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ECCO Guideline/Consensus Paper

ECCO Guidelines on Extraintestinal Manifestations in Inflammatory Bowel Disease

Hannah Gordon,[a] Johan Burisch,[b] Pierre Ellul,[c] Konstantinos Karmiris,[d] Konstantinos Katsanos,[e] Mariangela Allocca,[f] Giorgos Bamias,[g] Manuel Barreiro-de Acosta,[h] Tasanee Braithwaite,[i] Thomas Greuter,[j] Catherine Harwood,[k] Pascal Juillerat,[l] Triana Lobaton,[m] Ulf Müller-Ladner,[n] Nurulamin Noor,[o] Gianluca Pellino,[p] Edoardo Savarino,[q] Christoph Schramm,[r] Alessandra Soriano,[s] Jürgen Michael Stein,[t] Mathieu Uzzan,[u] Patrick F. van Rheenen,[v] Stephan R. Vavricka,[w] Maurizio Vecchi,[x] Stephane Zuily,[y] Torsten Kucharzik[z]

[a]Department of Gastroenterology, Barts Health NHS Trust, London, Centre for Immunobiology, Blizard Institute, Faculty of Medicine, Barts & The London Medical School, Queen Mary University of London, UK
[b]Gastrounit, medical division, Hvidovre Hospital, University of Copenhagen, Copenhagen Center for Inflammatory Bowel Disease in Children, Adolescents and Adults, Hvidovre Hospital, University of Copenhagen, Denmark
[c]Department of Medicine, Division of Gastroenterology, Mater Dei Hospital, Msida, Malta
[d]Department of Gastroenterology, Venizeleio General Hospital, Heraklion, Greece
[e]Department of Gastroenterology and Hepatology, Division of Internal Medicine, University and Medical School of Ioannina, Ioannina, Greece
[f]Department of Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele, Milan, Italy
[g]GI Unit, 3rd Academic Department of Internal Medicine, National and Kapodistrian University of Athens, Sotiria Hospital, Athens, Greece
[h]University Hospital Santiago De Compostela CHUS, Department of Gastroenterology – IBD Unit, Santiago De Compostela, Spain
[i]School of Immunology and Microbiology, King's College London, The Medical Eye Unit, Guy's and St Thomas' Hospital NHS Foundation Trust, London, UK
[j]Division of Gastroenterology and Hepatology, GZO – Zurich Regional Health Center, Wetzikon, Division of Gastroenterology and Hepatology, University Hospital Lausanne – CHUV, Lausanne, Switzerland; Department of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland
[k]Centre for Cell Biology and Cutaneous Research, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London; Department of Dermatology, Royal London Hospital, Barts Health NHS Trust, London, UK
[l]Gastroenterology, Clinic for Visceral Surgery and Medicine, Bern University Hospital, Bern, Switzerland; Crohn and Colitis Center, Gastro-entérologie Beaulieu SA, Lausanne, Switzerland
[m]Department of Internal Medicine and Pediatrics, Ghent University, Ghent; Department of Gastroenterology, Ghent University Hospital, Ghent, Belgium
[n]Department of Rheumatology and Clinical Immunology, Campus Kerckhoff, Justus Liebig University Giessen, Bad Nauheim, Germany
[o]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[p]Vall d'Hebron University Hospital, Universitat Autonoma de Barcelona UAB, Barcelona, Spain; Department of Advanced Medical and Surgical Sciences, Università degli Studi della Campania 'Luigi Vanvitelli', Naples, Italy
[q]Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy; Gastroenterology Unit, Azienda Ospedale Università di Padova, Padua, Italy
[r]Department of Internal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Martin Zeitz Center for Rare Diseases, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Hamburg Center for Translational Immunology (HCTI), University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[s]Gastroenterology Division and IBD Center, Internal Medicine Department, Azienda Unità Sanitaria Locale – IRCCS, 42122 Reggio Emilia, Italy
[t]Interdisciplinary Crohn Colitis Centre Rhein-Main, Frankfurt/Main, Department of Gastroenterology and Clinical Nutrition, DGD Clinics Sachsenhausen, Frankfurt/Main, Germany
[u]Department of Gastroenterology, Hôpital Henri Mondor, APHP, Créteil, France
[v]Department of Paediatric Gastroenterology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands
[w]Department of Gastroenterology and Hepatology, University Hospital, Zurich, Switzerland
[x]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy
[y]Vascular Medicine Division and French Referral Center for Rare Auto-Immune Diseases, Université de Lorraine, INSERM, DCAC and CHRU-Nancy, Nancy, France
[z]Department of Gastroenterology, Lüneburg Hospital, University of Münster, Lüneburg, Germany

Corresponding author: Hannah Gordon, Department of Gastroenterology, Barts Health NHS Trust, London, UK; and Centre for Immunobiology, Blizard Institute, Faculty of Medicine, Barts & The London Medical School, Queen Mary University of London, UK. Email: hannahgordon@doctors.org.uk

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1. Introduction

This is the second European Crohn's and Colitis Organisation [ECCO] evidence-based consensus on extraintestinal manifestations [EIMs] of inflammatory bowel disease [IBD] and anaemia.[1] Up to 50% of patients with IBD will develop at least one EIM, which may impact each body system[2]; hence they are a source of considerable morbidity, or even mortality in the case of primary sclerosing cholangitis [PSC] or venous thromboembolic events [VTE]. Broadly, EIMs can be categorized as classical, arising from inflammatory pathology at distant sites, the consequences of systemic inflammation and treatment, or wider associations[3] [summarized in Figure 1]. The underlying pathophysiology of extraintestinal inflammation is not fully understood. Potential driving forces include extension of the immune-mediated response from the inflamed gut to other organs, with shifts in leukocyte trafficking,[4] changes to the intestinal microbiota,[5] and underlying predisposing genetic factors.[6] The systemic consequences of IBD lead to broader associations, including VTEs and anaemia. Whether these are strictly EIMs is of debate,[3] but they are included within this guideline as they incur a considerable health burden to patients with IBD.

This guideline was created according to ECCO's standardized methodology. A panel of 20 gastroenterologists was selected by the ECCO Guidelines Committee from a competitive pool of applicants. Two guidelines committee members, HG and TK, were selected as project coordinators. Participating experts were split into four working groups [WGs], and a leader was selected for each. Topics were determined by the project coordinators and WG leaders and split between the four groups. ECCO recognizes the need for a multidisciplinary approach when managing EIMs in IBD. As such, we included the following invited experts from other disciplines from project onset: CB [dermatology], UM-L [rheumatology], SZ [vascular medicine], CS [hepatology], and TH [ophthalmology].

For each topic, a clinically relevant question was formulated and used to define a Population, Intervention, and Comparator[s] of interest. These informed a systematic literature search, performed by a professional librarian using PubMed/Medline, Embase, and the Cochrane Central databases. Abstracts from each literature search were screened by two participants. Full texts of potentially relevant abstracts were retrieved and evaluated in full by both authors, who reached agreement on which papers were most relevant to inform the answer to the clinical question.

A consensus statement and supporting text were drafted for each topic and posted on an online guidelines platform. Two rounds of online voting and revisions took place. During the second voting round, ECCO national representatives also participated, although consensus was calculated from votes cast by members of this project alone. The participants met in October 2022 to discuss and vote on statements and recommendations. Consensus was defined as agreement by 80% or more of participants. Resulting consensus statements [with percentage agreement] are presented in this paper. We would like to stress the importance of interpreting each statement within the context of the supporting text provided, which is designed to add context and is of particular relevance given the paucity of data available for some of these critically important topics. The level of evidence supporting all statements is defined using the Oxford methodology.[7]

2. Haematological, cardiovascular, and respiratory disease

2.1 Venous thromboembolic events in IBD

2.1.1 Prevalence of thrombotic events

Statement 1

Thrombotic events are more than twice as frequent in patients with IBD than in the general population, with similar prevalence in ulcerative colitis and Crohn's disease [EL2]. The most important risk factors are active disease, hospitalization, and surgery [EL2] [consensus: 100%]

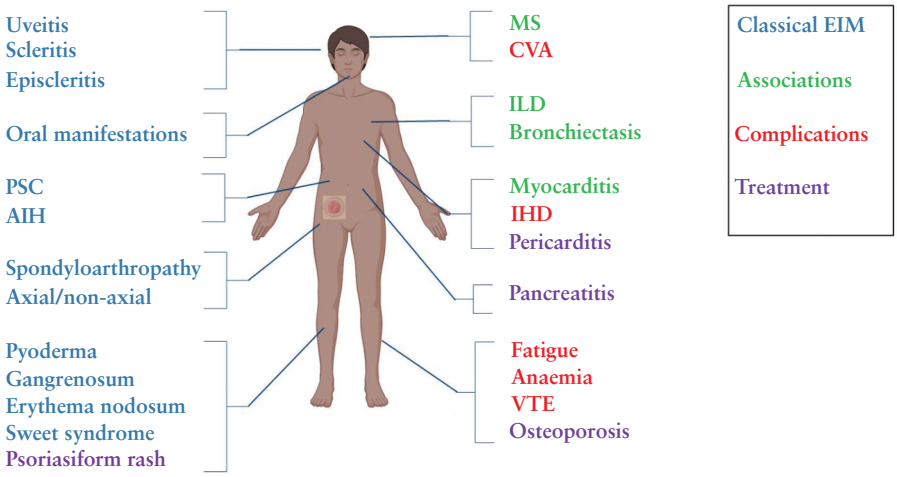

Figure 1. Extraintestinal manifestations in IBD [adapted from Hedin *et al* 2019, figure created with BioRender®]. Extraintestinal manifestations (EIMs) may occur in every system of the body and can broadly be classified as Classical: inflammatory process occurring at distant sites, Associations: associations with other immune-mediated disorders, and Complications: complications of systemic inflammation, Treatment: side effects of IBD therapy. PSC—primary sclerosis cholangitis, AIH—autoimmune hepatitis, MS—multiple sclerosis, CVA—cerebrovascular accident, ILD—interstitial lung disease, VTE—thromboembolic event.

The risk of VTE in IBD has been examined in three meta-analyses in the past decade[8–10] from a total of 18 studies.[11–28] The most recent assessment of relative risk [RR] for VTE in IBD was 2.03 (95% confidence interval [CI]: 1.72–2.39).[10] Recent population studies are consistent with these findings, despite increased treatment options for IBD adopted over the last 30 years.[29] Consistent with this, nationwide administrative data from the USA have suggested that rates of VTE are still increasing among hospitalized IBD patients.[30]

The studies included within the meta-analyses exhibited significant heterogeneity due to differences in study design, data source, type of thrombotic event, age, geographical area of origin, and concomitant risk factors. However, the overall thrombotic risk did not differ between genders or between patients with ulcerative colitis [UC] or Crohn's disease [CD]. Interestingly, the magnitude of increased risk is similar in Asian countries, although the prevalence of thrombotic events in the general population is lower compared to the Western population.[31]

Several studies of VTE identified both IBD-related and IBD-unrelated risk factors, the latter including previous history of thrombosis, pregnancy, and contraceptive use.[27,28] Thus, all factors should be considered to implement the best strategy to avoid thrombotic complications for the individual patient.

2.1.2 VTE prophylaxis

Statement 2.1

We recommend the use of a prophylactic dose of low-molecular-weight heparin or fondaparinux in patients with IBD during hospitalization for acute medical illness or major surgery [EL1]. IBD patients who underwent a major surgical procedure should receive a prophylactic dose of low-molecular-weight heparin until at least 3 weeks post-discharge [EL3]. For post-hospitalization patients or ambulatory patients with severe IBD flare, thromboprophylaxis can be considered [EL4] [consensus: 100%]

In line with haematological society guidelines and position papers,[32–34] we recommend pharmacological thromboprophylaxis as described in statement 2.1. In-hospital pharmacological thromboprophylaxis is associated with a 54% decreased risk of VTE in patients with IBD after discharge.[35] Therefore, all IBD patients hospitalized for any cause, including disease flare or surgery, should receive pharmacological thromboprophylaxis. A prophylactic dose of low-molecular-weight heparin [LMWH] is recommended over unfractionated heparin in acutely and critically ill patients.[34] Prophylactic doses of direct oral anticoagulants [DOACs] are approved after orthopaedic surgery but not in medically unwell patients due to an unfavourable benefit–risk ratio, as discussed in haematology society guidelines.[32]

For patients undergoing major surgery, we also concur with the stance advocated by haematology society guidelines, which recommend extended antithrombotic prophylaxis [3–6 weeks].[27,32–35] Benefit from extended prophylaxis after discharge in non-surgical hospitalized patients is unknown. Accordingly, extended prophylaxis is not currently routinely recommended.[34] However, following a study of 872 122 patients admitted with IBD, Faye *et al.* identified a post-discharge VTE risk of 0.13%, with most requiring readmission within 60 days of discharge.[36] Of this cohort, <10% had undergone surgery during their index presentation, thus suggesting a small yet significant risk of VTE in IBD patients following medical admission.[30] Risk factors identified included concurrent *Clostridium difficile* infection and length of stay. However, it is currently unknown whether extended prophylaxis following discharge significantly reduces risk.[36,37] Hence, further research is required to determine whether a subgroup of selected high-risk medically ill patients might benefit from prolonged VTE prophylaxis after discharge.[38]

Thromboprophylaxis during flares in the outpatient setting also has not been well studied. However, a large retrospective cohort study revealed that the risk of VTE at the time of flare when compared with matched healthy controls was greater in non-hospitalized patients than those admitted [RR: 15.8; 95% CI: 9.1–25.5 vs RR: 3.2; 95% CI: 1.7–6.30],[18] with most VTE events occurring in outpatients.[39] Given that the absolute risk of VTE remains low, initiation of pharmacological thromboprophylaxis in all ambulatory patients with active IBD is neither indicated nor cost-effective.[40] However, outpatients with a moderate or severe IBD flare and a high-risk profile for VTE either related to or unrelated to disease [Table 1][34] may benefit from pharmacological thromboprophylaxis until resolution of the flare. It is noteworthy that thromboprophylaxis with LMWH is not associated with an increased risk of major bleeding.[41,42]

2.1.3 Treatment of VTE

Statement 2.2

Administration of direct oral anticoagulants (DOACs) at therapeutic dose is recommended in patients with IBD presenting with an acute Venous Thromoboembolic Event (VTE) [EL1]. Risk factors for venous thromboembolism should be investigated to guide duration of anticoagulation [EL1] [consensus: 100%]

In patients eligible to receive therapeutic anticoagulation, we recommend treating VTE in IBD with DOACs at therapeutic dose.[45] DOACs are first-line therapy worldwide for the treatment of VTE[45] and should be considered in IBD accordingly. LMWH may serve as an alternative option during the acute phase.

DOACs may be of particular benefit in patients with portal or cerebral venous thrombosis and are associated with a four-fold greater chance of complete radiological resolution, better recanalization rate, and a favourable safety profile compared with warfarin.[40,46–48]

Risk stratification for VTE recurrence depends on the presence of a modifiable risk factor. Thus, risk factors for VTE should be investigated at the time of event onset to guide the optimal duration of anticoagulation. In case of an unprovoked VTE event, defined as a medical condition in the absence of a major risk factor for VTE, indefinite anticoagulation should be considered according to guidelines.[45] In case of a provoked VTE event triggered by a major risk factor for VTE, such as a recent surgical procedure, hospitalization, or an IBD flare, therapeutic anticoagulation can be stopped after 3 months. Control of IBD activity is crucial to prevent recurrence of VTE.

Table 1. Risk factors for VTEs[32,33,43–45]

Major risk factors	Minor/moderate risk factors
Active malignancy	Active IBD
Recent [within 3 months] surgery with general anaesthesia for >30 min	Older age [>65 years]
Immobilization [confinement to bed in hospital with bathroom privileges for an acute medical condition for >3 days]	Recent [within 3 months] surgery with general anaesthesia for <30 min
Trauma of lower limbs	Central venous catheter
High-risk thrombophilia [antiphospholipid syndrome, antithrombin deficiency]	Pregnancy and post-partum period [2 months after delivery]
	Oral contraceptives containing oestrogens
	Hormone-replacement therapy
	Lower-risk thrombophilia [factor V Leiden, protein C deficiency, protein S deficiency, polymorphism, prothrombin gene mutation, hyperhomocysteinaemia]
	Obesity
	Long-haul flights
	Autoimmune disease
	Blood transfusion and erythropoiesis-stimulating agents
	Congestive cardiac failure
	Respiratory failure
	Infection [specifically pneumonia, urinary tract infection, human immunodeficiency virus]

2.2 Cardiovascular disease in IBD

Statement 3

There is a marginally increased risk for cerebrovascular accidents [EL2], ischaemic heart disease [EL2], mesenteric ischaemia [EL4], atrial fibrillation [EL3], and heart failure [EL3] in patients with IBD compared with the general population, independent of IBD therapy. No difference was observed in cardiovascular mortality [EL2] [consensus: 94%]

Meta-analyses and population-based studies have shown that the risk for cerebrovascular accidents, ischaemic heart disease, mesenteric ischaemia, atrial fibrillation, and heart failure is higher in patients with CD or UC than in non-IBD matched controls. However, no difference was observed in cardiovascular mortality. The risk is more pronounced in patients with CD, females, and those of younger age. Results are conflicting regarding peripheral arterial disease. The risk for cardiac arrhythmias other than atrial fibrillation and conduction disorders was decreased in one study.[9,23,49–60]

The key studies outlining risks of cardiovascular and cerebrovascular disease in IBD are tabulated in the online supplementary material [Appendix 1]. A population study from Denmark demonstrated that IBD patients exhibited lower parameters for traditional risk factors for cardiovascular disease, including plasma total cholesterol, low-density lipoprotein cholesterol, and blood pressure when compared with the general population.[61] The same study revealed higher levels of C-reactive protein [CRP] in IBD patients, suggesting that increased cardiovascular risk may be driven by sustained systemic inflammation. A prospective follow-up of a UK bioresource also revealed elevated high-sensitivity CRP and disease severity to be predictive of future arterial adverse events.[62] A French nationwide cohort study demonstrated that patients with IBD treated with tumour necrosis factor-alpha [TNFα] antagonists had a decreased risk of acute arterial events (hazard ratio [HR]: 0.79; 95% CI: 0.66–0.95),[63] with subsequent analysis showing prior exposure to TNFα antagonists or thiopurines to be associated with reduced risk of recurrent arterial events.[64] Hence, uncontrolled inflammation in IBD is a potentially modifiable risk factor for cardiovascular disease.

2.3 Myocarditis and pericarditis

Statement 4

There is a small increased risk for developing myocarditis and pericarditis in patients with IBD, although the overall incidence of both in IBD is low [EL4] [consensus: 97%]

An increased risk of myocarditis and pericarditis exists across multiple immune-mediated inflammatory diseases, including IBD.[65] However, the absolute risk of developing myocarditis in IBD is low [8.3 per 100 000 patient-years in CD; 2.6 per 100 000 patient-years in UC].[66] Medications used to treat IBD have also been associated with myocarditis, including mesalazine[66–70] and TNFα antagonists.[71] Based on limited data, it remains difficult to determine whether the risk is driven by medications or IBD itself.

Pericarditis is also more likely to occur in patients with IBD compared to population controls.[72] Unlike myocarditis, pericarditis is almost universally driven by therapy, including TNFα antagonists,[73] with complete resolution after treatment withdrawal.[74–76]

2.4 Anaemia in IBD

2.4.1 Prevalence of anaemia

Statement 5.1

Anaemia is one of the most common EIMs of IBD. The World Health Organization definitions of anaemia are applicable to patients with IBD. Iron deficiency and anaemia of chronic disease are the most frequent types seen in IBD, either as sole conditions or in association with other micronutrient deficiencies [EL4] [consensus: 100%]

The World Health Organization [WHO] defines anaemia as a condition in which the number of red cells [and consequently their oxygen-carrying capacity] is insufficient to meet the body's physiological needs. In addition, WHO provides the following age- and gender-specific cut-offs for haemoglobin [Hb] concentration in anaemia: <130 g/L for adult men, <120 g/L for adult, non-pregnant women, and <110 g/L for children aged 6–59 months and increasing with age. Reports on the prevalence of anaemia in IBD are extremely variable [range 6–74%], probably due to heterogeneity of patient cohorts.[77–80] A meta-analysis revealed an overall prevalence of 27% in patients with CD and 21% in those with UC,[80] with the prevalence in children as high as 90% at diagnosis.[81,82]

The causes of anaemia in IBD are summarized in Table 2, with the two most frequent aetiologies being iron deficiency anaemia [IDA] and anaemia of chronic disease [ACD], frequently occurring in conjunction.

2.4.2 Determining the aetiology of anaemia

Statement 5.2

Patients with IBD should be regularly assessed for anaemia, due to its high prevalence and considerable impact on quality of life and comorbidity. Anaemia parameters should be evaluated every 6–12 months in patients in remission or with mild disease activity; patients with active disease should be monitored at least every 3 months [EL5]. In the presence of biochemical or clinical evidence of inflammation, the diagnostic criteria for anaemia of chronic disease (ACD) are serum ferritin >100 µg/L and transferrin saturation <16%. If the serum ferritin level is between 30 and 100 µg/L, a combination of true iron deficiency and ACD is likely [EL2] [Consensus: 100%]

Investigation of anaemia in IBD entails determining the aetiology, with the objective of identifying correctable factors and assessing disease activity. A normal mean corpuscular volume [MCV] does not exclude iron deficiency, since up to 40% of 'pure' IDA cases are normocytic. Conversely, the presence of microcytosis does not necessarily imply iron deficiency, since it can be induced by other types of anaemia and disease, such as ACD, sideroblastic anaemia, or thalassaemia, and indeed may also be affected by pre-analytical variables, including temperature and storage times.[84–87]

In clinical practice, iron status is frequently assessed with serum ferritin levels. However, serum ferritin is not only subject to gender differences but is also an acute-phase reactant and is thus prone to falsely elevated or normal levels in populations with inflammatory reactions, due to hepcidin-mediated iron sequestration. Therefore, the diagnostic work-up should include CRP and/or erythrocyte sedimentation rate [ESR] and transferrin saturation [TSAT], a marker of low iron availability for haematopoiesis that is less affected by inflammation.[88,89] TSAT < 16% can support the diagnosis of iron deficiency if the initial tests are inconclusive. However, diurnal fluctuations and clinical disorders, such as malnutrition and chronic disease, can also cause a decrease in transferrin synthesis and therefore increase TSAT.[90,91] Serum iron itself is not a useful parameter in the assessment of iron deficiency, other than to calculate TSAT.[90] In the presence of biochemical inflammation, the lower limit of ferritin consistent with normal iron stores should be increased to 100 µg/L; hypoferraemia should be considered likely if transferrin saturation is <16% and serum ferritin between 30 and 100 g/L. ACD is likely if serum ferritin is >100 µg/L and transferrin saturation <20%.[89,92,93]

Investigation of anaemia in IBD is summarized in Figure 2. Complete blood count with MCV, reticulocytes, serum ferritin, TSAT, CRP, vitamin B_{12}, and folate should be measured as part of the initial laboratory panel for anaemia investigation.[87,93] A more extensive workup includes serum concentrations of vitamin B_{12} [holotranscobalamin, HoloTC], haptoglobin, percentage of hypochromic erythrocytes [HYPO],[94,95] reticulocyte Hb content [CHr],[94–96] percentage of low Hb density [LHD],[97] zinc protoporphyrin [ZPP],[98,99] and soluble transferrin receptor [sTfR].[93,100] Mean CHr < 29 pg can support the diagnosis of iron deficiency, if the initial tests are inconclusive.[87] Low or 'normal' reticulocytes indicate an inability for a proper response to anaemia, due to deficiencies that result in an inappropriate erythropoiesis or primary bone marrow disease. Increased reticulocytes indicate increased red cell formation and therefore exclude such deficiencies.[93]

Table 2. Causes of IBD-related anaemia [adapted from Martin *et al.* [83]]

Very common	Iron deficiency anaemia Anaemia of chronic disease
Common	Cobalamin [vitamin B_{12}] deficiency Folate deficiency Drug-induced [sulfasalazine, 5-ASA, thiopurines, calcineurin inhibitors, JAK inhibitors]
Less common	Autoimmune haemolysis Myelodysplastic syndrome Aplastic anaemia Glucose-6-phosphate dehydrogenase deficiency
Rare	Vitamin D deficiency Vitamin A deficiency Vitamin B_6 deficiency Copper deficiency

5-ASA, 5-aminosalicylic acid; JAK, Janus kinase.

Statement 5.3

Patients at risk for vitamin B_{12} or folate deficiency, especially patients with small-bowel CD or resection and patients with macrocytosis, should have their serum levels of vitamin B_{12} and folate screened at least annually [EL4] [consensus: 95%]

Vitamin B_{12} and folate deficiency are common in IBD, particularly in CD with prior resections or small-bowel disease. As such, we recommend screening for deficiency at least annually.

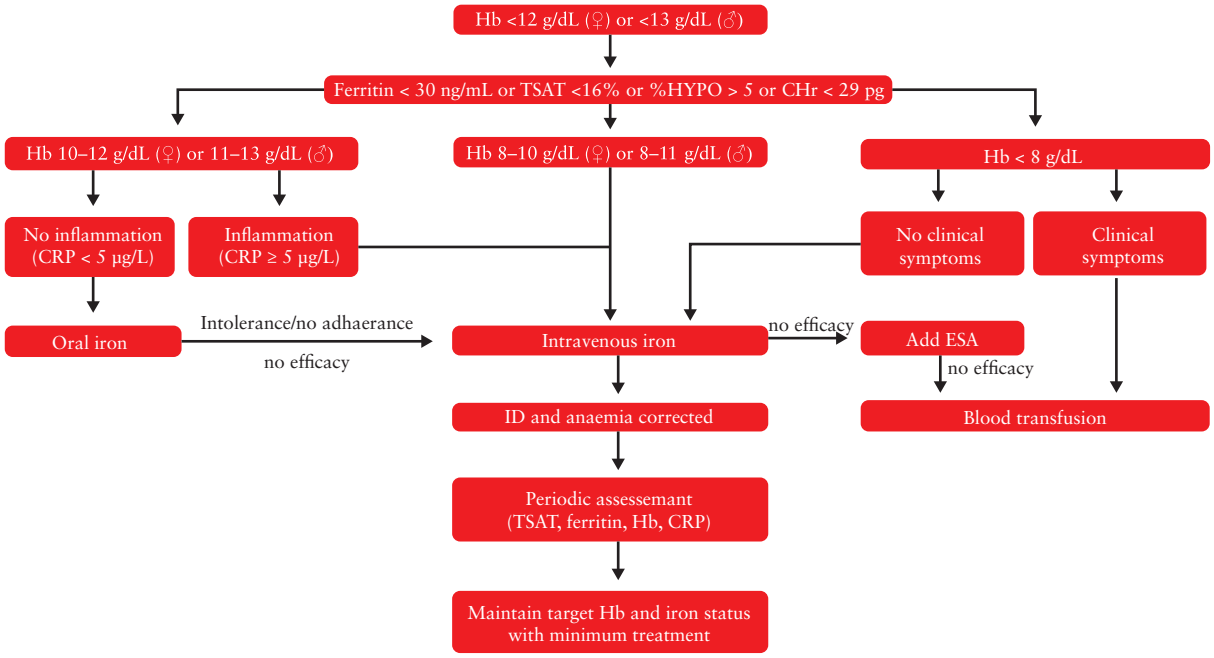

Figure 2. Workup for the management of iron deficiency anaemia in patients with IBD [adapted from Martin *et al.* 2017[83]. CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; TSAT, transferrin saturation.

Vitamin B_{12} deficiency occurs due to gastrointestinal disturbances or limited nutritional intake in patients with CD. This deficiency can lead to progressive and irreversible vision loss due to optic neuropathy and to neurological complications and memory impairment. It is also important not to overlook functional B_{12} deficiency at the tissue level, in which serum B_{12} is normal but homocysteine/methylmalonic acid [MMA] may be elevated and end-organ effects can develop. Monitoring of serum vitamin B_{12} levels and folate is indicated in all patients with macrocytic anaemia or anaemia unresponsive to iron supplementation, erythropoiesis-stimulating agents [ESAs], or both. Patients with small-bowel disease or prior resections require closer surveillance.

Replenishment adequacy should be assessed at least annually in all patients at risk or on treatment with cobalamin. Although there is no gold standard, diagnosis of vitamin B_{12} deficiency has traditionally been based on low serum vitamin B_{12} levels, usually <200 pg/mL [148 pmol/L]. However, a systematic review revealed that serum vitamin B_{12} levels in the range 200–400 pg [148–296 pmol/L] alone are not sufficient to diagnose deficiency in asymptomatic patients and that such a diagnosis must be verified by specific biomarkers. Plasma HoloTC [normal range: 20–50 pmol/L], plasma MMA [normal range: 0.210–0.470 µmol/L], or both may be considered as supplementary tests to determine biochemical cobalamin deficiency in the presence of clinical suspicion of deficiency but an indeterminate serum cobalamin level [200–400 pg; 148–296 pmol/L]. Although Schilling's test may be used to determine whether malabsorption is present, it is insufficient to quantify vitamin B_{12} deficiency.[101]

Serum folate concentration reflects recent folate status and intake. There is no clear consensus on the level of serum folate that indicates deficiency. The serum folate cut-off value has been set at 7 nmol/L, as the risk of megaloblastic anaemia greatly increases below this level. However, there is a sizeable 'indeterminate zone' [between ~7 and 10 nmol/L]. Therefore, a low serum folate level should be taken as suggestive of deficiency rather than as a highly sensitive diagnostic test.[102]

2.4.3 Management of anaemia

Statement 6.1

Patients with IBD and iron deficiency anaemia should receive iron supplementation to normalize haemoglobin levels and iron stores [EL1] [consensus: 97%]

It is important to treat anaemia in IBD with the aim of restoring Hb levels and iron stores to the normal range. Quality of life improves with correction, with improvement independent of clinical activity.[103–108] The development of anaemia from iron deficiency goes through an initial phase where body iron stores are depleted, resulting in hypoferritinaemia, but the Hb concentration is still within the normal range [non-anaemic iron deficiency; NAID]. Treatment of NAID is advisable, with clinical status and patient preference factoring into treatment decisions. The arguments for treating ferropaenia are based on the fact that iron is essential for all cells of the body and because symptoms of iron deficiency may occur without anaemia. Reduced physical performance and cognitive function, fatigue, headache, sleeping disorders, loss of libido, or restless-legs syndrome may be present without blunt anaemia and may improve upon iron supplementation.[109–114]

2.4.3.1 Iron replacement therapy

Statement 6.2

Intravenous iron is recommended as first-line treatment in patients with clinically active IBD, with previous intolerance to oral iron and in patients who need erythropoeitin stimulating agents [EL1]. Oral iron is recommended in patients with mild iron deficiency anaemia whose disease is clinically inactive [EL1] [consensus: 100%]

The usual treatment of IDA with oral iron has limitations in patients with IBD. A recently published Cochrane analysis showed that intravenous iron is associated with a more profound and rapid response with better tolerance than oral iron.[115] Thus, intravenous iron preparations are preferred for the correction of IBD-associated anaemia, as recommended in previous guidelines.[93] Intravenous iron is safe, effective, and well tolerated. Several intravenous iron preparations are currently available for the treatment of IDA. Such formulations differ by complex chemical synthesis and can be grouped into labile, semi-labile, and stable iron complexes.[116] Large trials have reported the efficacy of iron sucrose,[103,117–121] ferric carboxymaltose,[108,122–129] and ferric derisomaltose[129–132] in patients with IBD with small series also available for ferumoxytol.[133] Of note, ferric desiromaltose is also known as iron isomaltoside; iron isomaltoside is the generic name initially approved by the European Union, whereas ferric derisomaltose is the international nonproprietary name and United States adopted name.[134]

Erythropoietic agents should always be combined with intravenous iron supplementation, as functional iron deficiency, defined as an insufficient availability of iron for erythropoiesis despite normal body iron stores, is likely to develop.[135,136] Intravenous iron is also recommended in the perioperative setting, whereby a rapid response is required.

Severe infusion-related reactions are rare with modern intravenous iron preparations, although hypersensitivity reactions and infusion reactions are slightly more frequent than with oral iron, with an incidence of ~0.5%.[137] A test dose is required for iron dextran, as it carries a risk for anaphylaxis.[138–141] The risk of iron overload is low, although a TSAT of 50% and serum ferritin of 800 µg/L should be used as upper limits for guiding therapy. Intramuscular iron has been abandoned, as injections are painful and are associated with unacceptable side effects.[142]

Hypophosphataemia has been reported in association with all intravenous iron preparations; its prevalence is higher with ferric carboxymaltose [47%; 95% CI 36 - 58%] than with ferric derisomaltose [4%; 95% CI 2 - 5%].[143–145] However, the clinical importance of this outcome has not been established. Hypophosphataemia is related to the molecules complexed to the iron rather than to the iron itself. Most episodes are biochemically moderate [serum phosphate 0.32–0.64 mmol/L], asymptomatic, and resolve without intervention.[143,144] However, because of the albeit rare association with hypophosphataemic osteomalacia, the Medicines and Healthcare products Regulatory Agency recommends monitoring serum phosphate in patients with risk factors for hypophosphataemia and in those receiving long-term or multiple high-dose infusions of ferric carboxymaltose.[146]

When determining response to treatment, an increase of at least 2 g/dL within 4 weeks of treatment is an acceptable response rate.[147] The traditional Ganzoni formula captures the total body iron deficit in mg (body weight in kg × [target Hb – actual Hb in g/L] × 2.4 + 500).[148] However, the formula is inconvenient, may underestimate iron requirements,[122,130] and as such may be replaced by the scheme trialled by the FERGIcor trial, which demonstrated superior efficacy and a good safety profile.[123]

Mild anaemia has been defined by the WHO as Hb 11.0–11.9 g/dL in non-pregnant women and 11.0–12.9 g/L in men. Some comparative studies indicate that oral iron may be as effective as intravenous iron in correcting Hb in mild anaemia,[120,122,149–151] although a recent meta-analysis favours the intravenous route.[152] When the oral route is chosen, Hb response should be monitored over the first 4 weeks after supplementation initiation and treatment should be continued for a period of ~3 months after normalization of Hb to ensure adequate repletion of body iron stores.[153] Side effects from oral iron intake are dose dependent. Furthermore, absorption of iron from the gastrointestinal tract is limited,[154] and unabsorbed iron is exposed to the ulcerated intestinal surface and may alter intestinal microbiota.[155] Oral iron is known to increase hepcidin response, which may persist for 24 h [but subsides by 48 h]. Accordingly, there is some evidence to suggest one supplement of 60–120 mg iron given as ferrous salt as a single morning dose on alternate days to maximize absorption and minimize side effects.[156,157] Most studies on oral iron included patients treated with ferrous sulphate. However, studies of novel ferric formulations [such as ferric maltol] indicate satisfactory effectiveness with improved tolerance.[149–151,158]

2.4.3.2 *Monitoring treatment response*

Statement 6.3

Following treatment for iron deficiency anaemia, haemoglobin and ferritin should be monitored every 3–6 months for at least a year after deficiency restoration and every 6–12 months thereafter [EL4]. Re-treatment is recommended when ferritin drops <100 µg/L or haemoglobin <12 or 13 g/dL [depending on gender] [EL2]. The goal of preventive treatment is to maintain haemoglobin and serum ferritin levels within the normal range [EL3] [consensus: 95%]

After effective iron replenishment, anaemia recurs rapidly, typically by 50% within 10 months. Therefore, patients with IBD should be monitored for iron deficiency every 3–6 months using a combination of Hb, ferritin, TSAT, and CRP. Anaemia seems to recur frequently and rapidly after intravenous iron therapy. The speed of recurrence relates to the size of post-treatment iron stores [as reflected by serum ferritin].[131,159] Cost analysis favours a proactive approach to anaemia management in patients with prior IDA,[127,131] with the ferritin cut of off 100 µg/L an appropriate target in active disease.

2.4.3.3 *Erythropoiesis-stimulating agents*

Statement 6.4

Erytropoeitin stimulating agents can be considered in patients with inadequate response to intravenous iron with a target haemoglobin level not above 12 g/dL provided that IBD-related therapy has been optimized [EL5] [consensus: 95%]

Systemic inflammation exerts an inhibitory effect on erythropoietin response to anaemia and a direct inhibition on erythropoietic activity in the bone marrow. Inflammatory cytokines also reduce erythropoietin production and inhibit erythropoiesis.[160,161] Most patients with IBD respond to treatment with ESAs with an increase in Hb and improvement in quality of life.[162–165] In the setting of renal insufficiency or cancer, use of ESAs is limited to a maximal Hb value of 12 g/dL to minimize

the recognized risk of VTE and cardiovascular events. This should also be followed in IBD, where there are no studies evaluating long-term safety outcomes. Concomitant intravenous iron should be administered to prevent functional iron deficiency, and ferritin levels should be maintained at >200 µg/L [TSAT > 30%]. The erythroid response to intravenous iron can be verified by measuring the reticulocyte count after iron infusions. Patients with ACD exhibiting absence or partial response to TNFα antagonists and intravenous iron may also be considered for treatment with ESA.

2.4.3.4 Treatment of micronutrient deficiency

Randomized controlled trials and observational studies are lacking regarding parenteral administration of vitamin B_{12} and folate. An expert consensus recommended parenteral treatment with intramuscular hydroxocobalamin as the intervention of choice to replace vitamin B_{12}.[166] The standard initial regimen for patients without neurological involvement is 1000 µg intramuscularly three times a week for 2 weeks. If there are neurological symptoms, then 1000 µg intramuscularly on alternate days should be continued for up to 3 weeks or until there is no further improvement, followed by maintenance treatment.[166] Oral treatment [50 µg cyanocobalamin daily for 4 weeks] may be considered in patients with UC with mild or subclinical deficiency.[166]

The dosing scheme for folate-deficient megaloblastic anaemia [due to dietary insufficiency, pregnancy, or antiepileptics] is 5 mg folate daily for 4 months, except in pregnancy where it is continued until term, and up to 15 mg. When treating folate deficiency without anaemia, doses of 0.4–0.8 mg are typically required.[166] If there is concomitant vitamin B_{12} and folate deficiency, vitamin B_{12} must be started first to avoid precipitating sub-acute combined degeneration of the spinal cord.[167,168]

2.4.3.5 Blood transfusion

Blood transfusion is rarely required for the treatment of IDA because most patients with chronically developing anaemia adapt to the resulting physiological stress, and parenteral iron reliably produces a clinically meaningful Hb response within a week. Current policies restrict blood transfusion to specific clinical scenarios, including anaemia with haemodynamic instability, severe acute anaemia, presence of risk factors or warning signs of life-threatening cardiovascular disease, and failure of all other treatments.[169–171] Transfusion should be followed by adequate iron replacement, because a unit of packed red cells contains insufficient iron to replenish iron stores in severe IDA.

2.5 Lung disease [excluding pulmonary embolism]

Statement 7

There is an increased risk of bronchiectasis, interstitial lung disease, and granulomatous lung disease in patients with IBD [EL4] [consensus: 95%]

There is a broad spectrum of pulmonary disorders that are associated with IBD, including bronchiectasis, interstitial lung disease, and granulomatous lung disease.[172–175] Conflicting data exist for some other pulmonary conditions, such as asthma, with some studies suggesting that it may be associated with an increased[176,177] or decreased[178] risk of IBD. Clinical presentations of pulmonary disease in IBD are variable, with some patients asymptomatic and others having significant morbidity or even mortality. Although historical data have suggested that abnormalities in pulmonary function testing may be common, the actual prevalence of respiratory pathologies in patients with IBD remains relatively unknown.

A nationwide study demonstrated a higher incidence of idiopathic pulmonary fibrosis in patients with IBD compared with matched controls [HR 1.62; 95% CI 1.20–2.20, $p = 0.003$].[175] In addition, treatments for IBD, such as mesalazine[179] and TNFα antagonists,[180] are associated with pulmonary manifestations. Therefore, it may be difficult to determine whether a pulmonary manifestation is due to medications treating IBD, IBD itself, or a combination. Currently, there is insufficient evidence to support routine screening for pulmonary manifestations in IBD.[181]

3. Hepatobiliary manifestations of IBD

3.1 Investigation of liver disease

Statement 8

Alanine aminotransferase, alkaline phosphatase, γ-glutamyltransferase and total serum bilirubin should be determined in the treatment-naive patient with suspected IBD, and then at 6-month intervals throughout follow-up [EL4] [consensus: 97%]

A heterogenous group of hepatobiliary conditions can occur in IBD, ranging from a transient liver test abnormality [LTA] to life-threatening liver failure.[182] LTAs may already be present at IBD diagnosis or develop later. LTAs may be silent or appear in combination with non-specific symptoms, such as fatigue, nausea, and anorexia. Adult patients with IBD have an estimated risk of 5% of developing an immune-related liver disease, including PSC, autoimmune hepatitis [AIH], or both, with incidence more common in children.[183] Non-alcoholic fatty liver disease [NAFLD] is also a very common cause of disturbed liver function in IBD. A meta-analysis revealed that one-third of all IBD patients have NAFLD, a prevalence two-fold greater than that of healthy controls.[184] In addition, most drugs used to treat IBD have the potential to cause liver injury.[185]

A basic panel of liver tests, which includes alanine aminotransferase, alkaline phosphatase, γ-glutamyltransferase, and total serum bilirubin should be performed on the treatment-naive patient with suspected IBD and then repeated periodically throughout follow-up. For the majority of patients, this would entail 6-monthly monitoring, although in patients in long-term remission off therapy or on 5-aminosalicylates only, this interval could be extended to 12 months. Grading of liver test elevation is useful to determine the timing of the next diagnostic step [Table 3]. Mild incidental elevations [Table 3] typically require repeat testing in 1 month, with further evaluation if anomalies persist. If elevations are moderate or marked, investigation of aetiology should begin immediately.

When ascertaining the aetiology of abnormal liver function tests in IBD, diagnostic workup entails a combination of serological and radiological investigations and, on occasion, liver biopsy [Table 4].

3.2 Primary sclerosing cholangitis

3.2.1 Prevalence and diagnosis of PSC

Statement 9

Patients with IBD, especially with UC, are at increased risk of PSC. The prevalence of PSC in patients with IBD ranges from 2 to 8%. In IBD patients with persistent elevation of cholestatic liver enzymes, and symptoms of cholestasis, such as pruritus or prominent perihilar lymphadenopathy, PSC should be investigated with high-quality magnetic resonance cholangiopancreatography [EL2] [consensus: 100%]

PSC is a chronic cholestatic liver disease characterized by inflammation and fibrosis of the bile ducts and confers a significant risk of end-stage liver disease, malignancy, and mortality.[188] There is a high geographical variability in incidence and prevalence; in Northern Europe, the incidence of PSC reaches 1.58 and prevalence is 32/100 000 per population, with numbers increasing in recent years.[189–192] PSC is considerably more common in IBD than in the general population. A population-based Danish study showed PSC to have the highest odds ratio [OR] of all EIMs in both UC [OR: 189.5; 95% CI: 47.0–763.4] and CD [OR: 68.8%; 95% CI: 9.4–502.6].[193] The prevalence of PSC in IBD was estimated at 2.16% in a meta-analysis, with higher prevalence in UC compared with CD.[192,194] In the Swiss IBD cohort, PSC prevalence was 4% in UC and 0.6% in CD. Radiological screening of IBD patients for PSC using magnetic resonance cholangiopancreatography [MRCP] increased the frequency from 2.2% to 8.1%.[195] Risk factors for PSC are UC, male gender, pancolitis, non-smoking, and prior appendicectomy.[196]

Repeatedly elevated cholestatic liver enzymes should prompt diagnostic workup for PSC. However, liver enzymes, including alkaline phosphatase levels, may be normal in PSC,[197] and imaging signs such as periportal lymphadenopathy or enlarged gallbladder volume are also suggestive of PSC.[198]

MRCP is the method of choice to diagnose PSC. High-quality MRI is essential to capture early bile-duct pathology. Standards for performing and reporting of MRI findings have been published by the International PSC Study Group.[199,200] Liver biopsy should be performed on patients in whom markedly elevated transaminases, serum IgG levels, or both raise suspicion of additional features of AIH and in those with suspected small-duct PSC, defined by a normal cholangiogram.

It is important to diagnose PSC even in asymptomatic patients with IBD, as the presence of PSC increases mortality up to four-fold in population-based studies.[189,201,202] Mortality risk is higher in adult PSC patients <40 years as compared to older adults, although overall disease course is similar between children and adults.[203,204] PSC may progress to cirrhosis and end-stage liver disease within 12–20 years and thus represents an important indication for liver transplantation.[205] Additionally, PSC greatly increases the risk of hepatobiliary and colorectal cancer, with an HR of 2.4 for developing colorectal cancer (CRC), and up to 400-fold increased risk of cholangiocarcinoma compared with the general population.[202] Recommendations for malignancy screening are outlined in the recently published second ECCO Malignancy in IBD Guidelines.[206] A more detailed PSC overview is provided in the European Association for the Study of the Liver [EASL] Clinical Practice Guidelines on Sclerosing Cholangitis.[207]

3.2.2 Medical management of PSC in adults with IBD

Statement 10

Ursodeoxycholic acid may improve liver biochemistry in patients with PSC but has no demonstrated impact on disease progression [EL1] [consensus: 100%]

Although several drugs have been evaluated for the treatment of PSC, none have shown a benefit in slowing progression. Ursodeoxycholic acid [UDCA] [15–20 mg/kg/day] improves liver biochemistry but does not improve fatigue, pruritus, risk of cholangiocarcinoma, or mortality.[208,209] The role of UDCA on the risk of CRC development remains controversial. In some studies, a medium–low dose [<25 mg/kg/day] was associated with a reduced risk of neoplasia.[210,211] In other studies, a higher dose was associated with a higher risk[212] and more adverse events,[213] while other studies showed no difference.[213,214]

Vedolizumab has been evaluated in several retrospective studies. A clear benefit in PSC has not yet been demonstrated.[215–218] Similarly, adalimumab and infliximab have no influence on biochemical response in PSC.[219] Antibiotics and antifibrotics also have no demonstrated benefit.[220] Bezafibrate may be considered for the management of pruritus.[221]

In patients with the PSC/AIH variant, corticosteroids, immunosuppressants, or both can be considered.[222]

3.2.3 Hepatologist involvement and referral to transplant centres in PSC

Statement 11

Patients with PSC-IBD should be referred to a hepatologist with expertise in PSC at diagnosis, and thereafter joint care should continue [EL5] [consensus: 100%]

As discussed above, there is currently no effective therapy for PSC. A population-based study from the Netherlands

Table 3. Grading of liver test elevations[186]

Grading of elevation	Alanine aminotransferase (ALT)	Alkaline phosphatase (ALP)	γ-Glutamyltransferase (GGT)	Total serum bilirubin (TSB)	Timing of aetiology screen
Mild	>1–3× ULN	>1–2.5× ULN	>1–2.5× ULN	>1–1.5× ULN	Delay 1 month
Moderate	3–5× ULN	2.5–5× ULN	2.5–5× ULN	1.5–3× ULN	Immediately
Marked	>5× ULN	>5× ULN	>5× ULN	>3× ULN	Immediately

ULN, upper limit of normal.

Table 4. Suspected aetiology and first-line diagnostic workup for patients with IBD and abnormal liver function tests [adapted from van Rheenen][187]

Causes	Recommended tests
Autoimmune hepatitis [AIH]	Immunoglobulin G Autoantibodies [anti-smooth muscle, anti-nuclear, anti-soluble liver antigen, and anti-liver-kidney-microsome] Liver histology [interface hepatitis]
Primary sclerosing cholangitis [PSC]	MR cholangiopancreatography
PSC with autoimmune features	Autoantibodies [anti-smooth muscle, anti-nuclear, anti-soluble liver antigen, and anti-liver-kidney-microsome] Immunoglobulin G Magnetic resonance [MR] cholangiopancreatography Liver histology [interface hepatitis and bile-duct involvement]
Primary biliary cholangitis	Autoantibodies [anti-mitochondrial, anti-nuclear] Serum lipids [cholesterol, HDL, LDL, VLDL] MR cholangiopancreatography Liver histology
Viral hepatitis	Hepatitis A [IgM] Hepatitis B [HBsAg, anti-HBc IgM, anti-HBs, Hep B DNA] Hepatitis C [Anti-HCV, HCV RNA] Hepatitis E [IgM, HEV RNA] Cytomegalovirus [IgM, CMV-DNA] Epstein–Barr virus [IgM, EBV-DNA] Herpes simplex virus [HSV-1 DNA and HSV-2 DNA] Parvovirus [IgM]
Thiopurines, infliximab	Exclude other causes of liver injury Rechallenge [Do liver enzymes normalize?] Consider rechallenge [Recurrence on re-exposure?]; usually not done due to risk of inducing an even more severe reaction
Hepatic steatosis caused by obesity	Body mass index [BMI], ultrasound
Hepatic steatosis caused by starvation	BMI, ultrasound
Bile stones	Ultrasound
Choledochal malformation	Ultrasound, MR cholangiopancreatography
Portal or hepatic vein thrombosis	Doppler-ultrasound
Coeliac disease	tTG-IgA, total serum IgA
Wilson disease	Blood markers [ceruloplasmin, free copper, Coomb's test] Urine [24-h copper excretion] Liver biopsy [copper content] Ophthalmology [Kayser–Fleischer rings]
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin in serum
Hereditary haemochromatosis	Alpha-1-antitrypsin phenotyping Genetic testing [SERPINA1 variants] Ferritin, transferrin saturation

showed that 50% of patients require liver transplantation 15–20 years after PSC diagnosis.[205] In specialized hepatology centres, transplant-free survival is shorter [10–15 years] due to a different case mix.[223] As such, we strongly recommend that all patients with newly diagnosed PSC-IBD are referred to a hepatologist with expertise in PSC. Thereafter, joint care should continue to ensure timely identification of patients who should be listed for liver transplantation.

Traditionally, the Model for End-Stage Liver Disease [MELD] score is used to prioritize patients for liver transplantation. Apart from the MELD score, which is a proxy for the severity of hepatic dysfunction, there may be additional indications for transplant assessment in patients with PSC.[224] These additional indications include recurrent bacterial cholangitis, severe weight loss, relevant bile-duct strictures, intractable pruritis, and perihilar cholangiocarcinoma; the last of these warrants exploration of neoadjuvant chemoradiation and transplantation.

3.3 Autoimmune hepatitis and overlap syndrome

Statement 12

The prevalence of AIH in adult patients with IBD is less than 0.5%, with higher rates in children and adolescents [EL2] [consensus: 100%]

In people with AIH and IBD, the presence of additional sclerosing cholangitis should be investigated using high-quality MRCP [EL3] [consensus: 84%]

For the maintenance of remission in people with IBD and AIH, thiopurines should be considered as first-line treatment [EL2] [consensus: 85%]

AIH and IBD have a bidirectional association. In adolescents with IBD, the OR for AIH was 8 in patients with UC and 4 in patients with CD.[225] A Danish population-based study also confirmed a significant association with UC but not CD.[193] Furthermore, population-based studies of AIH revealed

that 2–7% have a concurrent diagnosis of PSC.[226] AIH/PSC overlap is common, with up to 10% of adult AIH patients exhibiting concurrent features of PSC.[227]

AIH presentation varies from insidious and asymptomatic elevation of liver enzymes to fulminant liver failure. In general, AIH diagnosis requires the exclusion of other causes of elevated liver enzymes. Elevation of serum transaminases, selective elevation of serum IgG levels, non-organ-specific autoantibodies, and a typical or compatible liver histology are hallmarks of AIH diagnosis.[227–229] The diagnostic scoring system typically used to diagnose AIH is based upon autoantibodies, IgG, exclusion of viral hepatitis, and histology.[230,231] However, this test has not been validated in the IBD population, where autoantibodies are frequently detected in IBD and in both AIH and PSC, rendering them less diagnostically useful.[232] When AIH is suspected, MRCP should be considered, especially in children and adolescents where there is a frequent occurrence of PSC/AIH overlap syndrome, also termed variant syndrome or autoimmune sclerosing cholangitis (ASC).[227,233,234]

We recommend management of AIH in IBD as per EASL guidelines.[227] For induction of remission, prednisolone/prednisone is recommended, although budesonide can be considered in patients without cirrhosis.[227,235] For the maintenance of remission, azathioprine is the standard treatment for AIH, usually started after 2 weeks, following biochemical response. In patients who are already receiving alternative immunosuppressive therapy for IBD, a switch to or additional treatment with thiopurines should be considered. Mycophenolate or mercaptopurine are second-line treatment options[227,236] and infliximab may be effective, even in refractory disease.[237] Maintenance therapy for AIH should be continued for at least 2 years with the patient in remission before treatment withdrawal is attempted.[227,238] Patients with features of both AIH and PSC should be treated for AIH; UCDA can be considered for the cholestatic component of disease. However, as in PSC alone, benefit beyond improving liver biochemistry is questionable, with no firm evidence to support improved prognosis.[227,234]

Prognosis of AIH in general is favourable, but overall mortality remains increased.[239] In patients with the AIH/PSC variant, the sclerosing cholangitis component negatively impacts prognosis.[233,234] Compared to patients with PSC alone, additional features of AIH may be associated with improved transplantation-free survival in adults.[204,223]

3.4 Pancreatitis

Statement 13

Acute pancreatitis in IBD is commonly associated with gallstone disease, alcohol intake, medications [thiopurines and 5-ASAs], and duodenal CD. Autoimmune pancreatitis may also occur in patients with IBD [EL3] [consensus: 90%]

Compared to the general population, patients with IBD have an increased risk of developing acute pancreatitis, with a pooled annual incidence of 210 per 100 000 patient-years.[240,241] The prevalence of autoimmune pancreatitis [AP] is three times higher in IBD [OR: 3.11; 95% CI: 2.93–3.30] and significantly higher in CD than UC [OR 4.12 vs 2.61].[240] Clinical presentation in IBD is similar to that of the general population.[242,243] Diagnosis can be made with the revised Atlanta classification, which requires at least two of the following three criteria to be present: upper abdominal pain, elevation of amylase or lipase three times the upper limit, and consistent radiology.[244] Nevertheless, recurrent abdominal pain is common in IBD, with asymptomatic increases in serum amylase, lipase, or both in 8–21% of IBD patients, which may lead to diagnostic uncertainty.[245]

Acute pancreatitis in IBD has multiple causes and is commonly associated with gallstone disease [21%], alcohol intake [15%], medications [12%], and duodenal CD [13%]. Less common causes include hypertriglyceridaemia, hypercalcaemia, sequelae following endoscopic procedures [endoscopic retrograde cholangiopancreatography, double-balloon enteroscopy], AP, PSC, and vascular disease such as thrombosis, ischaemia, or vasculitis.[242]

Drug-induced pancreatitis is largely associated with thiopurines. 5-Aminosalicylic acids [5-ASAs] and ciclosporin have also been implicated, as indeed have metronidazole or corticosteroids, although drug-induced pancreatitis due to the latter is rare.[246–249] Between 4% and 7.5% of patients with IBD treated with azathioprine develop AP.[242,249] Development is dose-independent and typically occurs within the first 3–4 weeks of treatment. Smoking and female gender are risk factors.[249] The pathophysiology of pancreatitis induced by 5-ASA is unknown; it is not dose-related, occurs regardless of the method of administration, and can present at any time during treatment.[248] In case of drug-induced pancreatitis, thiopurines and 5-ASAs should be immediately stopped and re-challenge should not be attempted.

Patients with CD have a three-fold increased risk of developing gallstones, thus increasing the risk of gallstone pancreatitis.[250] The prevalence of AP in IBD is 0.4–1.2%, with the association of these diseases hypothesized to be due to shared antigenic molecules triggering an immune-mediated response in both organs.[251,252]

AP in patients with IBD is managed similarly to other patients, including supportive care with fluids, pain control, and nutritional support.[253] Asymptomatic increases in lipase and amylase levels do not require therapy[253]; indeed, these tests should not be requested in the absence of symptoms of pancreatitis.

Chronic pancreatitis in IBD is characterized by the presence of pancreatic duct abnormalities, functional abnormalities, and, in most cases, absence of parenchymatous calcification.[251] Pancreatic duct changes, such as main duct obstruction, severe duct irregularity or dilatation, or ductal filling defects, have been found in 8% and 16% of patients with CD and UC, respectively.[254,255] In addition, 7–77% of patients with PSC have pancreatic duct changes.[256–258] Patients with IBD often have low faecal elastase levels, reflecting impaired exocrine function.[253,259] Exocrine pancreatic dysfunction is more common in patients with UC than in patients with CD [22% vs 14%, respectively].[260]

4. Bone and joint disease in IBD

4.1 Bone demineralization in IBD

4.1.1 Prevalence and investigation of osteoporosis and osteopenia

Statement 14

Patients with IBD have an increased risk of developing osteoporosis and osteoporotic fractures, particularly of

the spine [EL2]. In patients with IBD at high risk for osteoporosis, bone mineral density measurement through a dual-energy X-ray absorption scan is recommended [EL2] [consensus: 100%]

Osteoporosis and osteopenia are defined as a reduced bone mineral density [BMD], assessed through a dual-energy X-ray absorption [DEXA] scan. According to the WHO, a T-score lower than −2.5 SD is diagnostic for osteoporosis; a T-score between −1 SD and −2.5 SD is diagnostic for osteopenia.

Several systematic reviews have been published detailing the association between osteoporosis and risk of osteoporotic fractures and IBD.[261–266] A meta-analysis revealed a 32% increased risk of developing osteoporosis or osteoporotic fractures in IBD than control individuals [OR: 1.32; 95% CI: 1.20–1.45].[263] A study on the incidence of osteoporosis in a population-based inception cohort revealed a slightly higher OR of 2.9 [95% CI: 2.4–4.1] in CD and 2.8 [95% CI: 2.1–3.9] in UC.[267] There is a two- and three-fold increased risk of spinal and hip fractures, respectively.[264,265,268,269]

Several factors have been identified in the development of low BMD in IBD. These include systemic inflammation, frequent corticosteroid use, low body mass index [BMI], CD diagnosis, smoking, malabsorption of vitamins D and K and calcium, malnutrition, reduced physical activity, and genetic factors.[262] Whilst steroids are a known risk, IBD patients have an elevated risk independent of steroid therapy.[261]

In patients with IBD at high risk for osteoporosis, BMD measurement through a DEXA scan is recommended.

4.1.2 Management of bone demineralization

Statement 15

Appropriate daily dietary intake of calcium and vitamin D, smoking cessation, and physical activity should be promoted to prevent osteopenia and osteoporosis [EL5]

Supplementation with calcium and vitamin D is recommended in patients treated with corticosteroids and/or with known osteopenia or risk factors for low bone mineral density [EL2]

Treatment with bisphosphonates is recommended in patients with corticosteroid-induced or postmenopausal osteoporosis [EL1] [consensus: 84%]

As discussed above, IBD is an established risk factor for osteopenia and osteoporosis. Consistent with endocrinology guidelines, we recommend screening for vitamin D deficiency in at-risk patient populations.[270] Calcium intake is also frequently insufficient in IBD patients, as revealed by a recent meta-analysis,[271] potentially in part due to self-reported lactose intolerance. Supplementation of both calcium and vitamin D is effective at preventing bone loss, especially in corticosteroid-treated patients, as shown in several studies and a Cochrane meta-analysis.[272,273] Physical activity and smoking cessation have shown beneficial effects in patients with osteoporosis and should be encouraged.[262]

Several randomized controlled trials have shown the efficacy of bisphosphonates such as risedronate,[274–278] teriparatide,[279] zolendronate,[280] alendronate,[281] pamidronate,[282,283] and ibandronate[284] in preventing bone loss and increasing lumbar spine BMD, as confirmed in two recent meta-analyses.[285,286] Importantly, bisphosphonates also reduce the risk of fractures. Therefore, when osteoporosis is present, bisphosphonate use is recommended, particularly in postmenopausal or steroid-induced osteoporosis.[287]

The tolerability of bisphosphonates is generally good and adverse events are usually temporary. These include abdominal pain, diarrhoea, nausea, vomiting, rash, and muscle pain. Osteonecrosis of the jaw is a rare side effect [<1% of recipients].[287] A meta-analysis comparing different bisphosphonates suggests that zoledronate may be the most effective agent for increasing BMD, while risedronate has the most favourable safety profile.[285]

When possible, a multidisciplinary approach should be employed for decisions regarding bisphosphonate therapy.

4.2 Joint disease in IBD

4.2.1 Prevalence and clinical manifestations of rheumatological EIMs

Statement 16

Clinical symptoms of joint disease in IBD are common, such as peripheral and axial spondyloarthropathy [EL2]. Articular symptoms may occur before and after diagnosis of IBD [EL2] [consensus: 100%]

Spondyloarthritis [SpA] refers to a family of chronic immune-mediated inflammatory diseases of the joints, often occurring as an EIM of IBD.[288,289] The Assessment of SpondyloArthritis Society [ASAS] criteria distinguish between axial and peripheral spondyloarthritis based on clinical presentation. Axial spondyloarthritis [axSpA] presents with dominant axial symptoms, such as back pain and morning stiffness of the spine. Peripheral spondyloarthritis [pSpA] presents with symptoms predominantly affecting the upper and lower limbs.[290] The ASAS classification criteria for axSpA and pSpA are shown in Table 5[291] and Table 6, respectively.[292] ASAS recognizes the significant presence of IBD in SpA, with a reported lifetime IBD risk of 4–14%, and has included IBD as a classification criterion.[293–297]

A systematic review investigating the prevalence of SpA in IBD found that peripheral arthritis was the most common manifestation [13%; 95% CI: 12–15%], followed by sacroiliitis [10%; 95% CI: 8–12%] and ankylosing spondylitis [3%; 95% CI: 2–4%].[299] Another systematic review of radiological diagnosis of sacroiliitis in IBD revealed a pooled prevalence of 21% [95% CI: 17–26%].[300] SpA may occur before or after IBD diagnosis.[301–303]

The associations between IBD and SpA indicate a common inflammatory pathway. Genome-wide association studies have identified shared loci associated with the risk of developing both SpA and IBD, including association signals in or near to the IL-12/23 genes pathway.[304–307] Sacroiliitis and ankylosing spondylitis are associated with NOD2/CARD15 and IL23R.[301] The strongest genetic associations exist between ankylosing spondylitis and IBD.[3,305] Dysbiosis and alterations of the microbiota are also associated with an increased risk of arthropathies.[3,301] The mechanisms underlying this association include molecular mimicry, microbial communities in the joints, microbial translocation, soluble microbial-derived factors and metabolites, disruption of the gut barrier, and acquisition of deleterious microbiota early in life.[3] Of note, 25–78% of patients with IBD and ankylosing spondylitis are positive for HLA-B27, although it has been reported that

Table 5. Criteria for classification of axial spondyloarthropathy [axSpA][298] [adapted from Sieper *et al.*[291]]

ASAS classification criteria for axSpA **For patients with ≥3 months of back pain and age at onset <45 years**		
Sacroiliitis on imaging[a] plus ≥1 SpA feature[b]	Or	HLA-B27 positivity plus ≥2 other SpA features[b]
[a]SpA features: - Inflammatory back pain - Arthritis - Enthesitis [heel] - Uveitis - Dactylitis - Psoriasis - IBD - Good response to NSAIDs - Family history of SpA - HLA-B27 - Elevated CRP		[a]Sacroiliitis on imaging: - Active [acute] inflammation on MRI highly suggestive of sacroiliitis associated with SpA - Definite radiographic sacroiliitis according to modified New York criteria

Table 6. Criteria for classification of peripheral spondyloarthropathy [pSpA] [adapted from Rudwaleit *et al.*[292]]

Arthritis, enthesitis, dactylitis, or combinations thereof Plus		
≥1 of:	Or	≥2 of the remaining:
– Psoriasis – IBD – Preceding infection – HLA-B27 – Uveitis – Sacroiliitis on imaging [radiographs or MRI]		– Arthritis – Enthesitis – Dactylitis – Previous IBD – Positive family history for SpA

Final set of classification criteria for pSpA [set 2D] selected by Assessment of SpondyloArthritis Society [ASAS]. The criteria are applicable to patients with peripheral arthritis [usually predominantly of the lower limbs and/or asymmetric arthritis], enthesitis, dactylitis, or combinations thereof.

germ-free HLA-B27 transgenic rats do not develop gut or joint inflammation.[301] Disease duration and active inflammation also increase the risk of SpA onset, although they may also occur irrespective of gut inflammation.[299,302,303]

4.2.2 NSAID use in the management of joint disease in IBD

Statement 17

There is no evidence of an association between NSAID use and UC flare [EL1], although there is potentially an association with CD flare [EL2]. We recommend that the decision to use NSAIDs for the management of arthropathy is made on a case-by-case basis [EL3]. Selective COX-2 inhibitors may be used for short periods of time [EL2] [consensus: 91%]

Non-steroidal anti-inflammatory drugs [NSAIDs] are amongst the most prescribed drugs in the world and have a well-recognized association with gastrointestinal injury in both short- and long-term use.[308–310] Selective cyclooxygenase-2 [COX-2] inhibitors have fewer gastrointestinal side effects, especially when used for short periods.[309,310] While the association between the use of NSAIDs and gastrointestinal injuries is well established, the link between NSAID use and IBD flare is still debated.

A recent meta-analysis, including 13 studies and 6276 participants, did not find a consistent association between NSAID use and risk of CD or UC exacerbation [CD, RR: 1.42; 95%: CI 0.65–3.09; UC, RR: 1.52; 95% CI: 0.87–2.63]. However, sensitivity analyses limited to studies with low risk of bias (CD: $n = 1408$, UC: $n = 936$, three studies) showed a small but significantly increased risk of exacerbation with NSAID use in CD [RR: 1.53; 95% CI: 1.08–2.16] but not in UC.[311]

In 2014, Miao *et al.* conducted a systematic review aiming to assess the tolerability and safety of COX-2 inhibitors in IBD patients. Two randomized controlled trials were included. One study [$n = 159$] compared etoricoxib [60–120 mg/day] to placebo in patients with quiescent or active UC or CD. The other study [$n = 222$] compared celecoxib [200 mg twice daily] to placebo in patients with quiescent UC. There was no statistically significant difference in exacerbation of IBD,[312] with a subsequent study validating these findings.[313] Finally, a recent retrospective study on 764 patients with IBD showed that daily aspirin use did not impact need for hospitalization, surgery, or corticosteroids.[314] Accordingly, we recommend that these agents can be considered in patients with IBD.

4.2.3 Management of axial spondyloarthropathy

Statement 18

TNFα antagonists are recommended for treatment of axial spondyloarthropathy associated with IBD. Vedolizumab and ustekinumab are not recommended in axial spondyloarthropathy associated with IBD [EL2] [consensus: 96%]

When considering the management of axial spondyloarthropathy in IBD, no randomized controlled trial has evaluated the efficacy of any of the biologics, JAK inhibitors, or NSAIDs. Only four open-label trials [total 100 patients] have been performed that examined the effectiveness of TNFα antagonists in IBD.[315–319] Although outcomes and durations varied between studies, all showed a decrease in spondyloarthritis associated with TNFα antagonists. Etanercept for the management of spondyloarthritis is known to cause paradoxical gastrointestinal inflammation in a subset of patients and should be avoided in the IBD population.[320]

Studies of ustekinumab and vedolizumab in axial spondyloarthropathy are conflicting, with a paucity of prospective data for rheumatological EIMs and frequent combination of axial and non-axial spondyloarthropathy in analysis. One open-label trial demonstrated clinical response in 43% treated with ustekinumab [both axial and peripheral arthritis].[321] In contrast, one large retrospective cohort study demonstrated worsening of existing arthropathy in 35.9% of patients receiving vedolizumab and 22.5% of patients receiving ustekinumab for luminal IBD, with a small proportion also developing new-onset joint disease.[322] Flares of joint disease following treatment with vedolizumab were also noted in two small, uncontrolled studies in IBD patients; vedolizumab induced a flare of axial spondyloarth opathy.[323,324] A systematic review of nine studies [total 254

patients] also did not reveal efficacy of ustekinumab in axial spondyloarthritis.[325] Hence, we do not recommend vedolizumab or ustekinumab for axial inflammation in IBD, and we urge a degree of caution with vedolizumab use in patients with existing spondyloarthropathy. Due to the efficacy of JAK inhibitors in ankylosing spondylitis,[326,327] these may also be considered in axial spondyloarthropathy associated with IBD.

4.2.4 Management of non-axial spondyloarthropathy

Statement 19

TNFα antagonists are recommended for treatment of IBD-associated non-axial spondyloarthropathy [EL2]. There are also data to support use of methotrexate, sulfasalazine, and ustekinumab [EL3] [consensus: 100%]

As with axial spondyloarthropathy, there are no published randomized controlled trials of therapies directed at the management of non-axial spondyloarthropathy in IBD.

A systematic review of 21 studies addressing the effect of TNFα antagonists on various EIMs of IBD patients revealed a reduction of arthralgia prevalence from 47.1% to 26.8% in one open-label trial and reduction of arthritis from 8.7% to 2.1% and from 58% to 12.5% in two-open label trials.[328] A post hoc pooled analysis from 11 induction, maintenance, and open-label extension studies of adalimumab demonstrated resolution of arthritis and arthralgia in a significant proportion of CD patients compared with placebo at 6 months [54% vs 31%; $p < 0.001$] and 1 year [60% vs 42%; $p = 0.008$],[329] with predictors of response being male sex and moderate (as opposed to severe) disease activity. Another analysis of 300 patients with EIMs treated with adalimumab, certolizumab, or infliximab showed up to 73% improvement of arthralgia/arthritis.[330] Case reports also support golimumab use in peripheral joint disease.[331] The key trials of TNFα antagonists in IBD were not powered to assess treatment of EIMs, including peripheral arthritis. However, many studies reported a reduction in peripheral joint symptoms.[315–317,332]

A systematic review of patients receiving ustekinumab for arthralgia or arthritis, including nine studies and 254 patients with IBD, demonstrated its effectiveness in psoriatic arthropathy and arthralgia.[325] However, post hoc analysis of the UNITI studies did not reveal significant efficacy of ustekinumab for EIMs in CD.[333]

Published data on vedolizumab and peripheral arthropathy are conflictive. A post hoc analysis of the GEMINI studies demonstrated a decrease in severity of existing peripheral arthropathy and a reduction in new joint symptoms.[334] However, a recently published multicentre retrospective cohort study demonstrated an increased risk of new-onset arthralgia following vedolizumab use [adjusted OR: 2.28; 95% CI: 1.01–5.15; $p = 0.047$].[322] A post hoc analysis of tofacitinib trials did not suggest an effect on the frequency and severity of arthritis in UC.[335] Retrospective data suggest that both methotrexate and sulfasalazine have some efficacy in peripheral arthritis in IBD.[336,337]

Of note, this guidance specifically considers peripheral arthritis as an enteroarthropathy as opposed to a coexisting diagnosis of other immune-mediated rheumatological conditions, such as rheumatoid arthritis or psoriatic arthropathy. In cases of coexisting rheumatological conditions, choice of immunosuppressive therapy may vary depending upon whether intestinal or peripheral arthritic symptoms predominate, and treatment decisions should involve both a gastroenterologist and a rheumatologist.

The management options for both axial and non-axial [peripheral] spondyloarthropathies in IBD are summarized in Table 7.

5. Skin disease in IBD

5.1 General aspects

Statement 20

Skin diseases associated with IBD are among the most common EIMs and their relationship with underlying intestinal disease may be either specific [metastatic CD], reactive [pyoderma gangrenosum, Sweet syndrome, erythema nodosum, oral lesions], associated [hidradenitis suppurativa, psoriasis], or treatment-related [TNFα antagonist-induced skin lesions, other drug hypersensitivities, skin cancer] [EL3]. We recommend early involvement of a dermatologist when appropriate [consensus: 95%]

Approximately 15–20% of patients with IBD patients will develop cutaneous EIMs.[339,340] These EIMs can be categorized into four groups based on their pathophysiological mechanisms and association with underlying intestinal disease.[339–341]

(1) Reactive:
share common immune–pathogenic mechanisms, but not the same histopathological features [erythema nodosum, pyoderma gangrenosum, Sweet syndrome, oral lesions].

(2) Specific:
histopathological features are similar to the underlying intestinal disease but presenting outside of the gastrointestinal tract [metastatic CD].

(3) Associated:
inflammatory or autoimmune disorders more frequently observed in the context of IBD, but which do not share histological or pathogenic links. However, risk factors may be

Table 7. Management of axial and non-axial spondyloarthropathy in IBD [adapted from Greuter *et al*[338]

	Agent	Axial spondyloarthropathy	Non-axial spondyloarthropathy
	Sulfasalazine		
	Methotrexate		
TNF-antagonist[a]			
JAK inhibitor			
Anti-integrin	Vedolizumab		
Anti-IL-12/23	Ustekinumab		
S1P-R modulator	Ozanimod		

[a]Does not apply for etanercept.
Green: can be used.
Yellow: may be used.
Red: should not be used.

shared [hidradenitis suppurativa, psoriasis, atopic dermatitis, acne conglobata, rosacea, vitiligo, alopecia areata, leukocytoclastic vasculitis, systemic lupus erythematosus, polyarthritis nodosa, epidermolysis bullosa acquisita].

(4) Complications:
consequences of IBD or adverse reactions to IBD treatment [e.g. related to TNFα antagonists, thiopurines, sulfasalazine, methotrexate, vedolizumab].

The diagnosis of cutaneous EIMs is based principally on clinical examination. Racial or ethnic differences in the prevalence of cutaneous manifestations are reported and may be further complicated by variable clinical presentation and under-recognition of cutaneous disorders in skin of colour.[342] An overview of the epidemiological and diagnostic clinicopathological features of individual cutaneous manifestations and their pathogenesis is presented in the relevant sections and summarized in Appendix 2. Additionally, a summary of diagnostic features and treatment options of cutaneous EIMs is presented in Table 8.

5.2 Erythema nodosum

Statement 21

Erythema nodosum is very often associated with underlying active intestinal IBD, although other causes should be excluded and managed. When erythema nodosum is associated with IBD activity, the primary aim is control of underlying intestinal disease activity; the skin lesions usually resolve when intestinal disease activity is controlled [EL3] [consensus: 100%]

With a prevalence of up to 15% [CD: 4–15%; UC: 2.8–10%], erythema nodosum [EN] is the most common skin disorder in IBD.[328,339] EN is characterized by painful erythematous–violaceous subcutaneous plaques or nodules that are usually 1–5 cm in diameter. EN is often located symmetrically on extensor surfaces of the lower extremities [anterior tibia] but also on the thighs and forearms.[2,345,346] EIM in IBD may reflect a delayed type IV hypersensitivity reaction to common antigens of intestinal and skin bacteria, with an overlap between genetic risk loci for EN and IBD.[301,347]

Due to characteristic clinical findings, diagnosis is usually based on typical clinical presentation. Skin biopsy is needed only if presentation is atypical.[346] EN can also be triggered by a variety of other conditions, including infection [*Streptococcus*, tuberculosis], malignancies, medications [sulfonamides, oral contraception], pregnancy, and other non-IBD inflammatory diseases [Behçet disease, sarcoidosis].[339] Accordingly, these differentials should be considered.

EN is usually associated with IBD activity; most cases of EN are self-limited, require no treatment aside from control of intestinal disease, and usually resolve without scar formation.[339] Supportive treatment may include leg elevation, potassium iodide, compression stockings, or compression bandages. In cases where lesions are very painful, a short course of oral corticosteroids induces rapid resolution. In collaboration with a dermatologist, hydroxychloroquine can be used as second-line therapy.[339]

TNFα antagonists,[339] ustekinumab, or vedolizumab may also be used in the management of IBD-related EN, with efficacy probably related to control of intestinal inflammation.[348]

5.3 Pyoderma gangrenosum

Statement 22

Treatment with TNFα antagonists, particularly infliximab, is recommended for the treatment of pyoderma gangrenosum [EL2]. Early use should be considered, particularly for severe manifestations. Other treatments that may be considered include systemic steroids [EL3], ciclosporin [EL3], ustekinumab [EL4], dapsone [EL3], metronidazole [EL3], and tetracyclines [EL4]. For milder disease, topical steroids and topical calcineurin inhibitors may be considered [EL3]. We recommend early involvement of a dermatologist [consensus: 95%]

Pyoderma gangrenosum [PG] is the second most common reactive cutaneous EIM and is the most debilitating.[348] A systematic review of 14 studies revealed a prevalence in IBD from 0.4% to 2.6%. It is more common in females, black Africans, and those with a positive family history of UC.[345]

PG is characterized by the appearance of pustules or erythematous papules and plaques, often at a site of trauma.[349] Rapid ulceration with dermal necrosis leads to painful, deep ulcers with undermined, irregular violaceous [or hyperpigmented in darker skin] borders and a purulent but sterile base. It occurs on the legs [70–80%], peristomally [18%], head and neck [4–8%], and trunk [4–5%].[346,350,351] PG may be associated with malaise, fever, arthralgia, or myalgia[2,301] and is also associated with EN, hidradenitis suppurativa [HS], and ocular disease. It may have an unpredictable course complicated by pain, recurrences, secondary infections, and scarring. PG thus has a substantial impact on quality of life.[339]

PG may parallel IBD activity or run an independent course,[301,338] with 15% of PG pre-dating onset of IBD.[341] Approximately 30–50% of all PG is associated with IBD. PG is also associated with arthritis and haematological or solid malignancies.[349, 352–356] IBD is a more common cause in younger patients.[357] Differential diagnosis is broad and includes vascular disease, haematological diseases [polycythemia vera], cutaneous malignancies, skin infection, and necrobiosis lipoidica.[340] Diagnosis is usually based on clinical presentation and is a diagnosis of exclusion. Skin biopsies are non-specific but helpful in excluding other differentials. Misdiagnosis is common and diagnostic delay may significantly increase complication rates.

Early and proactive treatment is important, ideally in collaboration with dermatology, tissue viability, and stoma nurses [in the case of peristomal PG]. Such treatment includes pain management and wound care.[325,328,333,346,348,351,358,359] A suggested treatment algorithm is presented in Figure 3. PG has long been considered very difficult to treat, although TNFα antagonists have considerably changed medical management.[360] A systematic review demonstrated complete response following treatment with infliximab and adalimumab in 58% and 67%, respectively,[351] with response rates with TNFα antagonists higher than with intralesional corticosteroids.[351] Systemic steroids are most effective early in disease course, with time to remission reduced from 5 to 2 months with such an early steroid use strategy [$p = 0.0023$].[361] Other treatment options for PG include topical steroids, topical calcineurin inhibitors [tacrolimus], metronidazole, dapsone, and systemic steroids.[358,362,363] For refractory cases,

Table 8. Diagnosis and management of common cutaneous EIMs in IBD

Classification of EIM	Cutaneous EIM	Diagnostic features	Management
Reactive			
	Erythema nodosum	Symmetrical, raised, tender, erythematous, or violaceous subcutaneous nodules [1–5 cm] Extensor surface of lower limbs [pretibial] > head and neck, trunk, arms	– Treat underlying IBD – Supportive: bed rest, elevation, analgesia, compression hosiery – Skin directed: topical corticosteroids – Systemic: corticosteroids [if severe], potassium iodide, dapsone, TNFα antagonists, hydroxychloroquine
	Pyoderma gangrenosum	Single or multiple erythematous papules/pustules, rapid necrosis to excavating ulcers with irregular violaceous margins and purulent [sterile] material, 2–20 cm, often following trauma [pathergy], secondary infection may occur. Shins and peristomal areas most common	– Supportive: wound care, analgesia, avoidance of trauma – Skin directed: topical corticosteroids, topical tacrolimus – Systemic: corticosteroids, TNFα antagonists, dapsone, tetracyclines, metronidazole – Severe: IV cyclosporin, TNFα antagonists, ustekinumab, JAKi
	Sweet syndrome [acute febrile neutrophilic dermatosis]	Acute onset of tender erythematous papules and nodules on limbs, trunk, head, and neck; varying sizes, associated with fever and neutrophilia	– Treatment of underlying IBD – Skin directed: topical corticosteroids – Systemic: corticosteroids, immunomodulators, TNFα antagonists, granulocyte-monocyte apheresis
	Oral lesions	Aphthous ulcers: painful ovoid or round ulcers, labial or buccal mucosa, pseudomembranous base and erythematous margin Periodontitis: swelling, redness, bleeding of gingiva, loose teeth, associated with perianal disease and smoking Peristomatitis vegetans: pustules, haemorrhagic erosions, ulcers Orofacial granulomatosis: recurrent and persistent buccal swelling and oral ulcers, facial palsy, cervical lymphadenopathy	– Treat underlying IBD – Antiseptic and anaesthetic mouthwashes – Topical corticosteroids – Systemic: corticosteroids, TNFα antagonists
Specific			
	Metastatic CD	Extraintestinal sites: legs, intertriginous areas > facial, genital Abscesses, fistulae, ulcers, nodules	– Topical, intralesional, or systemic corticosteroids – Systemic: antibiotics [metronidazole], immunomodulators [azathioprine], TNFα antagonists
Associated			
	Hidradenitis suppurativa	Recurrent, painful inflamed skin lesions, developing abscesses and interconnected sinus tracts in flexural sites [axillae, inguinal, perianal]	– Supportive: pain management, wound care – Lifestyle modification: smoking cessation, optimize BMI – Skin directed: topical clindamycin, antiseptic wash – Systemic: antibiotics [tetracycline, clindamycin plus rifampicin], retinoids, dapsone, TNFα antagonists – Surgery in selected cases – Consensus management guidelines are available[343, 344]

Table 8. Continued

Classification of EIM	Cutaneous EIM	Diagnostic features	Management
Complications			
	TNFα antagonist adverse effects	Paradoxical psoriasis: erythematous, scaly plaques, pustules, itching and burning; body, scalp, face; flexures > extensors [in contrast to typical psoriasis], palmoplantar pustulosis, nail involvement Eczema-like/psoriasiform eczema: xerosis and itchy, erythematous, ill-defined plaques and vesicles, *Staphylococcus* superinfection may occur Paradoxical hidradenitis suppurativa: typical HS with recurrent inflamed nodules, abscesses, sinus tracts, fistulae and scarring	Paradoxical psoriasis: – Skin directed: emollients, soap substitutes, topical corticosteroids, vitamin D analogues – Discontinuation of TNFα antagonists [required in 5–35% of cases] – Systemic: consider ustekinumab if severe or recurrent; acitretin, methotrexate, or ciclosporin as alternatives Eczema-like and psoriasiform eczema: – Skin directed: emollients, soap substitutes, menthol cream, topical corticosteroids, topical corticosteroid/antibiotic combinations, topical tacrolimus – Systemic treatment: oral antibiotics for *Staphylococcus aureus* superinfections, antihistamines – Discontinuation of TNFα antagonist if severe and refractory, consider ustekinumab Palmoplantar pustulosis: – Skin directed: ultrapotent topical corticosteroid [with addition of salicylic acid or coal tar] – Systemic treatment: tetracyclines, acitretin, methotrexate ,or ciclosporin may be considered in severe or refractory cases

ustekinumab,[348] intravenous cyclosporin,[364,365] or JAK inhibitors such as tofacitinib may be considered.[366]

Peristomal PG represents an important complication in patients with ostomies. There are several treatment modalities available. Surgical options [stoma closure and surgical revision] are the most effective, with post-operative remission rates of 80–100%.[367,368]

5.4 Sweet syndrome

Statement 23

We recommend use of systemic corticosteroids as first-line treatment for Sweet syndrome [EL4]. TNFα antagonists may be used in steroid-dependent or refractory cases [EL4] [consensus: 95%]

Sweet syndrome [SS] is the prototype member of the group of neutrophilic dermatoses. Diagnosis of SS is based on the combination of sudden eruption of erythematous to violaceous tender papules and plaques with histological findings of neutrophilic infiltration of the dermis without vasculitis. Fever, peripheral neutrophilia, and ESR or CRP elevations are also typical features. Although SS is rarely diagnosed in patients with IBD,[369] IBD is the third most common underlying condition in SS,[340] after haematological malignancy and infection. Additionally, azathioprine may induce an SS-like dermatosis.[370] According to a recent systematic review, IBD-related SS more often affects middle-age female patients and occurs equally in UC or CD, more frequently in patients with colonic involvement.[371] SS presents early in the course of IBD and usually follows the activity of intestinal inflammation. Conversely, azathioprine-related SS typically occurs within the first month of treatment, has male predominance, and is primarily localized to the trunk [as opposed to the classical, extremity-dominant pattern of SS]. Differential diagnoses may include PG, erythema multiforme, cutaneous infection, and skin malignancy. Skin biopsy is usually needed to confirm diagnosis.

As SS parallels disease activity, a cornerstone of treatment is management of underlying IBD, although skin-directed treatment is also frequently required.[371,372] SS is typically treated with systemic steroids, which are usually very effective. In a recent systematic review of IBD-associated SS cases, 90.5% were successfully treated with intravenous or oral steroids.[371] Biological therapy, mainly with infliximab, is the second most reported therapy for SS and has been used in steroid-refractory or steroid-intolerant cases or combined with steroids. In addition, treatment with granulocyte-monocyte apheresis, NSAIDs, dapsone, colchicine, ciclosporin, methotrexate, and vedolizumab, golimumab, and ustekinumab have been tried in individual cases of IBD patients with concomitant SS. After treatment commencement, SS was successfully controlled within a median of 7 days [range 2–46].[371]

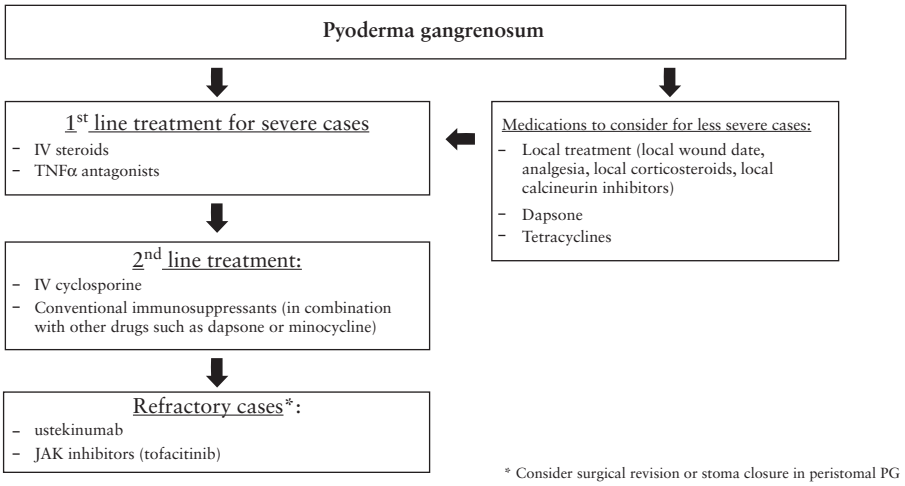

Figure 3. Management of pyoderma gangrenosum.

Recurrence of SS may occur following steroid tapering or IBD flare and uniformly after re-administration of azathioprine in drug-induced cases. Therefore, in azathioprine-induced SS, permanent cessation of the drug may be required.

5.5 Hidradenitis suppurativa

Statement 24

Hidradenitis suppurativa is a condition associated with IBD and is more commonly observed in CD than in UC. Topical treatment or systemic treatment [antibiotics and dapsone] may be used in mild-to-moderate disease. Adalimumab is recommended as first-line treatment for severe disease, with early dose intensification frequently required. Other management options include infliximab, ustekinumab, or surgery [EL3] [consensus: 100%]

HS is a chronic inflammatory skin condition characterized by recurrent painful boils in flexural sites, such as the axillae and groin, with onset typically in early adulthood. The formation of sinus tracts and scarring can sometimes be mistaken for perianal CD.[373]

Although it is unclear if HS can be considered a specific EIM or a complication of IBD, a bidirectional association between conditions is recognized.[339,373] We felt it was important to provide guidance on HS due to the substantial detrimental impact on quality of life. A meta-analysis of case-control and cross-sectional studies showed significant associations of HS with CD [pooled OR: 2.12; 95% CI: 1.46–3.08] and UC [pooled OR: 1.51; 95% CI: 1.25–1.82].[363] Genetic susceptibility, shared immune dysregulation, and microbial balance alteration are possible explanations for the association.[363,374,375]

Active IBD and perianal disease are risk factors for HS in IBD.[376] Smoking is a risk factor in non-IBD-associated HS; evidence in IBD is conflicting. Obesity is also a risk factor.[346,374,377] Differential diagnoses include skin infections with early carbuncles or furuncles. HS may also be difficult to distinguish from contiguous perianal CD,[374,378] although diagnosis can usually be made based on clinical presentation. At diagnosis, screening for other potential comorbidities associated with HS should be considered, including diabetes, dyslipidaemia, obesity, hypertension and metabolic syndrome, anxiety, and depression.[379,380]

Consensus management guidelines for treatment of HS are available.[344] For mild disease, antibiotics [such as a tetracycline or a combination of clindamycin and rifampicin] may improve clinical course. In the presence of moderate to severe HS, early specialist surgery consultation is recommended. For more severe disease, treatment modalities include TNFα antagonists, removal by surgical excision, or both.[343,344,381] TNFα antagonists approved for CD and UC are recommended for patients with HS and IBD, but only adalimumab is specifically approved for HS in both IBD and non-IBD contexts. In a meta-analysis of two studies with 124 participants, standard-dose adalimumab 40 mg every other week was ineffective compared with placebo, but 40 mg weekly improved quality of life. In a smaller study of 38 participants, of whom only 33 provided efficacy data, infliximab 5 mg/kg improved Dermatology Life Quality Index by 8.4 points after 8 weeks.[343] Data to support ustekinumab are limited to small retrospective studies or case series.[382,383]

5.6 Other associated inflammatory and autoimmune cutaneous disorders

There appears to be a bidirectional association between psoriasis and IBD, with the prevalence of psoriasis in patients with CD and UC being 3.6% and 2.8%, respectively.[384] The prevalence of CD and UC in patients with psoriasis is 0.7% and 0.5% respectively, in keeping with a significantly increased HR compared with the general population prevalence [2.19; 95% CI: 1.27–3.79].[302] Rosacea and atopic dermatitis are associated with IBD, with HRs of ~1.3–2.2.[342,385] These associations may be driven by shared genetic, microbiological, and environmental factors.[341,386] Acne onglobate may also be associated with IBD, with TNFα as a common mediator.[342] There is also evidence for a significant association with other inflammatory and autoimmune skin diseases, including systemic lupus erythematous,[387] vitiligo,[342] chronic urticaria,[388] leukocytoclastic vasculitis,[389] and alopecia areata. Subgroup analysis suggests a lower prevalence for alopecia areata in CD, whereas UC exhibited an increased prevalence, possibly because use of thiopurines in CD has a protective effect.[385]

5.7 Treatment-related skin disease

5.7.1 TNFα antagonists and paradoxical skin inflammation

With widespread use of TNFα antagonists, adverse skin effects are increasingly recognized.[346,390] Inflammatory skin disorders include xerosis, paradoxical psoriasiform reactions, psoriasiform eczema, and paradoxical HS. Injection-site and infusion reactions, skin infections [usually bacterial and viral and rarely opportunistic], drug-induced lupus erythematosus,[387] alopecia, and possible associations with skin cancer are also recognized.[390] The reported prevalence of paradoxical skin inflammatory lesions among IBD patients treated with TNFα antagonists ranges between 5% and 10% and does not appear to be related to age or treatment duration.[391] Paradoxical psoriasis often presents as erythematous, scaly plaques, similar to typical psoriasis. However, there may also be atypical features, such as involvement of flexural rather than extensor surfaces, scalp and facial involvement, more prominent pustule formation, itching, and burning. Palmoplantar pustulosis and nail involvement may also occur.[390] Eczema-like reactions may occur as well as coexisting overlap features of eczema and psoriasis [psoriasiform eczema].[346] Paradoxical HS has also been reported.[392,393] The pathogenesis of paradoxical skin inflammation with TNFα antagonists is not fully understood, although it may reflect perturbation of the TNFα/IFNγ/IL-17 axis within the dermis.[394,395] Diagnosis is usually made clinically, but skin biopsy may be used for differential diagnosis, including cutaneous EIMs or skin infections.

Management should involve close collaboration with dermatologists to ensure early diagnosis and management, with a view to avoiding TNFα antagonist discontinuation when possible.[390] These skin reactions can usually be controlled with skin-directed treatments, including topical corticosteroids [in combination with topical antibiotics], emollients, soap substitutes, vitamin D analogues [for psoriasis], topical tacrolimus, and ultraviolet therapy. However, TNFα antagonist discontinuation is required in 5–35% of cases due to the severity of the paradoxical skin reaction.[391] As this is generally a class effect, switching to another TNFα antagonist is not usually recommended.[390] Ustekinumab may be a therapeutic alternative in severe or recurrent lesions.[325,396]

5.7.2 Other IBD therapy and skin disease

Thiopurines are associated with increased susceptibility to skin infections (including chronic infection with human papillomavirus-related viral warts and recurrent herpes simplex virus [HSV]), Sweet syndrome,[397] and skin cancer.[206] Sulfasalazine may be associated with severe cutaneous adverse reactions, including exfoliative dermatitis, Stevens–Johnson syndrome/toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms [DRESS]. These should be managed in close collaboration with a dermatologist. Methotrexate skin reactions include alopecia and oral ulcers. Vedolizumab is associated with infusion-related hypersensitivity, pruritus, eczema, and acne.

5.8 Skin cancer

There are well-recognized associations between IBD and skin cancer, which are most frequently linked to specific therapies.[206] The most common skin cancers are non-melanoma skin cancers, specifically keratinocyte cancers [KCs], comprising cutaneous squamous and basal cell carcinomas [cSCC and BCC, respectively]. The risk of KCs is increased ~2–5-fold in IBD and is higher for cSCC than for BCC.[398–403] There is also a 1.5–2.8-fold increased risk of melanoma, particularly with CD.[403,404] Pathogenesis is multifactorial, with a complex interplay between UV radiation exposure, conventional skin cancer risk factors [male gender, increasing age, fair skin phototype], and drugs used in treatment of IBD.[346,402,405–408] The associations between specific IBD therapies and skin cancers, and how this should be approached in clinical practice, are discussed in more depth in the ECCO guidelines on IBD and malignancy.[206]

5.9 Metastatic CD

Statement 25

Metastatic CD is a rare extraintestinal manifestation affecting the skin and genital area. Systemic and intralesional corticosteroids, azathioprine, metronidazole, and TNFα antagonists can be used [EL3] [consensus: 90%]

Metastatic CD [MCD] shares the same non-caseating granulomatous histological features as CD but occurs at extraintestinal sites. This contrasts with continuous/contiguous CD at orofacial, peristomal, and perianal sites.[338,348] MCD can present as papules, plaques, nodules, and ulcers. The variable clinical presentation of MCD can make early diagnosis and initiation of appropriate management challenging. The condition usually manifests as chronic penile, scrotal, vulval, or perianal oedema but may affect the more extensive peri-genital area, including the mons pubis, buttocks, natal cleft, and even the nasal mucosa.[409–416]

Vulval and penile MCD is often unrecognized and misdiagnosed, as the condition is rare and presents with a great variety of signs and symptoms. Differential diagnosis includes sarcoidosis, tuberculosis, lymphogranuloma venereum and other sexually transmitted diseases, Behçet disease, pyogenic infections, hidradenitis suppurativa, intertrigo, and syphilitic lesions. Definitive diagnosis can only be achieved by skin biopsy, which reveals non-caseating granulomas.[410] The difficulty of early diagnosis is also due to the fact that 25% of these patients do not have gastrointestinal symptoms. Accordingly, clinicians should be vigilant. Vulval and penile lesions may precede the diagnosis of intestinal CD. In one study, the median interval of vulval CD to the diagnosis of intestinal CD was 3.5 years.[417]

For mild forms, skin-directed treatment, such as intralesional steroid injections and prolonged systemic metronidazole [10–20 mg/kg/day], is recommended. TNFα antagonists and azathioprine may be effective as second-line therapy.[418,419] Surgery remains restricted to medical treatment failures or resection of unsightly lesions.[420] Therefore, a multidisciplinary approach is required.[420]

5.10 Orofacial manifestations

Statement 26

Orofacial manifestations of IBD are common and include oral aphthous ulcers, periodontitis, pyostomatitis vegetans, and orofacial granulomatosis. In cases of orofacial and buccal IBD, we recommend management of underlying IBD and supportive mouth care, including topical steroids [EL5] [consensus: 95%]

According to a recent systematic review, the prevalence rates for oral manifestations range between 0.7% and 37% in the adult IBD population.[421] Aphthous stomatitis is the most common reactive oral manifestation of IBD and occurs in up to 20% of adults and 47% of children.[421,422] Other oral manifestations include periodontitis and specific EIMs, including pyostomatitis vegetans,[423] mucosal cobblestoning, and orofacial granulomatosis [Melkersson–Rosenthal syndrome/cheilitis granulomatosa of Meischer].[348,424,425] Most oral manifestations are more common in CD than in UC, with the exception of pyostomatitis vegetans, which is exclusive to UC.[421]

In addition to oral manifestations of IBD, there are several broader differentials that should be considered when patients with IBD develop oral lesions. These include herpes infections, human immunodeficiency virus, oral cancers, vasculitis such as Behçet's disease, mineral or vitamin deficiencies [iron, zinc, or vitamin B_{12}], drug side effects, and continuous/contiguous CD. The last can be differentiated from aphthous ulcers on biopsy, which reveals non-caseating granuloma-specific CD histology. It is usually possible to establish diagnosis on clinical presentation after infections such as HSV are excluded.[426]

CD-specific oral conditions include oral cobblestoning [deep mucosal ulceration alternating with normal-looking mucosa], granulomatous cheilitis [belonging to the spectrum of orofacial granulomatosis], and mucosal tags. Oral involvement in CD may be more prevalent in patients with perianal disease.[427] No treatment has proven efficacy in the management of aphthous ulcerations.

As most IBD-related oral manifestations follow the activity of gut disease, controlling intestinal inflammation should be attempted first in these cases. In addition, topical therapies consisting of antiseptic or steroid-based regimens [or both] may offer symptomatic relief.[428,429]

5.11 Aural and nasal manifestations

Statement 27

Aural and nasal manifestations in IBD are very rare and there is not sufficient evidence to recommend any specific treatment [EL5] [consensus: 94%]

The definition and prevalence of ENT manifestations in IBD have not been studied extensively. All information is based on case reports, case series, and expert opinions, in which TNFα antagonists are the most commonly used treatment.[430]

Cogan's syndrome [CSy] is a very rare autoimmune disorder that mainly affects the inner ear and the eye. In an ECCO CONFER project of 22 cases of concomitant CSy and IBD, the authors concluded that although CSy is considered to be an autoimmune disease and is associated with IBD, immunomodulatory maintenance treatment and even TNFα antagonists do not prevent disease onset.[431] Moreover, IBD disease activity does not seem to trigger CSy. However, vigilance may prompt early diagnosis, and directed intervention with corticosteroids at inception may potentially hinder audiovestibular deterioration.[2]

The prevalence of chronic sinonasal disease is increased in patients with IBD and occurs in approximately half of patients. Patients with CD who present with obstructive complications have significantly increased rates of sinonasal disease.[432]

6. Ocular manifestations

6.1 Ocular phenotypes associated with IBD

Statement 28

Ocular manifestations associated with IBD are relatively frequent. The most frequent ocular manifestation in patients with IBD is anterior uveitis. Less frequent manifestations are episcleritis, conjunctivitis, scleritis, optic neuritis, ischaemic optic neuropathy, other uveitis subtypes, central retinal vein occlusion, and orbital inflammation or myositis [EL3] [consensus: 100%]

Primary prevalence data from a systematic review and meta-analysis[433] and population-based or prospective cohort or registry studies[194,302,303,434–439] indicate that ocular manifestations associated with IBD are relatively frequent. A detailed discussion of the systematic review and meta-analysis that support the incidence and prevalence data within this guideline is presented in the supplementary material [Appendix 3]. Further details on the prevalence and incidence of specific conditions along with management are shown below. A summary of the key ocular manifestations of IBD is presented in Table 9.

6.2 Uveitis

Statement 29

The choice of optimal therapy for IBD-associated uveitis depends on the type of uveitis and the underlying IBD activity. We recommend topical corticosteroid drops as first-line treatment for anterior uveitis. Intravitreal or systemic corticosteroids, with or without second-line steroid-sparing agents, may be required in the management of intermediate, posterior, and panuveitis. We recommend the use of adalimumab or infliximab as third-line treatment when sight-threatening ocular inflammation persists and/or there is active underlying IBD [EL4]. There is currently no trial evidence regarding the efficacy of non-TNFα antagonist biologic agents and small molecules for IBD-associated uveitis. Uveitis should be jointly managed by a gastroenterologist and a specialized ophthalmologist on an urgent basis [consensus: 97%]

Uveitis is the most common ophthalmic EIM in IBD. Data on the incidence and prevalence of uveitis are heterogeneous due to differences in study design and populations. In the prospective Swiss IBD Cohort Study, a uveitis/iritis prevalence of 11.1% [n = 205/1840] in CD and 5.6% [n = 80/1426] in UC was reported.[435] A large US database study including 68 535 patients with IBD reported a 3.5 per 1000 person-years incidence of uveitis in IBD, reflecting a 10-fold increased risk compared with healthy controls [HR: 10.2; 95% CI: 9.5–11.0].[436] A large UK database of electronic primary care records also revealed a significantly elevated risk of uveitis in IBD [OR 2.81],[438] similar to several other large retrospective datasets, including a Danish population study.[194,302,303] Uveitis appears more prevalent in CD than in UC, where it may be associated with severe intestinal inflammation and other EIMs.[435,440] Conversely, risk in UC does not appear to vary with disease activity.[330]

Table 9. Ocular manifestations of IBD

Ocular EIM	Diagnostic features	Risk of vision loss	Management
Uveitis	Clinical: discomfort or pain, may be bilateral, hyperaemia [especially around the corneal limbus], blurred vision, headache, photophobia. May be associated with intestinal disease activity Assessment: Slit-lamp examination ± ophthalmic imaging, exclusion of infection, and differentiation between anterior, intermediate, posterior, or panuveitis	Yes	Urgent ophthalmology referral if suspected First line: topical steroids [in intermediate, posterior, or panuveitis, intravitreal or systemic steroids may also be needed] Second line: systemic steroids, steroid-sparing agents, or biologic therapy [TNFα antagonists]
Scleritis	Clinical: pain [severe, more often at night/waking from sleep], unilateral or bilateral, diffuse or focal/nodular hyperaemia in anterior scleritis; eye may appear white in posterior scleritis Associated with active intestinal disease Classification: location [anterior/posterior], severity, diffuse/nodular/necrotising Does not blanch with topical application of 10% phenylephrine DDX: episcleritis	Yes	Urgent ophthalmology referral if suspected First line: oral NSAIDS or oral steroids [especially for posterior and necrotizing] Adjuvant therapy to consider: topical NSAIDs, topical steroids [prolonged use increases risk of increased intraocular pressure and cataract], periocular steroid injection [in non-necrotizing] Second line: steroid-sparing immunomodulators, biologics [TNFα antagonists]
Episcleritis	Clinical: painless or mild discomfort, unilateral or bilateral, hyperaemia Associated with active intestinal disease Diagnosis: hyperaemia blanches with topical phenylephrine Differential diagnosis: conjunctivitis, dry eye	No	Treatment of underlying disease, topical lubricants, and cool compresses Topical NSAIDs may be considered

DDX, differential diagnosis; NSAID, non-steroidal anti-inflammatory drug.

CD-associated uveitis is frequently bilateral, insidious in onset, and persistent,[441,442] although sudden onset presentation may also occur. Classical features include eye pain, red eye, blurred vision, photophobia, and headache. Cases of suspected uveitis should be urgently referred to ophthalmology, due to the risk of vision loss associated with untreated inflammation.

Slit-lamp examination is performed to confirm the diagnosis and permits differentiation between anterior [presence of inflammatory cells circulating in the anterior chamber], intermediate, posterior, or panuveitis; this differentiation provides guidance for therapeutic decisions. It is important to exclude infectious causes of uveitis [e.g. herpes viruses, *Toxoplasma gondii*, *Treponema pallidum*, *Mycobacterium tuberculosis*] before initiating immunosuppressive therapy. Differential diagnosis should include other causes of non-infectious uveitis, including sarcoidosis.[443]

Topical steroids are first-line therapy for anterior uveitis. In intermediate, posterior, and panuveitis, oral steroids may be needed, with or without steroid-sparing agents [e.g. methotrexate, mycophenolate mofetil] or TNFα antagonists. Adjunctive local therapy with steroid intravitreal implants may be considered. In a recent phase 3 trial of chronic non-infectious steroid-dependant uveitis in 217 patients, adalimumab showed superiority over placebo in preventing treatment failure [HR: 0.50; 95% CI: 0.36–0.70; $p < 0.001$].[444] In a Swiss IBD cohort study, 72% [18/25] of patients with uveitis responded to infliximab or adalimumab.[330]

6.3 Scleritis and episcleritis

Statement 30

We recommend early use of oral NSAIDs and consideration of systemic corticosteroids for treatment of scleritis. Steroid-sparing agents, including TNFα antagonists, may be used in refractory cases or when corticosteroid response is incomplete [EL4]

We recommend topical lubricants and cool compresses for treatment of episcleritis [EL4]. Topical NSAIDs and corticosteroids should be considered if symptoms persist despite controlling IBD

Patients with symptoms suggestive of scleritis, in particular eye pain preventing sleep, should be urgently referred to an ophthalmologist, as correct classification and management impact severity and prognosis [EL4] [consensus: 100%]

Scleritis is a rare ocular manifestation with an incidence of ~2.8 per 100 000 person-years. Scleritis occurs in <1% of IBD cases.[445] In a large population-representative study in the UK, CD patients had an over three-fold increased risk of incident scleritis [OR: 3.6; $p < 0.001$] and UC patients had an over two-fold increased risk [OR: 2.2; $p < 0.001$].[445,446]

Patients with IBD who report eye pain sufficiently severe to wake them from sleep, with or without eye redness, should be suspected of having scleritis and urgently referred to an ophthalmologist, as correct diagnosis and treatment impact visual prognosis.

Scleritis is classified according to location [anterior or posterior, the latter typically presenting without ocular hyperaemia] and clinical phenotype [diffuse, nodular, and/or necrotizing].[446] Classification itself correlates with severity and prognosis; the necrotizing phenotype may predict poorer prognosis.[445,446] Symptoms as described above, together with vision blurring and scleral injection [which does not blanche after topical phenylephrine application], help differentiate scleritis from episcleritis.[447,448] Potentially severe ocular sequelae of untreated or relapsing scleritis include ocular hypertension, secondary glaucoma, retinal detachment, uveitis, and scleromalacia perforans.[445,446,448]

Management should be directed by an ophthalmologist, with treatment options largely underpinned by a limited evidence base. An oral course of selective COX-2 inhibitors is first-line therapy in milder cases, with some evidence that topical NSAIDs may also be effective.[301] Periocular corticosteroid injections may be adjunct in non-necrotizing scleritis.[449] Topical corticosteroids may be efficacious for pain management, but prolonged use may be associated with development of elevated intraocular pressure and cataract.[301] Systemic corticosteroids [1–1.5 mg/kg/day and then tapering] are usually necessary, especially in posterior and necrotizing scleritis[301,449] and when symptoms or vision impairment have not improved within a few days of starting NSAIDs. Immunosuppressive therapy [methotrexate as first choice, followed by azathioprine, mycophenolate mofetil, or calcineurin inhibitors] may be considered as steroid-sparing agents.[449] Biologic agents are recommended in severe sight-threatening cases that are refractory to immunomodulatory therapy, have incomplete response to corticosteroids, or both. Infliximab at the standard dose of 5 mg/kg has shown efficacy.[301,449]

Episcleritis is a common and relatively benign ophthalmic EIM, with a prevalence of 3.95 [95% CI: 2.91–4.99] per 1000 patients in CD and 4.73 [95% CI: 3.95–5.52] per 1000 patients in UC.[437] Episcleritis is a self-limiting condition strongly associated with IBD disease activity and usually resolves when disease activity is controlled.[301,446–448] It can be classified as nodular or diffuse and should be distinguished from conjunctivitis [for which it is frequently mistaken] and from scleritis. Painless hyperaemia or mild discomfort, absence of visual abnormalities, and injection blanching with topical phenylephrine application are characteristic. Treatment is usually symptomatic and conservative, consisting of topical lubricants [e.g. artificial tears] and cool compresses. Topical NSAIDs or corticosteroids can be added if symptoms persist or if resolution of intestinal inflammation is difficult to achieve.[447]

7. Central nervous system manifestations

Statement 31

Central nervous system manifestations may be more common in IBD patients than in the general population [EL4]. Such manifestations include venous sinus thrombosis, stroke, and central demyelination. In patients with IBD and central demyelination, TNFα antagonists are contraindicated [EL4] [consensus: 98%]

IBD is rarely associated with peripheral neuropathies [EL4]. Treatable causes should be identified. Central neuropathies have only been described in a case series [EL5] and drug adverse effects should be considered [consensus: 100%]

The prevalence of neurological manifestations or complications of IBD is heterogenous and varies between 0.2% and 36%.[450,451]

IBD may be associated with other immune-mediated disorders, particularly multiple sclerosis [MS], where there is a known bidirectional association between these conditions[74,452,453] due to shared genetic susceptibility.[454] A possible association with epilepsy has also been described.[450,451,455] As described in Section 2, there is also an association between IBD and VTE, which extends to cerebral venous thrombosis in addition to cerebrovascular accidents (CVAs); as such, these differentials should be considered in patients with IBD presenting with new neurological deficits.

Both headaches[456,457] and peripheral polyneuropathies[457–461] are 2–5 times more prevalent in IBD compared with the general population, which may reflect both underlying disease or drug side effects. Drug-associated neurological manifestations include the well-known association between peripheral neuropathy and metronidazole[462–464] and the association between central nervous system demyelination and TNFα antagonists.[465–468]

In cases of peripheral neuropathy in IBD, common underlying causes such as vitamin or mineral deficiencies [vitamins B_{12}, D, and E, red-cell folate, thiamine and nicotinamide, and copper] and metabolic diseases [hypothyroidism and diabetes mellitus] should be excluded and treated. Suspected small- and large-fibre axonal neuropathies should be evaluated with electromyography [EMG].[459,460]

Multiple case reports of cranial-nerve involvement in IBD have been described, including optic nerve [II],[469–472] oculomotor nerve [VI],[473] facial nerve [VII], and auditory nerve [VIII],[474] at times in association with oral granulomatosis. These may be independent of disease activity and may precede the onset of IBD but may also respond to immunosuppressive therapy. Management should be undertaken in conjunction with a neurologist to exclude alternative differentials and to consider treatment options, including potential use of intravenous immunoglobulins.[459,475]

8. Fatigue in IBD

Statement 32

Fatigue is more frequent and more severe in patients with IBD than in the general population; prevalence ranges from 40–60% in inactive to mild disease to >80% in active disease There is evidence for fatigue as an independent entity, as a prevalence of 40% in IBD patients in remission has been reported. Fatigue negatively impacts health-related quality of life, independent of disease activity or anaemia [EL4] [consensus: 96%]

Fatigue is a term used to describe an overall feeling of weariness, tiredness, or lack of energy and motivation.[476] Fatigue is strongly associated with poor health-related quality of life, disability, and depression[477] and is the most common reason for work absence in IBD.

Overall, fatigue is both more frequent and more severe in patients with IBD than in the general population.[478–480] Fatigue is more severe in CD than in UC. The prevalence of fatigue at follow-up usually ranges from 40% to 60% in IBD patients with mild to inactive disease[111,476,478,479,481–485] and can reach up to 86% in those with active disease, with hospitalization a specific risk.[476]

There is evidence for fatigue as an independent entity in IBD; a fatigue prevalence of 40% has been reported in patients in remission.[486] Although sarcopenia and increased CRP have been suggested as causative factors,[487] low-grade immune activity does not account for fatigue in deep remission.[481] Although both higher total fatigue scores and chronic fatigue were associated with increased disease activity scores in patients with UC and CD, this was not related to increased CRP or faecal calprotectin.[488]

The aetiology of fatigue in IBD is poorly understood. Disease-related factors [such as inflammation] and pharmacological treatments negatively impact skeletal muscle and brain physiology. Secondary factors, such as malnutrition, anaemia, sleep disturbance, and psychological comorbidity, are potential determinants.[476]

Fatigue in IBD is most apparent for patients <60 years of age,[111] those with younger age at diagnosis,[478] and in women.[478,479,481,489,490] Fatigue may also be associated with body image dissatisfaction,[491] anxiety, and depression.[478,483,484,487–489,492] An aggressive IBD phenotype may be associated with more severe fatigue.[479] However, as discussed above, there is a high prevalence of fatigue even in deep remission, and the data on whether fatigue severity is proportional to disease activity are conflicting and sparce.[480] Additional risk factors are nocturnal diarrhoea and presence of EIMs. The association between anaemia and fatigue is also complex, with anaemia an independent risk factor for fatigue.[493] However, in IBD, fatigue frequently occurs independently of anaemia or iron deficiency.[111,484,494]

A multimodal approach is required to treat fatigue in IBD.[476,479,480] Potentially reversible causes should be investigated and corrected, including management of active disease and correction of underlying deficiencies, including treatment of anaemia and vitamin B deficiency.[495] Psychosocial intervention shows potential efficacy in reducing fatigue perception in quiescent disease, and exercise training may improve fatigue burden, although the evidence to date is inconclusive.[476] TNFα antagonist therapy is associated with improvement in fatigue after 1 year.[479] Avoidance of corticosteroids and cessation of immunomodulator therapy may be beneficial, although this should be balanced with risk of disease flare.[480,482]

9. Endocrine manifestations

9.1 Glucocorticoid-induced adrenal insufficiency

9.1.1 Epidemiology and risk factors

The risk of glucocorticoid-induced adrenal insufficiency in IBD is estimated at 52.2%, based on analysis of two small studies.[496] Identified risk factors include duration of disease and longer exposure to steroids.[497,498] The risk with budesonide or topical steroids is much lower, although case reports exist.[496,499–502] Patients taking budesonide doses >6 mg for more than 8 weeks may be at risk.[496,499–501]

9.1.2 Clinical symptoms

Usually, glucocorticoid-induced adrenal insufficiency defined biochemically (low baseline cortisol and/or low/no response to synthetic adrenocorticotropic hormone [ACTH]; thresholds depend on assay) is not accompanied by clinical symptoms.[503] However, patients often present with non-specific symptoms that can be attributed to alternative diagnoses. If undiagnosed, glucocorticoid-induced adrenal insufficiency can be precipitated by a potentially life-threatening adrenal crisis by events including infections and surgery.[504] There is a wide range of severity and clinical presentations. Additionally, many patients with glucocorticoid-induced adrenal insufficiency may present without any symptoms, or insidious symptoms of fatigue and abdominal pain that may be mistakenly attributed to underlying IBD.

9.1.3 Management

It is important to emphasize judicious use of steroids, with alternative agents used when possible, especially for maintenance therapy.

Glucocorticoid-tapering regimens are not standardized, and no specific regimen has shown superiority for the duration of hypothalamic–pituitary–adrenal axis recovery.[503] At present, routine monitoring for adrenal recovery in steroid-tapering regimens is not common. However, in patients who have received prolonged steroids, such as in steroid-dependent disease, evaluation of the hypothalamic–pituitary–adrenal access should be performed before cessation.

The ACTH test, which evaluates the recovery of the hypothalamic–pituitary–adrenal axis, can be performed when the dose of glucocorticoids has been decreased to 5 mg of prednisone daily. If negative, ACTH tests may be re-performed every 3 months until recovery occurs. If glucocorticoid-induced adrenal insufficiency persists, the ACTH test may be performed every 6–12 months. In patients with glucocorticoid-induced adrenal insufficiency, the time to full recovery of the hypothalamic–pituitary–adrenal axis may take years. Adrenal insufficiency may be permanent in a small proportion of patients who will require hydrocortisone supplemental therapy.[503] Specifically, adrenal crisis management depends on urgent in-hospital care with hydrocortisone bolus injections.

9.2 Thyroidopathies

Several large cohorts did not find an association between autoimmune thyroiditis and IBD.[505,506] In an Israeli administrative database of 12 625, autoimmune thyroiditis occurred in 1.5% of IBD patients and in 1.2% of controls. Interestingly in this study, all autoimmune diseases except for thyroiditis were more prevalent among IBD patients, similar to previous studies.[505,506] Some authors have even suggested that the risk of thyroid dysfunction was lower in IBD.[506,507] However, one Danish epidemiolocal study revealed a significant association between UC and Grave's disease.[193]

9.3 Hypogonadism

While ageing is the main factor driving the risk of hypogonadism in both men and women, hypogonadism can occur in patients with IBD and can be secondary to medication, chronic inflammation, or both. Proinflammatory cytokines, such as TNFα, IL-1, and IL-6, are known to inhibit testosterone production of Leydig cells and steroidogenesis of ovarian cells.[508] Hypogonadism results in many potential clinical features including fatigue, changes in sexual function, erectile dysfunction in men, urogenital atrophy, and worsening body image in women.[509] In the context of IBD, hypogonadism may also be a consequence of opioid use.[510,511]

Conflict of Interest

ECCO has diligently maintained a disclosure policy of potential conflicts of interests [CoI]. The conflict-of-interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI disclosures are not only stored at the ECCO Office and the editorial office of JCC, but are also open to public scrutiny on the ECCO website [https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html], providing a comprehensive overview of potential conflicts of interest of the authors.

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Supplementary Data

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

Data Availability Statement

No new data were generated in support of this research.

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