ken217
37. Scarallo L, Maniscalco V, Marrani E, et al. Prevalence and outcomes of arthritis in pediatric IBD: a multicenter study from the Italian Society of Pediatric Gastroenterology Hepatology and Nutrition. Dig Liver Dis. 2025;57(3):716–723. doi: 10.1016/j.dld.2024.12.010
38. Karreman MC, Luime JJ, Hazes JMW, et al. The prevalence and incidence of axial and peripheral spondyloarthritis in inflammatory bowel disease: a systematic review and meta-analysis. J Crohns Colitis. 2017;11(5):631–642. doi: 10.1093/ecco-jcc/jjw199
39. Lakatos L, Pandur T, David G, et al. Association of extraintestinal manifestations of inflammatory bowel disease in a province of western Hungary with disease phenotype: results of a 25-year follow-up study. World J Gastroenterol. 2003;9(10):2300–2307. doi: 10.3748/wjg.v9.i10.2300
40. Rogler G, Singh A, Kavanaugh A, et al. Extraintestinal manifestations of inflammatory bowel disease: current concepts, treatment, and implications for disease management. Gastroenterology. 2021;161(4):1118–1132. doi: 10.1053/j.gastro.2021.07.042
41. Horton DB, Sherry DD, Baldassano RN, et al. Enthesitis is an extra-intestinal manifestation of pediatric inflammatory bowel disease. Ann Paediatr Rheumatol. 2012;1(4):214. doi: 10.5455/apr.102920121510
42. Derfalvi B, Boros KK, Szabo D, et al. Joint involvement, disease activity and quality of life in pediatric Crohn's disease – a cross-sectional study. Pediatr Rheumatol Online J. 2022;20(1):6. doi: 10.1186/s12969-022-00664-z
43. He R, Zhao S, Cui M, et al. Cutaneous manifestations of inflammatory bowel disease: basic characteristics, therapy, and potential pathophysiological associations. Front Immunol. 2023;14:1234535. doi: 10.3389/fimmu.2023.1234535
44. Yüksel İ, Başar Ö, Ataseven H, et al. Mucocutaneous manifestations in inflammatory bowel disease. Inflamm Bowel Dis. 2009;15(4):546–550. doi: 10.1002/ibd.20807
45. Freeman HJ. Erythema nodosum and pyoderma gangrenosum in 50 patients with Crohn's disease. Can J Gastroenterol. 2005;19(10):603–606. doi: 10.1155/2005/323914
46. Antonelli E, Bassotti G, Tramontana M, et al. Dermatological manifestations in inflammatory bowel diseases. JCM. 2021;10(2):364. doi: 10.3390/jcm10020364
47. Pagani K, Lukac D, Bhukhan A, et al. Cutaneous manifestations of inflammatory bowel disease: a basic overview. Am J Clin Dermatol. 2022;23(4):481–497. doi: 10.1007/s40257-022-00689-w
48. Timani S, Mutasim DF. Skin manifestations of inflammatory bowel disease. Clin Dermatol. 2008;26(3):265–273. doi: 10.1016/j.clindermatol.2007.10.018
49. Greuter T, Navarini A, Vavricka SR. Skin manifestations of inflammatory bowel disease. Clinic Rev Allerg Immunol. 2017;53(3):413–427. doi: 10.1007/s12016-017-8617-4
50. Kilic Y, Kamal S, Jaffar F, et al. Prevalence of extraintestinal manifestations in inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis. 2024;30(2):230–239. doi: 10.1093/ibd/izad061

•• **The first meta-analysis evaluating the pooled prevalence of joint, ocular, and skin EIMs in IBD, based on a large sample size.**

51. Biemans VBC, van der Meulen - de Jong AE, van der Woude CJ, et al. Ustekinumab for Crohn's disease: results of the ICC registry, a nationwide prospective observational cohort study. J Crohn's Colitis. 2020;14(1):33–45. doi: 10.1093/ecco-jcc/jjz119
52. States V, O'Brien S, Rai JP, et al. Pyoderma gangrenosum in inflammatory bowel disease: a systematic review and meta-analysis. Dig Dis Sci. 2020;65(9):2675–2685. doi: 10.1007/s10620-019-05999-4
53. Orchard T. Extraintestinal complications of inflammatory bowel disease. Curr Gastroenterol Rep. 2003;5(6):512–517. doi: 10.1007/s11894-003-0042-6
54. Rothfuss KS, Stange EF, Herrlinger KR. Extraintestinal manifestations and complications in inflammatory bowel diseases. WJG. 2006;12(30):4819. doi: 10.3748/wjg.v12.i30.4819
55. Callen JP. Pyoderma gangrenosum. Lancet. 1998;351(9102):581–585. doi: 10.1016/S0140-6736(97)10187-8
56. Hughes AP. Clinical features and treatment of peristomal pyoderma gangrenosum. JAMA. 2000;284(12):1546. doi: 10.1001/jama.284.12.1546
57. Gellert A, Green ES, Beck ER, et al. Erythema nodosum progressing to pyoderma gangrenosum as a complication of Crohn's disease. Postgrad Med J. 1983;59(698):791–793. doi: 10.1136/pgmj.59.698.791
58. Powell RJ, Holbrook MR, Stevens A. Pyoderma gangrenosum and its treatment. Lancet. 1997;350(9093):1720–1721. doi: 10.1016/S0140-6736(05)63568-4
59. Wollina U, Haroske G. Pyoderma gangraenosum. Curr Opin Rheumatol. 2011;23(1):50–56. doi: 10.1097/BOR.0b013e328341152f
60. de risi-Pugliese T, Seksik P, Bouaziz J-D, et al. Ustekinumab treatment for neutrophilic dermatoses associated with Crohn's disease: a multicenter retrospective study. J Am Acad Dermatol. 2019;80(3):781–784. doi: 10.1016/j.jaad.2018.06.065
61. Arun Kumar AU, Elsayed ME, Alghali A, et al. Sweet syndrome: a rare feature of ANCA-associated vasculitis or unusual consequence of azathioprine-induced treatment. Allergy Asthma Clin Immunol. 2018;14(1):46. doi: 10.1186/s13223-018-0265-6
62. Treton X, Joly F, Alves A, et al. Azathioprine-induced sweet's syndrome in Crohn's disease: inflammatory bowel diseases. Inflamm Bowel Dis. 2008;14(12):1757–1758. doi: 10.1002/ibd.20518
63. Ickrath F, Stoevesandt J, Schulmeyer L, et al. Metastatic Crohn's disease: an underestimated entity. J Deutsche Derma Gesell. 2021;19(7):973–982. doi: 10.1111/ddg.14447
64. Schneider SL, Foster K, Patel D, et al. Cutaneous manifestations of metastatic Crohn's disease. Pediatr Dermatol. 2018;35(5):566–574. doi: 10.1111/pde.13565
65. Palamaras I, El-Jabbour J, Pietropaolo N, et al. Metastatic Crohn's disease: a review. Acad Dermatol Venereol. 2008;22(9):1033–1043. doi: 10.1111/j.1468-3083.2008.02741.x
66. Lauritano D, Boccalari E, Di Stasio D, et al. Prevalence of oral lesions and correlation with intestinal symptoms of inflammatory bowel disease: a systematic review. Diagnostics (Basel). 2019;9(3):77. doi: 10.3390/diagnostics9030077

•• **A detailed presentation of oral extraintestinal manifestations in IBD patients, highlighting the clinical relevance of timely diagnosis.**

67. Shazib MA, Byrd KM, Gulati AS. Diagnosis and management of oral extraintestinal manifestations of pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2022;74(1):7–12. doi: 10.1097/MPG.0000000000003302
68. Jang H-J, Kang B, Choe B-H. The difference in extraintestinal manifestations of inflammatory bowel disease for children and adults. Transl Pediatr. 2019;8(1):4–15. doi: 10.21037/tp.2019.01.06
69. Muhvić-Urek M, Tomac-Stojmenović M, Mijandrušić-Sinčić B. Oral pathology in inflammatory bowel disease. World J Gastroenterol. 2016;22(25):5655–5667. doi: 10.3748/wjg.v22.i25.5655
70. Cuny A, Guillo L, Baumann C, et al. Ocular manifestations in patients with inflammatory bowel disease in the biologics era. J Clin Med. 2022;11(15):4538. doi: 10.3390/jcm11154538

71. Shah J, Shah A, Hassman L, et al. Ocular manifestations of inflammatory bowel disease. Inflamm Bowel Dis. 2021;27(11):1832–1838. doi: 10.1093/ibd/izaa359
72. Ottaviano G, Salvatore S, Salvatoni A, et al. Ocular manifestations of paediatric inflammatory bowel disease: a systematic review and meta-analysis. J Crohns Colitis. 2018;12(7):870–879. doi: 10.1093/ecco-jcc/jjy029
73. Daum F, Gould HB, Gold D, et al. Asymptomatic transient uveitis in children with inflammatory bowel disease. Am J Dis Child. 1979;133(2):170–171. doi: 10.1001/archpedi.1979.02130020062012
74. Naviglio S, Parentin F, Nider S, et al. Ocular involvement in children with inflammatory bowel disease. Inflamm Bowel Dis. 2017;23(6):986–990. doi: 10.1097/MIB.0000000000001079
75. Ben-Tov A, Achler T, Patalon T, et al. The prevalence and characteristics of inflammatory bowel disease-related ocular involvement in children. Inflamm Bowel Dis. 2025;31(5):1256–1262. doi: 10.1093/ibd/izae160
76. Alizadeh M, Motwani K, Siaton BC, et al. Factors associated with extraintestinal manifestations of inflammatory bowel disease in SPARC-IBD. Inflamm Bowel Dis. 2024;30(11):2027–2036. doi: 10.1093/ibd/izad280
77. Pytrus W, Akutko K, Pytrus T, et al. A review of ophthalmic complications in inflammatory bowel diseases. J Clin Med. 2022;11(24):7457. doi: 10.3390/jcm11247457
78. Jansen FM, Vavricka SR, den Broeder AA, et al. Clinical management of the most common extra-intestinal manifestations in patients with inflammatory bowel disease focused on the joints, skin and eyes. Ueg J. 2020;8(9):1031–1044. doi: 10.1177/2050640620958902
79. Li J-X, Chiang C-C, Chen S-N, et al. The prevalence of ocular extra-intestinal manifestations in adults inflammatory bowel disease: a systematic review and meta-analysis. Int J Environ Res Public Health. 2022;19(23):15683. doi: 10.3390/ijerph192315683
80. Biedermann L, Renz L, Fournier N, et al. Uveitis manifestations in patients of the Swiss Inflammatory Bowel Disease Cohort Study. Therap Adv Gastroenterol. 2019;12:1756284819865142. doi: 10.1177/1756284819865142
81. Rodriguez Duran M, Gad O. Ocular extraintestinal manifestations and treatments in patients with inflammatory bowel disease. Front Ophthalmol. 2023;3:1257068. doi: 10.3389/fopht.2023.1257068
82. Abdel-Aty A, Gupta A, Del Priore L, et al. Management of noninfectious scleritis. Ther Adv Ophthalmol. 2022;14:25158414211070879. doi: 10.1177/25158414211070879
83. Jaffe GJ, Dick AD, Brézin AP, et al. Adalimumab in patients with active noninfectious uveitis. N Engl J Med. 2016;375(10):932–943. doi: 10.1056/NEJMoa1509852
84. Mugheddu C, Atzori L, Del Piano M, et al. Successful ustekinumab treatment of noninfectious uveitis and concomitant severe psoriatic arthritis and plaque psoriasis. Dermatol Ther. 2017;30(5):e12527. doi: 10.1111/dth.12527
85. Chapman MH, Thorburn D, Hirschfield GM, et al. British Society of Gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis. Gut. 2019;68(8):1356–1378. doi: 10.1136/gutjnl-2018-317993
86. van Munster KN, Bergquist A, Ponsioen CY. Inflammatory bowel disease and primary sclerosing cholangitis: one disease or two? J Hepatol. 2024;80(1):155–168. doi: 10.1016/j.jhep.2023.09.031
87. Karlsen TH, Folseraas T, Thorburn D, et al. Primary sclerosing cholangitis – a comprehensive review. J Hepatol. 2017;67(6):1298–1323. doi: 10.1016/j.jhep.2017.07.022
88. Boonstra K, Weersma RK, van Erpecum KJ, et al. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis: boonstra et al. Hepatology. 2013;58(6):2045–2055. doi: 10.1002/hep.26565
89. Kaplan GG, Laupland KB, Butzner D. The burden of large and small duct primary sclerosing cholangitis in adults and children: a population-based analysis. Am J Gastroenterol. 2007;102(5):1042–1049. doi: 10.1111/j.1572-0241.2007.01103.x
90. Weismüller TJ, Trivedi PJ, Bergquist A, et al. Patient age, sex, and inflammatory bowel disease phenotype associate with course of primary sclerosing cholangitis. Gastroenterology. 2017;152(8):1975–1984.e8. doi: 10.1053/j.gastro.2017.02.038
91. Ji S-G, Juran BD, Mucha S, et al. Genome-wide association study of primary sclerosing cholangitis identifies new risk loci and quantifies the genetic relationship with inflammatory bowel disease. Nat Genet. 2017;49(2):269–273. doi: 10.1038/ng.3745
92. Chazouilleres O, Beuers U, Bergquist A, et al. EASL clinical practice guidelines on sclerosing cholangitis. J Hepatol. 2022;77(3):761–806. doi: 10.1016/j.jhep.2022.05.011
93. Villard C, Friis-Liby I, Rorsman F, et al. Prospective surveillance for cholangiocarcinoma in unselected individuals with primary sclerosing cholangitis. J Hepatol. 2023;78(3):604–613. doi: 10.1016/j.jhep.2022.11.011
94. Leung KK, Deeb M, Fischer SE, et al. Recurrent primary sclerosing cholangitis: current understanding, management, and future directions. Semin Liver Dis. 2021;41(3):409–420. doi: 10.1055/s-0041-1730950
95. Deneau M, Jensen MK, Holmen J, et al. Primary sclerosing cholangitis, autoimmune hepatitis, and overlap in Utah children: epidemiology and natural history. Hepatology. 2013;58(4):1392–1400. doi: 10.1002/hep.26454
96. Adike A, Carey EJ, Lindor KD. Primary sclerosing cholangitis in children versus adults: lessons for the clinic. Expert Rev Gastroenterol Hepatol. 2018;12(10):1025–1032. doi: 10.1080/17474124.2018.1521719
97. Hensel KO, Kyrana E, Hadzic N, et al. Sclerosing cholangitis in pediatric inflammatory bowel disease: early diagnosis and management affect clinical outcome. J Pediatr. 2021;238:50–56.e3. doi: 10.1016/j.jpeds.2021.07.047
98. Ricciuto A, Kamath BM, Hirschfield GM, et al. Primary sclerosing cholangitis and overlap features of autoimmune hepatitis: a coming of age or an age-ist problem? J Hepatol. 2023;79(2):567–575. doi: 10.1016/j.jhep.2023.02.030
99. Kellermayer R, Carbone M, Horvath TD, et al. Identifying a therapeutic window of opportunity for people living with primary sclerosing cholangitis: embryology and the overlap of inflammatory bowel disease with immune-mediated liver injury. Hepatology. 2024. doi: 10.1097/HEP.0000000000000926
•• **An interesting contribution exploring the shared pathogenesis of immune-mediated liver injury and IBD, with focus on pediatric onset.**
100. Jerregård Skarby A, Casswall T, Bergquist A, et al. Good long-term outcomes of primary sclerosing cholangitis in childhood. JHEP Rep. 2024;6(8):101123. doi: 10.1016/j.jhepr.2024.101123
101. Olén O, Askling J, Sachs MC, et al. Childhood onset inflammatory bowel disease and risk of cancer: a Swedish nationwide cohort study 1964–2014. BMJ. 2017;358:j3951. doi: 10.1136/bmj.j3951
102. Olén O, Askling J, Sachs MC, et al. Increased mortality of patients with childhood-onset inflammatory bowel diseases, compared with the general population. Gastroenterology. 2019;156(3):614–622. doi: 10.1053/j.gastro.2018.10.028