ECCO Guideline/Consensus Paper

The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease


1. Introduction

This is the first European Crohn’s and Colitis Organisation [ECCO] consensus guideline that addresses extra-intestinal manifestations [EIMs] in inflammatory bowel disease [IBD]. It has been drafted by 21 ECCO members from 13 European countries. Although this is the first ECCO consensus guideline that primarily addresses EIMs, it is partly derived from, updates, and replaces previous ECCO...
consensus advice on EIMs, contained within the consensus guidelines for Crohn’s disease [CD] and ulcerative colitis [UC]. The strategy to define consensus was similar to that previously described in other ECCO consensus guidelines [available at www.ecco-ibd.eu]. Briefly, topics were selected by the ECCO guidelines committee [GuiCom]. ECCO members were selected to form working groups. Provisional ECCO Statements and supporting text were written following a comprehensive literature review, then refined following two voting rounds which included national representative participation by ECCO’s 35 member countries. The level of evidence was graded according to the Oxford Centre for Evidence-based Medicine [www.cebm.net]. The ECCO Statements were finalised by the authors at a meeting in Vienna in October 2014 and represent consensus with agreement of at least 80% of participants. Complete consensus [100% agreement] was reached for most statements. The supporting text was then finalised under the direction of each working group leader [VA, SV, FC, MH] before being integrated by the two consensus leaders [MH, FC]. This consensus guideline is pictorially represented within the freely available ECCO e-Guide [http://www.e-guide.ecco-ibd.eu/].

Up to 50% of patients with inflammatory bowel disease [IBD] experience at least one extra-intestinal manifestation [EIM], which can present before IBD is diagnosed. EIMs adversely impact upon patients’ quality of life and some, such as primary sclerosing cholangitis [PSC] or venous thromboembolism [VTE], can be life-threatening. The probability of developing EIMs increases with disease duration and in patients who already have one EIM. EIMs are more common in CD than UC, particularly in patients with colonic CD; some EIMs, such as iritis/uveitis, are more common in women whereas PSC and ankylosing spondylitis are more common in males. Most EIMs run in parallel with intestinal disease activity, with the exception of ankylosing spondylitis and uveitis and with uncertainty regarding PSC and pyoderma gangrenosum [PG]. The management of complex EIMs should be discussed in a multidisciplinary team meeting.

2. Arthropathy and arthritis

2.1. Investigation and diagnostic criteria

ECCO Statement 2A

Both peripheral and axial arthropathies occur in UC and CD, and belong to the spondyloarthritides [SpA] group of conditions (evidence level 2 [EL2]). They should be distinguished from arthralgia, which is more common. The prevalence of axial disease is equal between sexes and forms of IBD, but peripheral arthropathies are more common in CD [particularly affecting the colon] and in females [EL3].

ECCO Statement 2B

Diagnosis of axial SpA is based on the clinical feature of inflammatory low back pain associated with magnetic resonance imaging [MRI] or radiographic features of spondilitis [EL2]. Human leukocyte antigen B27 [HLA-B27] is associated with axial arthritis, but it has a lower prevalence than in idiopathic ankylosing spondylitis, making it unreliable as a diagnostic test in IBD [EL2].

ECCO Statement 2C

Radiological evidence of sacroiliitis occurs in 20–50% of patients with UC and CD, but progressive ankylosing spondylitis occurs in only 1–10% of patients [EL2]. MRI may identify early sacroiliitis in symptomatic patients with normal plain radiology [non-radiographic SpA] [EL2].

Arthropathies associated with IBD belong to the SpA group of conditions. According to the Assessment in Spondyloarthritis International Society [ASAS] classification of 2009, SpA are divided into axial and peripheral SpA, depending on the predominant symptoms. Diagnosis of axial SpA is based on magnetic resonance imaging [MRI] or radiographic features of spondilitis associated with clinical features of inflammatory low back pain. Radiological evidence of sacroiliitis is common in both UC and CD, occurring in 20–50% of patients, but progressive AS with syndesmophytes occurs in only 1–10% of patients. Early assessment using T1-weighted spin-echo [T1SE], short tau inversion recovery [STIR], and fat-saturated T2-weighted sequences, are recommended for patients aged less than 40 years with inflammatory back pain lasting more than 3 months, to identify non-radiographic sacroiliitis. Human leukocyte antigen [HLA]-B27 is found in 25–75% of patients with IBD and AS, but only in 7–15% of patients with isolated sacroiliitis. HLA-B27 positive IBD patients seem to be at risk for the development of AS but, due to a lower prevalence than in idiopathic AS, it is unreliable as a diagnostic test in IBD.

ECCO Statement 2D

Diagnosis of peripheral arthropathy and/or enthesitis associated with IBD is based on signs of inflammation and exclusion of other specific forms of arthritis [EL3]. Type I is an acute pauciarticular arthritis, affecting large joints, and is usually associated with active IBD. Type II is polyarticular, affecting a larger number of peripheral joints, and is independent of IBD activity [EL4].

The peripheral arthritis of IBD is an inflammatory arthropathy but, unlike psoriatic arthritis and other inflammatory arthropathies, it is generally non-erosive. The ASAS guidelines for peripheral SpA included only six patients with IBD, so the clinical classification of IBD-related peripheral arthropathies is usually based on a larger study of IBD patients. On the basis of articular involvement and natural history, two different types have been empirically identified. Type 1 is defined as joint pain with evidence of swelling or effusion affecting fewer than five joints, mainly the large weight-bearing joints of the lower limb. The symptoms are usually acute and self-limiting [less than 10 weeks] without permanent joint damage, and usually correlate with IBD flares. Type 2 affects more than five joints, has a symmetrical distribution, and predominantly affects the upper limbs. Symptoms persist for months or years, independent of IBD activity. Diagnosis is made on clinical grounds based on characteristic features of inflammation and exclusion of other specific forms of arthritis. Imaging excludes deformity, in contrast to osteoarthritis, rheumatoid arthritis, and connective tissue diseases. IBD-associated peripheral arthritis has to be differentiated from arthralgia [which may complicate corticosteroid withdrawal], osteonecrosis related to corticosteroids, and infliximab-related lupus-like syndrome.

Enthesopathies and dactylitis have been studied less extensively in IBD. Enthesitis describes inflammation at the insertion of a tendon to the bone leading to erosions and bone proliferation [spur formation]. Patients suffer pain, tenderness, and swelling. Dactylitis [sausage-like
fingers or toes] is characteristic of SpA, with a prevalence of 2–4% in IBD.\(^{21,23}\)

2.2. Natural history and pathogenesis
Peripheral arthritis in IBD is usually asymmetrical and oligoarticular, and more common in CD, particularly in those with colonic disease. Its onset may precede that of bowel symptoms, although it usually coincides with or presents after the appearance of IBD.\(^{27,28}\) Its prevalence in IBD ranges from 5% to 20% \(^{5–14}\%\) in UC and 10–20% in CD.\(^{14,26,27}\) In general, the prognosis of peripheral arthritis is good, only becoming chronic and erosive in a minority of patients. The prognosis of axial involvement is less favourable and is related to the prognosis of AS, and not the progress of IBD. Classic AS is a progressive condition with structural damage and disability affecting patients’ quality of life. It is important to identify early non-radiological axial SpA, to try prevent the progression to radiographic axial SpA that occurs in 10–20% by 2 years in those with an elevated C-reactive protein [CRP] or with active inflammation on MRI.\(^{29}\)

The importance of IBD in the pathogenesis of SpA is underscored by the finding that sacroiliitis and spondylitis occur in up to 20% of patients with IBD, whereas up to 70% of patients with AS or SpA have microscopic evidence of gut inflammation, although only 7% develop CD.\(^{30}\) The association of HLA-B27 with AS is seen in IBD, but to a lesser degree than in idiopathic AS \(≈70\%\) vs 94%).\(^{26}\)

This may relate to the overlap between the genetics of AS and IBD. Genome-wide association studies [GWAS] and meta-analyses have discovered more than 160 loci for IBD susceptibility. Notably, in an extensive meta-analysis and validation in over 75,000 IBD cases and controls,\(^{32}\) 8 of 11 identified loci for AS were shared by IBD with a 13-fold enrichment above that expected. These are: IL23R, IL12B, STAT3, and PTGER4 linked to the T\(^{13}\)pathway; CARD9 linked to the NFKB pathway; and ILR2 and ORMDDL3 linked to immune responses. These associations corroborate a common genetic background beyond the major histocompatibility complex [MHC].\(^{13}\)

2.3. Treatment

ECCO Statement 2E

Patients with axial SpA should be jointly managed with rheumatologists. Intensive physiotherapy and short-term non-steroidal anti-inflammatory drugs [NSAIDs] are effective [EL 3], but long-term treatment with NSAIDs is not recommended [EL2]. Sulfasalazine [EL2] and methotrexate [EL2] are of limited efficacy; therefore early anti-tumour necrosis factor [TNF] is the preferred treatment for those intolerant or refractory to NSAIDs [EL2]

ECCO Statement 2F

Treatment of underlying gut inflammation is often sufficient to treat peripheral arthritis [EL2], although short-term NSAIDs or local steroid injection provide symptomatic relief [EL4]. Short-term oral corticosteroids are effective [EL3], but should be discontinued as soon as practicable. In persistent arthritis, sulfasalazine [EL2] and methotrexate [EL4] may have a role. Anti-TNF therapy is appropriate and effective in resistant cases [EL2]

Recommendations for the treatment of IBD-related arthropathy are based on studies in SpA, predominantly AS. Prospective controlled trials in IBD have not been published; only small open-label trials or case reports are reported.\(^{34,35,36,37}\)

Patients with axial SpA should be jointly managed with rheumatologists because of the potential disabling disease course. Evidence supports the use of intensive physiotherapy and non-steroidal anti-inflammatory drug [NSAIDs] in axial arthropathy, but long-term treatment with NSAIDs is best avoided in IBD.\(^{38}\) Although NSAIDs increase the risk for relapse,\(^{39,40}\) a larger cohort study including 426 CD patients and 203 UC patients illustrated that short-term therapy with low doses of NSAIDs was well tolerated;\(^{41}\) use of high-dose NSAIDs was associated with higher disease activity among those with Crohn’s colitis, but this was not reflected by a significant increase in disease flares. The use of COX-2 inhibitors such as etoricoxib and celecoxib may be safer, with a lower risk of disease flare, than conventional NSAIDs. Methotrexate and thiopurines, in contrast, are of limited efficacy.\(^{44}\)

Anti-tumour necrosis factor [TNF] is the preferred treatment in patients intolerant or refractory to NSAIDs.\(^{44}\) Conclusive data on the long-term effect of anti-TNF on radiographic progression are lacking, though recent data report less pronounced bone formation.\(^{46,47}\) Anti-TNF therapy may reduce progression of early non-radiological axial SpA \(^{46,47}\) although results of large prospective follow-up studies are required.

Effective treatment of underlying gut inflammation is often sufficient to treat peripheral arthritis. However, there is general support for the use of short-term systemic corticosteroids, NSAIDs, and local steroid injections for symptomatic relief.\(^{10}\) Although sulfasalazine and methotrexate are ineffective or only marginally effective in ankylosing spondylitis,\(^ {44}\) a 2014 Cochrane review reported effectiveness of sulfasalazine in patients with peripheral disease, and recommended the drug for patients with short disease duration and increased erythrocyte sedimentation rate [ESR],\(^ {13}\) although a review in 2012 concluded that sulfasalazine was not superior to placebo.\(^ {12}\) A recent study supports the current recommendation that sulfasalazine be an optional treatment in SpA patients with peripheral disease, although overall responses are modest. Initial treatment with sulfasalazine does not seem to impair later anti-TNF responses.\(^ {13}\) Sulfasalazine can be effective in large-joint arthropathy.\(^ {5,45}\) Anti-TNF therapy has been shown to be effective in small case series in patients with persistent disease impacting on quality of life.

Arthralgia [joint pain without inflammation] is common in IBD and may be associated with the introduction of thiopurines or the withdrawal of corticosteroids. Arthralgia associated with azathioprine is often associated with myalgia and usually appears during the first 3 months of therapy. Switching to mercaptopurine is usually effective.\(^ {14}\)

3. Metabolic bone disease

3.1. Investigations and diagnostic criteria

ECCO Statement 3A

Diagnosis of osteoporosis in adults is best made from a T-score < –2.5 on radiographic bone densitometry [EL1]. Osteoporosis is a risk factor for fracture and identifies patients who should receive treatment [EL2]

Low bone mass and osteoporosis are common in male and female patients with IBD [20–50%]. Contributing factors include chronic inflammation, corticosteroid treatment, extensive small-bowel disease or resection, age, smoking, low physical activity, and nutritional deficiencies.\(^ {37}\)}
The diagnosis of osteoporosis in adults is based on assessment of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA). Osteoporosis is defined as a BMD value at least 2.5 standard deviations lower than the mean BMD for young healthy adults [T-score ≤ −2.5].18 In children, the relationship between BMD and fracture risk is not well established and reference to the Z-score has been recommended. A Z-score < −2 should be reported as ‘below expected range for age’ and the need for treatment interpreted in the context of fracture risk factors [e.g., low weight, previous fracture, medication, IBD activity].29

Incidentally performed abdominal computed tomography (CT) is able to measure lumbar spine BMD accurately and so can be reviewed to exclude osteoporosis,60,61 although multi-detector CT and high-resolution peripheral quantitative CT, quantitative ultrasonography, MRI, and MR spectroscopy are research applications and not recommended as elective screening techniques.62

Screening recommendations for IBD patients do not differ from those for the general population and are based on risk factors such as postmenopausal state, ongoing corticosteroid treatment, cumulative corticosteroid use > 3 months, history of low-trauma fracture, and age.63,64 Annual DXA scans have been recommended in those receiving long-term corticosteroids, especially in the context of risk factors, when the T-score approaches the threshold for treatment with bisphosphonates [T < −1.5].47 Osteoporosis identifies patients at above average risk for fractures of the spine and peripheral long bones; they should receive treatment, since the fracture risk increases about 2-fold for each standard deviation decline in BMD below the population mean.66,67 Vertebral fractures have been documented in patients with both reduced and normal bone density, challenging the concept that osteoporosis is the main risk factor for vertebral fractures in young patients with IBD.65,66,70 No linear association between lumbar bone density and spontaneous fracture risk exists. The strongest predictor of future fracture is a previous vertebral fracture.

3.2. Natural history and pathogenesis
When measured by DXA, bone density of the lumbar spine is significantly reduced in the majority of patients with IBD, who are predominantly young patients aged between 20 and 40 years; 40–50% of all patients have osteopenia, with a T-score < −1 and > −2.5. Osteoporosis has been reported in 5–37% of IBD patients.71,72,73,74,75

A significant proportion of IBD patients can normalise their bone density after 3 years in stable remission.76 Only a few studies have investigated longitudinal changes in BMD prospectively. Treatment with anti-TNF often improves bone density.77 Population-based studies have shown that factors predicting changes in BMD are similar in IBD to those seen in the general population.21,22 The relative importance of each risk factor remains to be established.

Recently there has been increasing recognition of the immunological role of vitamin D.79,79,80,81,82 Deficiency can be a consequence of IBD.81,82,83 Vitamin D deficiency is common in newly diagnosed IBD patients, and so may contribute to increased risk of IBD.84 A recent cohort study suggests a possible role for vitamin D in IBD pathogenesis: women living in southern latitudes had a lower risk of CD (hazard ratio [HR] 0.48, 95% confidence interval [CI] 0.3–0.7) and UC (HR 0.62, 95% CI 0.4–0.9) than those living in northern latitudes.85 These findings are consistent with previous data suggesting a north-south gradient in disease incidence,86 mimicking exposure to ultraviolet light, a major determinant of vitamin D status.87,88

3.3. Treatment

ECCO Statement 3B
Weight-bearing exercise [EL2], stopping smoking [EL3], and maintaining adequate dietary calcium [1 g/day] [EL2] are beneficial in preventing bone loss. Patients receiving systemic steroid therapy should receive calcium and vitamin D for prophylaxis for the duration of treatment [EL5]

ECCO Statement 3C
Osteopenia is a prognostic marker for osteoporosis [EL3], therefore calcium and vitamin D are recommended if the T score is less than −1.5 [EL4]. In these patients, a history of pre-existing fracture should prompt consideration for more intensive treatment [EL4]

ECCO Statement 3D
Management of underlying disease activity is important, particularly in the young whereas, in postmenopausal women or those with previous spontaneous fractures, regular use of bisphosphonates and other therapies can prevent further bone loss [EL2]

Treatment should be considered in patients with low BMD and/or additional risk factors. Fracture prediction tools such as FRAX, which calculates fracture risk in the absence of a direct measurement of BMD, may be useful in determining who requires treatment,69,70 although FRAX has not been validated in IBD populations nor in individuals aged < 50 years. Exposure to factors known to increase bone loss and/or fracture should be limited. Measures like weight-bearing or resistive exercises, smoking and excess alcohol cessation, and maintaining adequate dietary calcium [1 g/d]78 from diet and/or supplements should be implemented.

Vitamin D should be maintained in the recommended range; this usually requires supplements at a dose of ~ 1000 IU [25 µg] daily, or higher dose if known vitamin D deficiency. Supplemental calcium should be given only if dietary calcium is < 800 mg/d. Treatment with calcium 500–1000 mg/day and vitamin D [800–1000 IU/day] increases bone density in patients with IBD.77 A recent large study in CD showed that tight control of disease activity and supplementation of calcium and vitamin D were associated with a median annual increase in BMD of 0.76% over 4 years.78 The value of calcium and vitamin D in preventing fractures has not been demonstrated in patients with IBD, although efficacious in postmenopausal or steroid-induced osteoporosis.85 Vitamin D deficiency is common in patients with IBD and should be corrected as necessary.24 Patients receiving systemic steroid therapy should receive calcium and vitamin D for prophylaxis.

Meta-analysis showed that bisphosphonates are effective for the treatment of low BMD in IBD and reduce the risk of vertebral but not non-vertebral fractures79 and can therefore be recommended for fracture prevention in IBD patients. Due to the heterogeneity of studies, a general recommendation for fracture prevention with bisphosphonates is not feasible in young, premenopausal women or young men. Bisphosphonate-related osteonecrosis of the jaw is a rare side effect [< 1%] and should be considered in patients with poor dental status or insufficient dental hygiene. In these patients, a dental examination including radiographs before therapy might
be appropriate. Other emergent side effects are atypical femoral fracture and oesophagitis. Rheumatologists have virtually stopped using calcitonin or raloxifene as these are associated with only small increases in bone density and small reductions in vertebral fracture risk. There is no evidence that they reduce hip or other peripheral fractures.

The evidence for treatment and prevention of osteoporosis in young patients is limited. All patients with persistently active disease should be treated according to guidelines with immunosuppressive therapy [thiopurines, anti-integrins, anti-TNF] to avoid prolonged steroid treatment and inflammatory activity, in order to prevent bone loss. Newer drugs like teriparatide, strontium ranelate, or denosumab should be prospectively studied in patients with IBD before their use can be recommended. Recent data showed an incremental cardiovascular risk for patients treated with strontium ranelate, opposed to scleritis which is often very painful. Uveitis is less common but has potentially more severe consequences. When related to CD, uveitis is frequently bilateral, insidious in onset, and long-lasting, although characteristic acute anterior uveitis with sudden onset may occur. Patients complain of a variety of symptoms including the classical features of uveitis: eye pain, blurred vision, photophobia, and headache. The possibility of progression to loss of vision should prompt urgent referral to an ophthalmologist with expertise in the management of ocular inflammation, and the use of immunomodulatory and biological agents. Slit-lamp examination will confirm the diagnosis and permit the differentiation between anterior and posterior uveitis.

Mild pain associated with hyperaemia of the conjunctiva and episclera, without visual changes, often allows episcleritis to be differentiated from scleritis. Visual disturbance, photophobia, moderate to severe pain, or other ocular involvement should prompt ophthalmic referral for examination using a slit-lamp to assess for the presence of inflammatory cells and/or scleritis.

For uveitis, both the SUN guidelines and those of the International Uveitis Study Group [IUSG] are useful in disease classification. Severity assessment may also be useful in episcleritis and scleritis.

4. Eye disease

4.1. Investigation and diagnostic criteria

**ECCO Guideline/Consensus Paper**

**ECCO Statement 4A**

Simple episcleritis does not require referral to an ophthalmologist. This should be differentiated from uveitis and scleritis, based upon the absence of moderate-severe eye pain, photophobia, blurring, and diminished vision. When this is not possible, or in patients with possible sight-threatening ocular manifestations [scleritis and uveitis], patients should be treated by an ophthalmologist with expertise in ocular inflammatory disease [EL5]

Anterior uveitis and episcleritis are the most common ocular manifestations of IBD. Some ocular manifestations in IBD can be secondary to treatment and/or effects of the intestinal disease itself. The classification of uveitis has been set out in the Standardization of Uveitis Nomenclature [SUN] guidelines [Table 1].

The most commonly reported ocular manifestations are dry eye, blepharitis, episcleritis, or anterior uveitis. Scleritis and intermediate or posterior uveitis [which are more likely to be sight-threatening] are much rarer, occurring in less than 1%, but left untreated may progress to permanent visual deficits. Reports of posterior uveitis include a series of 13 cases exhibiting a spectrum of features from choroiditis to retrolubular neuritis. Whereas episcleritis tends to reflect disease activity in the bowel and other extra-intestinal sites, uveitis can be independent of bowel symptoms and other EIMs and may precede the onset of bowel symptoms. Other rare causes of ocular involvement with devastating consequences include vascular occlusion potentially secondary to vasculitis [including central retinal artery occlusion], anterior ischaemic optic neuropathy, and orbital inflammation.

Episcleritis may be relatively painless, presenting with hyperaemic sclera and conjunctiva, and itching and burning may occur, as opposed to scleritis which is often very painful. Uveitis is less common but has potentially more severe consequences. When related to CD, uveitis is frequently bilateral, insidious in onset, and long-lasting, although characteristic acute anterior uveitis with sudden onset may occur. Patients complain of a variety of symptoms including the classical features of uveitis: eye pain, blurred vision, photophobia, and headache. The possibility of progression to loss of vision should prompt urgent referral to an ophthalmologist with expertise in the management of ocular inflammation, and the use of immunomodulatory and biological agents. Slit-lamp examination will confirm the diagnosis and permit the differentiation between anterior and posterior uveitis.

Mild pain associated with hyperaemia of the conjunctiva and episclera, without visual changes, often allows episcleritis to be differentiated from scleritis. Visual disturbance, photophobia, moderate to severe pain, or other ocular involvement should prompt ophthalmic referral for examination using a slit-lamp to assess for the presence of inflammatory cells and/or scleritis.

For uveitis, both the SUN guidelines and those of the International Uveitis Study Group [IUSG] are useful in disease classification. Severity assessment may also be useful in episcleritis and scleritis.

4.2. Natural history and pathogenesis

Reports of the incidence of ocular manifestations range from 4–12% of IBD cases although in some cohorts this rises to 29%. None of these percentages is population based, and they tend to be limited to small numbers of patients studied in tertiary centres—hence are probably overestimates. One community study [only surveying 112 individuals of whom only 88 had IBD] showed that patients with IBD are more likely to complain of ocular symptoms compared with controls.

Ocular [episcleritis and scleritis] and intraocular inflammatory disease [uveitis] as EIMs of IBD represent diverse pathologies, associated with activation and infiltration of both innate and adaptive immune cells into the tissue or intraocular environment. In severe cases, this may be associated with scleritis with fibrinoid necrosis and vasculitis. Genetic associations supporting innate activation in uveitis include association with NOD2 mutations and MICA on MHC class I and are supported by animal models.

4.3. Treatment

**ECCO Guideline/Consensus Paper**

**ECCO Statement 4B**

Episcleritis may self-resolve. Topical or systemic NSAIDs or topical corticosteroids can be used for symptomatic treatment [EL4]. Treatment for scleritis or uveitis should be guided by an ophthalmologist, and includes topical or systemic corticosteroids, conventional immunosuppressants, and anti-TNF agents [EL4].

Once a firm diagnosis is established, the treatment of most ocular symptoms is straightforward. Dry eyes may be treated with topical lubricants. Episcleritis responds following management of the underlying bowel disease, and to the addition of topical NSAIDs [for analgesia] and glucocorticoids. Anterior uveitis should be treated with topical corticosteroids and cycloplegics. For refractory uveitis and other rarer manifestations, the level of evidence remains low, with the evidence for efficacy of therapies being higher in patients with uveitis but without IBD. Successful use of topical and systemic corticosteroids, immunomodulator therapy, or biologicals.

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**Table 1. Classification of uveitis.**

| Anterior uveitis: Primary site of inflammation: anterior chamber |
| Intermediate uveitis: Primary site of inflammation: vitreous |
| Posterior uveitis: Primary site of inflammation: retina or choroid |
| Pan-uveitis: Primary site of inflammation: anterior chamber, vitreous, retina or choroid |
have all been reported, mainly from non-controlled retrospective cohorts [level 3 or 4 evidence]. Expert opinion favours the use of immunomodulators and biologics in posterior uveitis and scleritis,\textsuperscript{111,112,113} but is based upon evidence taken from the treatment of uveitis, where only a minority had IBD. Azathioprine, methotrexate, infliximab, and adalimumab have each been reported to be valuable in resistant cases.

5. Oral, aural and nasal disease

Oral CD includes deep ulcerations, pseudopolyps, and labial or buccal swelling. It is often associated with perineal disease and has a protracted course.\textsuperscript{114} Metastatic CD involvement of nasal mucosa, and aseptic nasal septal abscess associated with UC, have been reported.\textsuperscript{115,116,117} Sensorineural hearing loss has been described in association with IBD, particularly in patients with UC,\textsuperscript{118} and may be due to inner-ear obliteration, demonstrated by inner-ear T2-weighted MRI.\textsuperscript{119} Cogan’s syndrome is a rare autoimmune disease that results in non-syphilitic keratitis and vestibular-auditory symptoms that often lead to deafness. It can be associated with IBD.\textsuperscript{120}

6. Skin disease

6.1. Erythema nodosum

ECCO Statement 6A

Diagnosis of erythema nodosum [EN] is made on clinical grounds. In atypical cases a skin biopsy might be helpful [EL3]. Treatment is usually based on that of the underlying IBD. Systemic corticosteroids are required in severe cases [EL4]. Relapsing and resistant forms can be treated with immunomodulators or anti-TNF [EL4].

6.1.1. Investigation and diagnostic criteria

EN is readily recognised and characterised by raised, tender, red, or violet subcutaneous nodules, of 1–5 cm in diameter. It commonly affects the extensor surface of the extremities, particularly the anterior tibial areas, and usually occurs at times of IBD activity. EN often presents in association with systemic symptoms including arthralgia and fatigue. The differential diagnosis includes metastatic CD, which may appear at any site as solitary or multiple nodules, plaques, ulcers, or violaceous perifollicular pustules, with non-caseating granulomas present histologically.\textsuperscript{121} EN can also involve the trunk or upper extremities.\textsuperscript{7} A firm clinical diagnosis can normally be made and biopsy is not usually appropriate. If performed, the histology reveals a non-specific focal panniculitis.\textsuperscript{122,123}

6.1.2. Natural history and pathogenesis

The prevalence of EN in IBD ranges from 4.2% to 7.5%,\textsuperscript{124,125,126} higher in CD than UC\textsuperscript{4,127} and more common among female IBD patients.\textsuperscript{128} The pathogenesis of EN is not well understood. Some data suggest that it could be a type IV hypersensitivity reaction, because the trigger can be identified in almost 40% of patients.\textsuperscript{127}

6.1.3. Treatment

EN is normally associated with IBD flares, but not always with severity.\textsuperscript{129} Because it is closely related to disease activity, treatment is based on that of the underlying IBD. Systemic corticosteroids may be required in severe cases. In resistant cases or when there are frequent relapses, immunomodulation with azathioprine, infliximab, or adalimumab may be used.\textsuperscript{128,129}

6.2. Pyoderma gangrenosum

6.2.1. Investigation and diagnostic criteria

Pyoderma gangrenosum [PG] can occur anywhere on the body, including the genitalia, but the commonest sites are the shins and adjacent to stomas.\textsuperscript{7} Initially PG takes the form of single or multiple erythematous papules or pustules, but subsequent necrosis of the dermis leads to the development of deep excavating ulcerations that contain purulent material that is sterile on culture unless secondary wound infection has occurred. PG is characterised by the appearance of a skin pustule that quickly becomes a burrowing ulcer with violaceous edges, with a size between 2 cm and 20 cm in diameter. It can expose tendons, muscles, and deep tissues. PG is usually diagnosed clinically, based on the characteristic appearance of the lesions following exclusion of other possible skin diseases [e.g. ecthyma, necrotising vasculitis, necrobiosis lipoidica, arterial or venous insufficiency ulceration]. Since PG is a diagnosis of exclusion, it can be misdiagnosed in a substantial percentage of cases.\textsuperscript{130} In some cases a biopsy from the periphery of the lesion can help; findings in PG are non-specific, but biopsy can be helpful to exclude other skin disorders.

6.2.2. Natural history and pathogenesis

In recent publications, 0.6–2.1% of UC patients developed PG, a higher frequency than that observed in CD.\textsuperscript{131,132,133,134} The pathophysiology is unknown, but PG has been hypothesised to involve abnormal neutrophil function and impaired cellular immunity.\textsuperscript{113} Lesions are often preceded by trauma [pathergy].\textsuperscript{135} Controversy exists regarding the correlation between PG and IBD activity, as it may parallel IBD activity or run an independent course. PG has a tendency to recur following successful treatment in more than 25% of cases, often in the same place as the initial episode.\textsuperscript{124}

6.2.3. Treatment

ECCO Statement 6B

Pyoderma gangrenosum [PG] can be treated with systemic corticosteroids, infliximab [EL1b] or adalimumab [EL3b], or topical or oral calcineurin inhibitors [EL4].

The therapeutic goal should be rapid healing, as it can be a debilitating skin disorder. There is no evidence that the efficacy of treatment strategies for PG differs between IBD and non-IBD patients.

Immunosuppression is the mainstay of treatment. Traditionally the most commonly used drugs were systemic corticosteroids and ciclosporin. Corticosteroids were considered first-line treatment, with oral ciclosporin and oral or intravenous tacrolimus reserved for refractory cases.\textsuperscript{135,136,137,138} Infliximab has, however, changed the management of PG in patients with UC. Its effectiveness was first reported in small case studies.\textsuperscript{139} The largest study on the treatment of PG with infliximab was a multicentre, randomised, placebo-controlled trial of 30 patients, including 19 patients with IBD.\textsuperscript{140} Infliximab 5 mg/kg or placebo was given at Week 0. At Week 2 [the primary endpoint], significantly more patients in the infliximab group had improved compared with placebo [46% vs 6%, p = 0.025]. Thereafter, subjects in both arms were offered open-label infliximab. Overall, 29 patients received infliximab with the majority demonstrating improvement [response 69%, remission 31% at
6.3. Sweet syndrome [acute febrile neutrophilic dermatosis]

6.3.1. Investigation and diagnostic criteria
Sweet's syndrome is part of the group of acute neutrophilic dermatoses that includes PG, but can be distinguished by its appearance, distribution, and histological features. It is characterised by tender, red, inflammatory nodules or papules, usually affecting the upper limbs, face or neck. Fever can be present. It can be preceded by trauma [pathergy]. It has only been recognised as an IBD EIM recently. It is more common in women and in patients with colonic involvement or other EIMs. The rash is mostly associated with active disease.

6.3.2. Natural history and pathogenesis
Accurate data about incidence or prevalence are lacking. The pathogenesis remains unclear, although several potential mechanisms have been suggested, such as a type III hypersensitivity, T-lymphocyte dysfunction, or an association with histocompatibility antigens. There are various associations, including para-inflammatory, drug-induced, pregnancy-related, and para-neoplastic disease.

6.3.3. Treatment
Systemic corticosteroids have been reported to be effective; immunosuppressants should be considered in resistant or highly relapsing cases.

6.4. Anti-TNF induced skin inflammation
Immunomodulators and anti-TNF may induce cutaneous side effects, such as infection, malignancy, allergic reactions, and paradoxical inflammation [see Table 2].

6.4.1. Investigation and diagnostic criteria
Several centres have reported the development of psoriatic and eczematous lesions in patients with CD and UC receiving anti-TNF therapy, an observation which does not seem to relate to the age of the patient or the duration of treatment. Psoriasiform eczema, eczema, and xerosis were the most commonly observed type of skin lesions. Case reports have been described, and controlled case series have been published.

6.4.2. Natural history and pathogenesis
Skin lesions are reported in approximately 22% of patients treated with anti-TNF. Rahier et al. assessed clinical characteristics, risk factors, and outcomes of skin disease in patients with IBD that presented with psoriatic and eczematous lesions induced by anti-TNF. A total of 85 patients developed psoriatic [62 patients] and eczematous lesions [23 lesions]. Locations of eczematous lesions varied, whereas scalp and flexural varieties were mostly psoriatic. Skin lesions were not associated with IBD activity, but were more frequent among females and occurred with any type of anti-TNF agent [infliximab, adalimumab, or certolizumab]. Anti-neutrophilic antibodies were positively associated with skin paradoxical inflammation. A role for T helper 17 and interferon-γ-secreting T helper 1 cells, and IFN-α-expressing cells, has been described.

6.4.3. Treatment

**ECCO Statement 6C**

Anti-TNF treatment can induce paradoxical inflammation of the skin [EL3], which is a drug-class effect and is usually reversible upon drug cessation. Referral to a dermatologist is recommended. Most cases are controlled with topical treatment and anti-TNF can usually be maintained [EL3].

All cases should be managed together with the advice of a dermatologist. Topical therapy with corticosteroids, keratolytics [salicylic acid, urea], emollients, vitamin D analogues, and ultraviolet therapy [UVA or narrow-band UVB] result in partial or total remission in almost 50% of patients. Patients with psoriatic lesions that did not improve with topical therapy and who switched anti-TNF therapies occasionally developed recurrent lesions, suggesting a class effect. Ustekinumab has been reported to be useful in the treatment of the paradoxical effects of anti-TNF therapy. However, recent reports have also emerged of pusular psoriasis attributed to treatment with ustekinumab. The largest case series, however, is derived from the rheumatology literature, and the treatment is mainly based on expert opinion.

7. Hepato-pancreato-biliary disease

7.1. Primary sclerosing cholangitis

7.1.1. Investigation and diagnostic criteria
Up to 30% of patients with IBD have altered biochemical liver tests. PSC, drug-induced liver injury [DILI], and liver disease independent of IBD should be considered. PSC is the most common liver disease specific to IBD, and may affect up to 4–5% of patients in some geographical areas. Biliary strictures have been observed in IBD patients with normal liver function tests. In populations of Northern European descent, 70–80% of patients with PSC have concomitant IBD. According to standard clinical, endoscopic and histological criteria, IBD in PSC is mainly classified as UC and less frequently as Crohn’s disease.

Causes of secondary sclerosing cholangitis such as infection, immunodeficiency, ischaemia, pancreatic disease, or immunoglobulin [Ig]G4-related conditions have to be excluded. Secondary sclerosing cholangitis has similar histopathological and/or radiological features, but usually in the absence of IBD.

Symptoms of PSC include malaise, pruritus, fever, chills, night sweats, and right upper abdominal quadrant pain. Symptoms are intermittent and may be confined by those of underlying IBD. In patients with IBD, a high clinical awareness for PSC is needed as this disease commonly presents asymptomatically.

In patients with cholestasis in whom secondary causes of sclerosing cholangitis have been excluded, a diagnosis of PSC can be made if magnetic resonance cholangiography [MRC] shows typical findings. Although common practice at some centres, it has not been demonstrated that endoscopic retrograde cholangiography [ERC] is of added benefit to establish a diagnosis of PSC when the result of MRC is unclear and clinical suspicion of PSC is high. The ECCO consensus...
Table 2. Dermatological drug adverse events.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse events</th>
<th>Prevalence/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopurines</td>
<td>Skin and soft tissue infection</td>
<td>Frequently cellulitis</td>
</tr>
<tr>
<td></td>
<td>Non-melanoma skin cancer</td>
<td>Patient education, sun protection, and routine annual</td>
</tr>
<tr>
<td></td>
<td>Drug hypersensitivity</td>
<td>skin check important</td>
</tr>
<tr>
<td></td>
<td>Shingles</td>
<td>Prevalence up to 10%</td>
</tr>
<tr>
<td>Anti TNF</td>
<td>Skin reactions</td>
<td>Patients aged &gt; 60 years treated in combination with</td>
</tr>
<tr>
<td></td>
<td>Drug-induced lupus erythematosus [DILE]</td>
<td>systemic corticosteroids are at higher risk</td>
</tr>
<tr>
<td></td>
<td>Skin and soft-tissue infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paradoxical skin reactions:</td>
<td>Subcutaneous injection site reaction and delayed</td>
</tr>
<tr>
<td></td>
<td>eczema-like, psoriasis-like</td>
<td>infusion reaction</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Exfoliative dermatitis, StevensJohnson syndrome, and toxic epidermal</td>
<td>Rare; no class effect</td>
</tr>
<tr>
<td></td>
<td>necrolysis</td>
<td>Cellulitis, erysipelas, abscess [0.1% to 7%]</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Alopezia</td>
<td>Slight increased risk</td>
</tr>
<tr>
<td></td>
<td>Generalised skin rash</td>
<td>Psoriasis: pustular phenotype [commonly palms and soles];</td>
</tr>
<tr>
<td></td>
<td>Oral and intertriginous lesions</td>
<td>eczema: atopic diathesis</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>Infusion-related and hypersensitivity reactions</td>
<td>Rare but serious skin reactions; discontinue drug if skin</td>
</tr>
<tr>
<td></td>
<td>Rash, pruritus, eczema, acne</td>
<td>or mucosal lesion</td>
</tr>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

Increased serum alkaline phosphatase [ALP] should raise the suspicion of accompanying PSC in an IBD patient, although values are normal in 10% of PSC patients. Serum aminotransferase levels [ALT, AST] are usually below 300 IU/l. Hypergammaglobulinaemia is observed in approximately 30% of PSC patients and should raise the prospect of AIH, which is found in up to 10% of PSC patients. If concomitant features of AIH are suspected, serum autoantibodies [ANA, SMA, LKM etc] should be analysed, but have a low specificity. Atypical perinuclear antineutrophil cytoplasmic antibodies are observed in 30–80% of PSC individuals, but are also found in AIH and IBD patients without PSC. IgG4-associated sclerosing cholangitis must be considered if serum IgG4 is elevated. A diagnosis of IgG4-associated sclerosing cholangitis is made according to the amended HISORt [histology, imaging, serology, other organ involvement, and response to therapy] criteria, and is classified as secondary sclerosing cholangitis in recent guidelines. Slightly elevated levels of serum IgG4 [up to 5 g/l] may be detected in PSC patients not fulfilling the criteria for IgG4-associated sclerosing cholangitis. These patients may exhibit a more severe disease course but specific management recommendations are lacking.

### 7.1.2. Natural history and pathogenesis

The presence of PSC in an IBD patient dramatically affects prognosis. It is however important to acknowledge that median survival without liver transplantation reported from tertiary referral centres [10–12 years] is lower than that of population-based studies [> 20 years]. The use of clinical models [eg the Mayo risk score] for predicting outcome at the individual level is not recommended, and there is a need for research in determining prognosis and treatment response in PSC.

Complications of PSC include cholestasis, cholangitis, cholecystolithiasis, cholangiocarcinoma, colorectal carcinoma, osteoporosis, vitamin deficiency, and steatorrhea. PSC may be associated with autoimmune diseases such as autoimmune thyroid disease, type 1 diabetes, and coeliac disease.

PSC often leads to fibrosis and stricture development in the intra- and extra-hepatic biliary tree, mainly affecting medium and large bile ducts and bile ductules. Increased serum alkaline phosphatase [ALP] should raise the suspicion of accompanying PSC in an IBD patient, although values are normal in 10% of PSC patients. Serum aminotransferase levels [ALT, AST] are usually below 300 IU/l. Hypergammaglobulinaemia is observed in approximately 30% of PSC patients and should raise the prospect of AIH, which is found in up to 10% of PSC patients. If concomitant features of AIH are suspected, serum autoantibodies [ANA, SMA, LKM etc] should be analysed, but have a low specificity. Atypical perinuclear antineutrophil cytoplasmic antibodies are observed in 30–80% of PSC individuals, but are also found in AIH and IBD patients without PSC. IgG4-associated sclerosing cholangitis must be considered if serum IgG4 is elevated. A diagnosis of IgG4-associated sclerosing cholangitis is made according to the amended HISORt [histology, imaging, serology, other organ involvement, and response to therapy] criteria, and is classified as secondary sclerosing cholangitis in recent guidelines. Slightly elevated levels of serum IgG4 [up to 5 g/l] may be detected in PSC patients not fulfilling the criteria for IgG4-associated sclerosing cholangitis. These patients may exhibit a more severe disease course but specific management recommendations are lacking.

### ECCO Statement 7A

High-quality MRC is recommended for an unexplained persistent or fluctuating biochemical cholestatic pattern, independent of symptoms of cholestasis [EL1]. Secondary sclerosing cholangitis should be excluded when diagnosing large-duct PSC.

### ECCO Statement 7B

If high-quality MRC is normal in a patient with IBD and suspected PSC, a liver biopsy should be considered to diagnose small-duct PSC [EL2].

### ECCO Statement 7C

A liver biopsy is recommended in PSC patients with features of AIH [eg raised transaminases, high serum IgG, relevant autoantibodies] [EL1]. High serum concentrations of IgG4 and/or an elevated IgG4/IgG1 ratio should prompt consideration of IgG4-associated sclerosing cholangitis [EL4].
ducts. Progressive inflammation ultimately destroys the bile ducts, resulting in end-stage liver disease, and associates with an increased risk of cholangiocarcinoma. Patients with concurrent IBD have a significantly higher rate of colorectal carcinoma compared with IBD patients without PSC or normal controls.

Off patients with PSC and IBD, 55–95% present with extensive colitis. Backwash ileitis is reported in 20–51%, rectal sparing in 18–65%, and 10–15% develop colorectal carcinoma. These features clearly suggest that although PSC is commonly associated with UC, PSC-associated IBD has specific features. For example, disease severity is often mild or quiescent, without the typical ‘distal-to-proximal’ distribution as right-sided inflammation dominates including ileal inflammation. This is paralleled by the right-sided dominance of colorectal carcinoma. This cannot be explained currently by genetic findings. It suggests that PSC-associated IBD has a unique phenotype that may require separate classification.

PSC has a strong hereditary component. Early studies showed that PSC is associated with prototypical HLA, as in many other autoimmune diseases. Recent genome-wide association studies (GWAS) have identified new loci. The first GWAS study identified important associations in MSTR1 and BCL2L11. Interestingly, MSTR1 has been linked to IBD pathogenesis in contrast to BCL2L11, which is mainly involved in apoptotic processes. IL-2, CARD9, and REL are further susceptibility loci in PSC; they all play a role in innate and adaptive immunity. The largest genetic study was reported in 2013. Here, the authors investigated 3789 PSC cases of European ancestry using the immunochip and identified 12 genome-wide significant associations outside the HLA complex, increasing the number of known PSC risk loci to 16. Six of these 12 loci showed a much stronger association with PSC than with IBD, suggesting the presence of genetically determined disease processes in PSC that are distinct from those of IBD.

### 7.1.3 Treatment

#### ECCO Statement 7D

No medical therapy has been shown to reduce time to liver transplantation, cholangiocarcinoma, or death in PSC or small-duct PSC [EL1]. Although ursodeoxycholic acid [15–20 mg/kg/d] improves serum liver tests [EL1], higher doses should be avoided [EL1]. Corticosteroids and/or immunosuppressants should be considered in patients with features of AIH [EL3].

Currently, the evidence for medical treatment in PSC is in turn based on little evidence. There is no medical therapy consistently proven to improve clinical endpoints. Medium dose [15–20 mg/day] ursodeoxycholic acid has been abandoned by most countries although an appropriately sized study to address potential benefit will most likely not be performed. High-dose ursodeoxycholic acid [28–30 mg/day] should be avoided in patients with PSC, and therapies such as anti-TNF or vedolizumab have not been appropriately studied. There is an urgent need for better therapies; several approaches [bile acid therapies, lymphocyte trafficking blockade, antibiotics] are under investigation.

#### ECCO Statement 7E

In PSC patients with clinical or radiological suspicion of significant strictures or cholangiocarcinoma, an ERC is recommended to diagnose strictures that may be amenable to endoscopic dilation [with or without stenting] and for brush cytology specimen evaluation [EL2]. Prophylactic antibiotic therapy is recommended [EL1].

The proper treatment and early recognition of complications such as strictures and cholangiocarcinoma are seminal to the management of patients with PSC. Brush cytology assessment for the detection of biliary dysplasia is necessary when strictures are present. In the future, surrogate biomarker analyses and novel imaging modalities may allow differentiation between benign and malignant strictures in PSC. Endoscopic retrograde cholangiopancreatography should be performed after antibiotic prophylaxis in patients with PSC, as this may reduce the risk of cholangitis, bacteraemia, and septicemia, particularly in patients in whom biliary obstruction is not resolved after ERCP.

In most centres, cholangiocarcinoma is a contraindication for liver transplantation except in highly selected cases of extra hepatic cholangiocarcinoma that also require neo-adjuvant chemoradiotherapy.

### ECCO Statement 7F

PSC patients with end-stage liver disease or with debilitating symptoms of cholestasis should be considered for liver transplantation [EL1]. Liver transplantation may be considered in selected patients with cholangiocellular dysplasia on brush cytology [EL5].

Liver transplantation is the only therapy that can cure PSC. Outcomes are favourable, with 5-year survival rates close to 85%. PSC patients with end-stage liver disease should be assessed for liver transplantation according to standard guidelines. Patients with intractable pruritus and selected cases with recurrent, severe bacterial cholangitis can be referred for liver transplantation. The selection for, and timing of, transplantation in PSC patients is difficult, due to the unpredictable disease course and the risk of cholangiocarcinoma. Selected PSC patients with biliary brush cytology dysplasia may benefit from liver transplantation, although this indication has not been widely implemented. There is a definite need for novel biomarkers that can improve the diagnostic accuracy of malignancy in biliary specimens.

#### 7.1.3.1 Follow-up

#### ECCO Statement 7G

Surveillance colonoscopy in PSC patients with IBD is recommended every 1 to 2 years after diagnosis of PSC [EL1]. Chromo-endoscopy with targeted biopsies is the recommended surveillance strategy [EL2]. In PSC patients without evidence of IBD, colonoscopy is recommended every 5 years [EL5].

PSC is associated with a 4-fold increased risk of colorectal neoplasia [dysplasia and cancer] in patients with associated IBD, both before and after liver transplantation. Colorectal neoplasia may appear soon after IBD and PSC have been diagnosed. Surveillance chro-mocolonoscopy with targeted biopsies is recommended at diagnosis and every 1 to 2 years thereafter. This programme should be continued after liver transplantation.

#### ECCO Statement 7H

There is no evidence-based follow-up regimen proven to detect biliary neoplasia earlier in PSC. Annual ultrasonography to detect gallbladder mass lesions is recommended [EL4]. Additional imaging [MRI/MRC, CT, ERC] should be performed without delay if cholangiocarcinoma is suspected [EL1].
An algorithm for screening and surveying cholangiocarcinoma in PSC, including an annual measurement of serum carbohydrate antigen 19-9 [CA 19-9] and abdominal ultrasound evaluation, has been proposed but not validated. Gallbladder mass lesions are associated with a high risk [up to 56%] of malignancy in PSC patients. On this background, annual ultrasound to detect gallbladder polyps has been recommended or considered, but not validated.

7.2. Non-PSC liver disease in IBD

ECCO Statement 7J

Apart from PSC, patients with IBD can develop non-alcoholic fatty liver disease, drug-induced liver injury, hepatic and portal vein thrombosis, hepatic abscesses, liver amyloidosis, and granulomatous hepatitis [EL 3].

7.2.1. Non-alcoholic fatty liver disease

The prevalence of non-alcoholic fatty liver disease ranges between 1.5% to 55% in ulcerative colitis and 1.5% to 39.5% in Crohn’s disease [overall mean prevalence 23%]. Risk factors are those of the metabolic syndrome and IBD-specific factors that include intraabdominal abscesses, fistulising disease, colitis severity, malnutrition, protein loss, and drugs [eg corticosteroids or methotrexate].

7.2.2. Drug-induced liver injury

DILI affects many IBD patients, so laboratory monitoring of liver tests may be required every 1–3 months. DILI is uncommon and usually mild with S-aminosalicylic acid [5-ASA] drugs, but chronic hepatitis has been described. Increased aminotransferase levels are observed in approximately 10% of IBD patients started on methotrexate. Additional risk factors for liver disease [eg obesity and alcohol use] increase the risk of methotrexate-induced liver injury. Withdrawal of methotrexate because of hepatotoxicity is unusual [%]. Fibrosis may occur in patients treated with methotrexate, and can be assessed using serum biomarkers and transient elastography. It has been observed in 8.5% of patients treated with methotrexate. The reported incidence of azathioprine- and 6-mercaptopurine-hepatotoxicity varies among studies [% to 15%]. Most cases occur within the first few months of treatment. The hepatotoxic effect may be dose-dependent and usually manifests with aminotransferases and/or cholestatic enzyme elevation that return to normal after discontinuation of the drug. Up to 81% of patients who have liver toxicity while receiving azathioprine tolerate 6-mercaptopurine.

7.2.3. Portal vein thrombosis

Portal vein thrombosis is a severe complication of IBD. It is more frequent in the postoperative setting. Measures to prevent thromboembolism during hospitalisation or IBD exacerbations are recommended. After diagnosis, appropriate assessments for both underlying [IBD-related] acquired prothrombotic conditions and inherited thrombophilia are indicated. Treatment with anticoagulants in accordance with international guidelines is recommended.

7.2.4. Hepatic amyloidosis

Secondary hepatic amyloidosis is a rare complication of IBD, with a reported frequency of 0.9% in CD and 0.07% in UC patients. Longstanding active inflammation of the bowel may result in amyloid fibril deposition in hepatic blood vessels and sinusoids. There is no specific therapy, other than treatment of the underlying active IBD, although a direct effect of anti-TNF agents on serum amyloid protein levels has been reported.

7.2.5. Granulomatous hepatitis

Granulomatous hepatitis in IBD may be an EIM of: CD, DILI [eg sulfasalazine]; an associated inflammatory disease such as primary biliary cirrhosis, sarcoidosis, Wegener’s disease; infection; or lymphoma.

7.2.6. Hepatic abscess

Hepatic abscesses are uncommon in IBD patients. However, an association with transmural inflammation has been suggested, including direct extension of intra-abdominal abscesses, portal pylephlebitis, or secondary to fistulising disease.

7.3. Acute pancreatitis in IBD

ECCO Statement 7J

Acute pancreatitis is usually associated with gallstone disease, alcohol intake, drug side effects [especially azathioprine and 6-mercaptopurine], and duodenal CD [EL3]. Cases of granulomatous pancreatitis have been reported. Pain due to chronic pancreatitis is rare in IBD patients. In contrast, pancreatic exocrine insufficiency and pancreatic duct abnormalities are more frequent [EL3].

7.3.1. Investigation and diagnostic criteria

The standardized incidence ratio for acute pancreatitis is approximately 4 in CD and 1.5–2 in UC. The clinical presentation and course of acute pancreatitis in IBD are similar to the general population. Diagnosis is based on the presence of at least two of three criteria: upper abdominal pain, elevated serum lipase, elevated amylase level [above three times the upper limit of normal], and consistent abdominal imaging. These criteria are sometimes difficult to apply in IBD, as abdominal pain due to pancreatitis can be difficult to differentiate from that caused by active IBD. In addition, an asymptomatic elevated lipase is found in 7% of IBD patients.

7.3.2. Natural history and pathogenesis

Two IBD-specific forms of acute pancreatitis exist. The first is presumed to be related to shared pathogenic pathways and comprises autoimmune pancreatitis, idiopathic pancreatitis, granulomatous pancreatitis, and pancreatitis associated with PSC. The second is due to the management of IBD or due to its associated diseases [eg PSC], which includes biliary pancreatitis, drug-induced pancreatitis, pancreatitis secondary to duodenal CD, and post-ERCP or post-enteroscopy pancreatitis.

The most common causes are, by decreasing order of frequency, drugs [mostly thiopurines], gallstones, alcohol, and ERCP.

Autoimmune, IgG4-related pancreatitis has been described in IBD. Azathioprine- or 6-mercaptopurine-induced pancreatitis is dose independent. It occurs in approximately 4% of treated IBD patients. There is no evidence that monitoring lipase can
predict disease risk, which typically occurs within the first 3 to 4 weeks of treatment and has a mild course. The risk seems to be higher in CD. Patients who carry the HLA-DQA1*02:01-HLA-DRB1*07:01 haplotype are more prone to develop pancreatitis after thiopurine administration. The risk of 5-ASA induced pancreatitis is much lower, similarly without evidence for a dose-response. Gallstones are an important cause, both within the general and IBD population. The risk of gallstones is increased in CD but not in UC.

7.3.3. Treatment

Treatment of pancreatitis in IBD is in line with international guidelines.

74. Chronic pancreatitis

Morphologically, chronic pancreatitis in IBD is characterised by the presence of pancreatic duct abnormalities, sometimes a pseudotumour pattern; and, in most cases, absence of parenchymatous calcification. The prevalence of pancreatic duct changes such as main duct obstruction, severe duct irregularity or dilatation, or ductal filling defects have been found to be 8% and 16% in patients with CD and UC, respectively, using ERCP and MRCP. In addition, 7% to 77% of patients with PSC have pancreatic duct changes. Pancreatic autoantibodies directed against the exocrine pancreas are found in about one-third of CD and 4% of UC patients. These autoantibodies are correlated with pancreatic exocrine insufficiency.

8. Neurological disease

**ECCO Statement 8A**

Peripheral neuropathy is very rarely associated with IBD (EL 3). Treatable causes [eg vitamin and micronutrients deficiencies, metronidazole] need to be identified.

**ECCO Statement 8B**

Central nervous system manifestations may be more common in IBD patients than in the general population (EL 4). Causes to be considered include venous sinus thrombosis, stroke, and central demyelination. The latter may worsen with, and is a contraindication to, anti-TNF therapy (EL 4).

8.1. Investigation and diagnostic criteria

A case series identified and followed 33 IBD patients with peripheral neuropathy from a tertiary centre. Middle-aged males predominated, often with involvement of sensory fibres causing paraesthesia and pain. Demyelinating neuropathy was proportionally more common in women, with proximal and distal symmetrical weakness and distal sensory impairment/loss. All neuropathies [demyelinating, small-fibre sensory, large-fibre sensory, and sensorimotor] were present equally in IBD patients. Peripheral neuropathy was related to disease activity in only about one-third of patients. Immunotheapy [often IV IgG] was associated with improvement in the majority. Anecdotal reports describe other types of neuropathy, including myositis, myasthenia gravis, and myelopathies.

Neuropathies affecting the central nervous system comprise cranial neuropathies, with case reports describing visual loss due to optic neuritis, ophthalmoplegia affecting the lateral rectus muscle, and hearing loss. Demyelinating diseases have also been reported. For the latter, IBD patients have been described with asymptomatic central nervous system white-matter lesions, epilepsy, and multiple sclerosis. Recently, several cases of posterior reversible encephalopathy syndrome [PRES], an entity characterised by headache, seizures, visual disturbance, altered mental status, and vasogenic oedema on neuro-imaging, have been reported in CD patients who received infliximab. Vasculitis and Takayasu’s arteritis have been reported, as well as acute disseminated encephalomyelitis. Central neuropathies have been described that are independent of disease activity and may precede the onset of IBD. Cerebral sinus venous thrombosis should be suspected in patients with a severe headache during a flare of IBD, with or without neurological deficit or seizure.

IBD-related peripheral neuropathy can be considered after well-known risk factors have been excluded, such as vitamin and mineral deficiencies [in particular vitamins B12, D, E, red-cell folate, thiamine, and nicotinamide, and copper], hypothyroidism, monoclonal gammapathies, hepatitis C infection [cryoglobulins], and diabetes mellitus. A temporal association to predisposing medication [mostly metronidazole, but also anti-TNF agents] should lead to their discontinuation. Electromyography, nerve conduction studies, and MRI are often required. Central nervous system manifestations due to IBD are very rare and therefore a thromboembolic event should first be excluded when symptoms involving the central nervous system occur.

8.2. Natural history and pathogenesis

Single centres report wide-ranging values for the prevalence of neurological manifestations in IBD, from 3% to 39%. However, a University of Manitoba population-based case-control study analysing more than 8000 IBD cases did not reveal an association for neuropathy, multiple sclerosis, or myasthenia when applying stringent diagnostic criteria, except for an increased risk of multiple sclerosis in middle-aged men with UC (risk ratio [RR] 1.90; 95% CI, 1.19–3.03) that may have represented a chance finding.

A retrospective, population-based cohort of 772 IBD patients, recruited between 1940 and 2004 at the Mayo clinic, reported the cumulative incidence of peripheral neuropathy as 0.7% after 10 and 20 years, and 2.4% after 30 years of IBD, concluding that neuropathy is uncommon in IBD. There are insufficient publications to predict the natural history.

Several mechanisms of peripheral neuropathy have been described comprising malnutrition, malabsorption with vitamin and micronutrient deficiencies, intercurrent infection (eg zoster viruses, Epstein-Barr virus [EBV], cytomegalovirus [CMV], and human immunodeficiency virus [HIV]), and iatrogenic causes [medication side effects, surgical trauma]. Mechanisms of central nervous system manifestations include thromboembolism and inflammation.

8.3. Treatment

Treatment requires avoiding exposure to implicated medication, treating comorbidities, and normalising vitamin levels. Since peripheral neuropathy is usually unrelated to IBD activity, treatment of the underlying bowel activity does not improve the neuropathy. There are no controlled trials to guide therapeutic recommendations.


### Table 3. Neurological drug adverse events.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse events</th>
<th>Prevalence/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>PN&lt;sup&gt;395,396,397,398&lt;/sup&gt;, diarrhea</td>
<td>21–39% of users</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>PN, myelitis, meningitis, GBS&lt;sup&gt;399&lt;/sup&gt;</td>
<td>25% of neurological symptoms [at risk with low cholesterol, low Mg&lt;sup&gt;++&lt;/sup&gt;, hypertension, previous seizure]</td>
</tr>
<tr>
<td>Ciclosporin A</td>
<td>Tremor, epilepsy, PN, central leukoencephalopathy, paraesthesia, ataxia, aphasia&lt;sup&gt;390,391&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>Central demyelination&lt;sup&gt;392,393,394,395&lt;/sup&gt; Optic neuritis&lt;sup&gt;400,401,402,403,404,405&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td>PN&lt;sup&gt;406&lt;/sup&gt;</td>
<td>25% of users</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>PML&lt;sup&gt;407&lt;/sup&gt;</td>
<td>1/1000, due to JC virus</td>
</tr>
</tbody>
</table>

PML, progressive multifocal leukoencephalopathy; PN, peripheral neuropathy; GBS, Guillain-Barré syndrome; JC, John Cunningham.

#### 9. Cardiovascular manifestations of IBD

**ECCO Statement 9A**

The risks of ischaemic heart disease, cerebrovascular accident, and mesenteric ischaemia are modestly increased in IBD [EL 2], particularly in women [EL 3]. Systemic inflammation predisposes to premature atherosclerosis [EL 3]. Cardiovascular mortality has not been shown to be increased in IBD [EL 2]

#### 9.1. Investigations and diagnostic criteria

Two recent meta-analyses of cohort and case-control studies in Western populations report a modestly increased risk of arterial thromboembolism in IBD,<sup>293,294</sup> particularly ischaemic heart disease, stroke, and mesenteric ischaemia.

The increased risk of ischaemic heart disease in IBD was confirmed by both meta-analyses (OR 1.19 [95% CI, 1.08–1.31])<sup>293</sup> and (RR 1.35 [95% CI, 1.19–1.52]),<sup>294</sup> whereas the increased risk of cerebrovascular accident (OR 1.18 [95% CI, 1.09–1.27])<sup>295</sup> and of mesenteric ischaemia (RR 3.46 [95% CI, 1.78–6.71])<sup>296</sup> were each reported by one meta-analysis. No differences were observed between CD and UC.<sup>293,294</sup>

The meta-analysis by Fumery et al.<sup>294</sup> analysed only two studies of non-hospitalised patients, comprising 8866 IBD patients, and one very large database of hospital admissions that may be subject to methodological defects. By comparison, the earlier meta-analysis<sup>293</sup> analysed five studies, comprising 98 240 IBD patients. Women primarily accounted for the increased risk of cerebrovascular accident (OR 1.28 [95% CI, 1.17–1.41])<sup>293</sup> and ischaemic heart disease (OR 1.26 [95% CI, 1.18–1.35]).<sup>293</sup> There was a higher risk of cerebrovascular accident in young IBD patients [< 40–50 years old].<sup>293</sup> Mesenteric ischaemia was addressed in one meta-analysis assessing only two studies.<sup>294</sup> This occurred in approximately 1/10000 patients admitted to hospital, with a pooled risk ratio of 3.46 [95% CI, 1.78–6.71].

There appears to be no increased risk of peripheral arterial disease, based on meta-analyses pooling data from two studies, including one large population-based study (OR 1.15 [95% CI, 0.96–1.38])<sup>297</sup> and (OR 0.78 [95% CI, 0.46–1.32]).<sup>298</sup> The rate of peripheral vascular disease is low in IBD, affecting only 0.5% of patients.<sup>293</sup>

Studies have not demonstrated an increased cardiovascular mortality in IBD, in contrast to rheumatoid arthritis. This is likely due to inadequate power in the context of falling mortality rates, relatively short-term follow-up, and low prevalence studies in predominantly youthful IBD cohorts.

The majority of studies assessing cardiovascular risk factors [hypertension, diabetes, dyslipidaemia, obesity, or the composite Framingham risk score] in IBD patients report a low prevalence.<sup>293,297,298</sup> This could underestimate the risk in IBD patients who have chronic systemic inflammation leading to premature atherosclerosis. Recently an association between IBD activity and myocardial infarction, stroke, and cardiovascular death was demonstrated in a Danish population-based study. However, the risk of cardiovascular complications and mortality was similar to the general population in patients with quiescent disease.<sup>299</sup> In detail, the relative risk was 1.49 [95% CI, 1.16–1.93] and 2.05 [95% CI, 1.58–2.65] for myocardial infarction, 1.53 [95% CI, 1.22–1.92] and 1.55 [95% CI, 1.18–2.04] for stroke, and 2.32 [95% CI, 2.01–2.68] and 2.50 [95% CI, 2.14–2.92] for cardiovascular mortality during disease flares, or with persistent activity, respectively.

Clinical features, investigations and diagnostic criteria of cardiovascular events are similar in patients with and without IBD

#### 9.2. Natural history and pathogenesis

The largest meta-analysis of cardiovascular mortality in IBD<sup>300</sup> identified 15 studies containing 69 383 patients and, concordant with previous meta-analyses,<sup>300,301,302,303</sup> did not reveal increased mortality in comparison with the general population. However, a population-based study from Denmark<sup>299</sup> and a nationwide register from Finland,<sup>303</sup> neither included in the meta-analysis, have shown increased cardiovascular mortality in IBD during periods of inflammatory activity,<sup>299</sup> and have shown that patients with UC, but not CD, have increased mortality for cardiovascular disease (RR 1.14 [95% CI, 1.06–1.22]).<sup>304</sup>

Systemic inflammation predisposes to atherosclerosis and coronary artery disease.<sup>305</sup> This has been demonstrated in rheumatoid arthritis,<sup>306,307</sup> and in IBD.<sup>299</sup> Raised CRP has been independently associated with coronary artery disease.<sup>308</sup> Intima-media thickness, a surrogate of atherosclerosis, is increased in IBD.<sup>309</sup> Premature
atherosclerosis in IBD patients occurs due to a combination of inflammation, endothelial dysfunction, calcification, and hypercoagulability.\textsuperscript{310,311,312} Hyperhomocysteinaemia, a well-established risk factor for arterial and venous thrombosis, is four times more prevalent in IBD than in the general population.\textsuperscript{311} Furthermore, hypercoagulability due to systemic inflammation contributes to earlier atherosclerosis and therefore an elevated risk of arterial thrombotic events.\textsuperscript{310} Impaired coagulation factors include: elevated factors V, VII, VIII, fibrinogen, and prothrombin fragments; lower plasma levels of thrombin inhibitors such as anti-thrombin III as well as abnormal fibrinolysis; and abnormal platelet activation evidenced by increased circulating platelet numbers and platelet-leukocyte aggregates. Finally, smoking is over-represented in CD patients and predisposes to atherosclerosis.

9.3. Treatment

It has been speculated that IBD treatment could reduce cardiovascular risk by suppressing inflammatory activity.\textsuperscript{314} Recent Danish population-based studies\textsuperscript{309,311} analysed the effect of therapy upon cardiovascular complications. In one study, ischaemic heart disease was lower in patients using 5-aminosalicylic acids (RR 1.16 [95% CI, 1.06–1.26]) than non-users (RR 1.36 [95% CI, 1.22–1.51]); treatment with thiopurines and TNF-alpha antagonists was associated with less ischaemic heart disease, the lowest risk being observed in those treated with combination therapy.\textsuperscript{311} In the other study, myocardial infarction, cerebrovascular accident, and cardiovascular death did not occur in patients treated with anti-TNF agents, whereas the risk was comparable to the total IBD population in patients treated with immunosuppressants, although the value of this finding was limited by the small sample size.\textsuperscript{309} Patients should be advised to avoid known cardiovascular risk factors, including cigarette smoking.

10. Pulmonary manifestations of IBD

10.1. Investigation and diagnostic criteria

\textbf{ECCO Statement 10A}

Different types of airway disease, involving different parts of the bronchial tree from the glottis to small airways, can occur as an extra-intestinal manifestation of IBD [EL4], most commonly the large airways [EL4]. There is an association between IBD and chronic obstructive pulmonary disease [EL3].

\textbf{ECCO Statement 10B}

Interstitial pneumonia associated with IBD has been described, the most common form being organising pneumonia [EL4]. Infections or medication [salicylates, methotrexate, thiopurines, anti-TNF] can cause parenchymal lung disease [EL3].

Bronchopulmonary disease is a rare EIM of IBD.\textsuperscript{314,315} The true prevalence is unknown. Pulmonary function tests are frequently abnormal in IBD, even in the absence of respiratory symptoms. Several studies report latent interstitial pulmonary involvement in 20% to 55% of IBD patients. These abnormalities include bronchial hyper-responsiveness, ventilation defects, and sputum or bronchoalveolar lavage lymphocytosis, as well as histological and radiological abnormalities.\textsuperscript{318,319,320,321,322,323} Infections and adverse drug reactions frequently cause parenchymal lung disease in IBD patients and should always be excluded. The presentation of other bronchopulmonary manifestations is polymorphic, as all segments of the respiratory tract can be affected. Respiratory symptoms in patients receiving corticosteroids, immunomodulators, and/or anti-TNF therapy should not be ignored, because they may indicate the onset of a serious opportunistic infection.\textsuperscript{324}

10.1.1. Drug-induced manifestations

The most common pulmonary manifestation of IBD is drug-induced lung disease, frequently attributed to 5-ASA or methotrexate. Salicylates [sulfasalazine, 5-ASA] induce different types of interstitial lung disease.\textsuperscript{325} The most common symptoms are dyspnoea, fever, chest pain, and cough. Peripheral eosinophilia is found in almost half the cases.\textsuperscript{316} Methotrexate may cause severe hypersensitivity pneumonitis or pulmonary fibrosis.\textsuperscript{323} Granulomatous inflammation compatible with sarcoidosis has been documented in patients receiving anti-TNF monoclonal antibodies.\textsuperscript{326} This paradoxical inflammation improves with cessation of the anti-TNF agent and/or steroid treatment.

10.1.2. Broncho-pulmonary manifestations specific to IBD

Bronchopulmonary involvement in IBD encompasses a wide range of manifestations.\textsuperscript{316,317,327,328,329,330,331,332} In most cases, IBD precedes the pulmonary manifestations. Different patterns of respiratory involvement can be defined [Table 4]. The most common pattern is airway inflammation, involving the bronchial tree from the glottis to small airways. Bronchiectasis is most commonly reported.\textsuperscript{316,330} The inflammatory lesions are similar to those observed in the digestive tract. Persistent airway inflammation can result in airway narrowing and expose patients to the risk of irreversible destruction of the airways, resulting in subglottic/tracheal strictures,\textsuperscript{329,331,332,333,334,335,336,337,338,339,340} chronic bronchitis, bronchiectasis, or bronchiolitis obliterans. These manifestations are more frequently observed after colonic surgery.\textsuperscript{329,341} Chronic bronchitis is diagnosed with cough and mucus expectoration for more than 3 months a year during 2 consecutive years, with a normal high resolution CT scan. Bronchiectasis is diagnosed by high resolution CT, with a bronchial calibre greater than the adjacent vessel. Bronchiolitis or small airway diseases are diagnosed by high resolution CT, with centrolobar micro-nodules and a ‘tree in a bud’ aspect, with air trapping on the expiratory sequence.

Interstitial lung diseases are caused by infiltration of the alveolar air spaces or thickening of pulmonary interstitial structures. A classification can be used to distinguish the different types of interstitial pneumonia.\textsuperscript{342} Granulomatous interstitial lung disease, mimicking parenchymal sarcoidosis, may be observed in CD patients. Many patients with CD and concomitant sarcoidosis have been reported in the literature, suggesting a link between the two diseases.\textsuperscript{343,330} Which share susceptibility genes.\textsuperscript{341} Other types of interstitial pneumonia have been described in IBD patients. These include non-specific interstitial pneumonia, usual interstitial pneumonia, organising pneumonia (formerly termed bronchiolitis obliterans with organising pneumonia [BOOP]), lymphocytic interstitial pneumonia, desquamative interstitial pneumonia, eosinophilic interstitial pneumonia, and hypersensitivity interstitial pneumonia. In most patients the development of pulmonary disease parallels that of the intestinal disease activity and/or other EIMs.\textsuperscript{332} The most common pattern of interstitial lung involvement is organising pneumonia, which may also occur secondary to other inflammatory disorders such as rheumatoid arthritis. It is characterised histologically by intraluminal plugs of connective tissue in the bronchioles that extend distally into adjacent alveolar ducts and alveoli. Pulmonary infiltrates with eosinophilia have been reported in
Table 4. Respiratory manifestations associated with IBD—sites and patterns of involvement.

<table>
<thead>
<tr>
<th>Anatomical site</th>
<th>Pathology</th>
<th>Symptoms/investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larynx, glottis, trachea</td>
<td>Inflammation and stenosis</td>
<td>Stridor, hoarseness, cough</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchoscopy + biopsy</td>
</tr>
<tr>
<td>Bronchi</td>
<td>Chronic bronchitis [non-specific, granulomatous]</td>
<td>Cough, sputum production</td>
</tr>
<tr>
<td></td>
<td>Bronchiectasis</td>
<td>Bronchoscopy + biopsy</td>
</tr>
<tr>
<td>Bronchioles</td>
<td>Granulomatous bronchiolitis</td>
<td>High resolution CT scan</td>
</tr>
<tr>
<td></td>
<td>Diffuse pan-bronchiolitis</td>
<td>Dyspnoea, cough, bronchorrhoea, wheezing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchoscopy + biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High resolution CT scan</td>
</tr>
<tr>
<td>Parenchymal tissues</td>
<td>Usual interstitial pneumonia</td>
<td>Dyspnoea, fever, acute respiratory failure, chest pain</td>
</tr>
<tr>
<td></td>
<td>Organising pneumonia</td>
<td>High resolution CT scan</td>
</tr>
<tr>
<td></td>
<td>Lymphocytic interstitial pneumonia</td>
<td>Lung biopsy</td>
</tr>
<tr>
<td></td>
<td>Desquamative interstitial pneumonia</td>
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</tr>
<tr>
<td></td>
<td>Eosinophilic interstitial pneumonia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Granulomatous interstitial lung disease</td>
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</tbody>
</table>

IBD patients who did not receive salicylates. Diagnosis of these entities relies on clinical presentation, high resolution CT, and bronchoalveolar lavage, and may require lung biopsy. Other rare bronchopulmonary manifestations have been reported including pulmonary fistulae of ileal, colonic, or even oesophageal origin, necrotic nodules due to neutrophilic infiltrates, pulmonary vasculitis, and pleuritis.344,345,346

10.2. Natural history and pathogenesis

There is an association between IBD and chronic obstructive pulmonary disease, characterised by chronic inflammation of the airways. A population-based cohort study showed that patients with chronic obstructive pulmonary disease had a significantly higher risk of both UC (HR 1.83 [95% CI, 1.61–2.09]) and CD (HR 2.72 [95% CI, 2.33–3.18]), as compared with healthy controls.347 The risk of CD among patients with chronic obstructive pulmonary disease was greater than the risk reported for smoking alone. A meta-analysis of population-based studies of mortality in CD found a significant, increased risk of death from pulmonary cancer (summary measure of risk [SMR] 2.72 [95% CI, 1.35–5.45]), as well as chronic obstructive pulmonary disease (SMR 2.55 [95% CI, 1.98–3.27]).348 In another population-based study, CD and UC patients had an increased risks of asthma and bronchitis.349

Gastrointestinal and respiratory tracts share components of the common mucosal immune system.350 Hence, epithelial and mucosal immune defects associated with IBD may affect the respiratory tract. Trafficking of immune cells from inflamed intestinal tissue to the periphery and then to extra-intestinal mucosal surfaces may also be responsible for respiratory tract inflammation. Among first-degree relatives of chronic obstructive pulmonary disease patients, there is an overall increased risk of CD (HR 1.25 [95% CI, 1.09–1.43]) but not of UC (HR 1.09 [95% CI, 0.96–1.23]),348 suggesting that chronic obstructive pulmonary disease and IBD may share common inflammatory pathways, including variants of genes predisposing to both diseases.

10.3. Treatment

In all cases, drug-induced pulmonary disease must be excluded. In patients receiving salicylates or methotrexate, it is reasonable to consider the drug as a potential cause and withdraw it. Most of the respiratory changes associated with IBD respond to corticosteroids. The route of administration depends on the pattern of respiratory involvement. Inhaled corticosteroids [budesonide and beclomethasone] are particularly effective in large-airway involvement and represent first-line treatment. Systemic corticosteroids are used in parenchymal involvement and in large-airway disease resistant to inhaled corticosteroids. Ineffectiveness of inhaled corticosteroids may be due to limited diffusion in secretion-filled airways; nebulised corticosteroids can be used in these cases. Patients with steroid resistance or high-dose steroid-dependent refractory lung disease should be treated with immunomodulators and/or biological therapy. Efficacy of anti-TNF therapy has been reported in lung disease associated with CD.351

11. Urogenital manifestations of IBD

The prevalence of renal insufficiency has been reported to be 2% in CD patients352 and as high as 15% in a series of inpatients with CD or UC.353 Risk factors for renal insufficiency were length of resected small bowel, duration of disease, age, and a history of renal stones. Patients with IBD, particularly those with CD, are prone to nephrolithiasis containing uric acid or calcium oxalate.354 Secondary amyloidosis [AA-type] is a rare but severe complication of IBD. Patients at risk of amyloidosis are male, with ileocolonic and/or perianal CD.355 Some patients have responded to infliximab.356 Tubulo-interstitial nephritis, including granulomatous interstitial nephritis, has been reported as an EIM of IBD. Several cases of glomerulonephritis associated with IBD, including IgA nephropathy, have been reported, suggesting that it could be an EIM of IBD.357

Sulphasalazine and 5-ASA may cause renal toxicity [glomerulonephritis, nephrotic syndrome and, most importantly, interstitial nephritis]. Salicylates may cause either acute or chronic interstitial nephritis, independently of the dose administered.358 Renal impairment may be isolated or associated with fever, eosinophilia, and rash. The injury is reversible, except when the diagnosis is delayed. Since the risk is higher during the first few months of treatment,359 it is recommended to monitor renal function either every 4 weeks during the first 3 months or 3-monthly for the first year and then every year.360 Ciclosporin can cause acute renal failure due to afferent arteriolar constriction, resulting in decreased renal blood flow and glomerular filtration rate.361 Reduction or discontinuation of ciclosporin usually improves renal function after 5–7 days. Ciclosporin may also cause chronic renal impairment [interstitial fibrosis, tubular nephropathy, and/or arteriolar injury] in up to 20% of patients.362
Penile and scrotal swelling have been reported as metastatic [granulomatous] CD manifestations.\textsuperscript{118} Metastatic, granulomatous, vulvar involvement [induration and/or swelling] has also been reported and may reveal CD.\textsuperscript{119}

12. Coagulopathy in IBD

12.1. Investigation and diagnostic criteria

**ECCO Statement 12A**

Venous thromboembolism [VTE] is related to IBD activity [EL 2]. Prophylaxis is recommended for all IBD patients admitted to hospital, and should be considered following discharge from hospital and after recent surgery, and in outpatients with active disease [EL 3].

**ECCO Statement 12B**

The risk of VTE is at least 2-fold higher in IBD than in the general population and therefore the threshold to perform investigations is lower, especially in those with active disease [EL3]. Treatment should follow established antithrombotic therapy guidelines.

IBD patients have a higher risk of VTE than healthy controls. The most common forms of VTE are deep-vein thrombosis [DVT] and pulmonary embolism. A recent meta-analysis\textsuperscript{100} of 11 case-control and cohort studies found the relative risk for DVT and pulmonary embolism among IBD patients to be 2.20 [95% CI, 1.83–2.65]. A separate meta-analysis of three large population-based, retrospective cohort studies revealed a 2.85-fold increased risk.\textsuperscript{101} Another meta-analysis of 33 observational studies reported an increased risk of DVT (RR, 2.42 [95% CI, 1.78–3.30]) and pulmonary embolism (RR, 2.53 [95% CI, 1.95–3.28]).\textsuperscript{214} In a series of 10431 IBD patients who underwent surgery, VTE occurred in 1.4% of CD and 3.3% of UC patients.\textsuperscript{212}

VTE is associated with disease activity; therefore patients may have signs of active and complex IBD. Although the risk of VTE is greater during hospitalisation,\textsuperscript{163,164} the majority of VTE events occur in outpatients who have risk factors [recent hospitalisation or surgery, active disease].\textsuperscript{162,216} VTEs often manifest with nonspecific symptoms and their presence should be considered in all patients.

VTE is diagnosed by standard protocols in patients with IBD, while trying to minimise radiation exposure.\textsuperscript{216} The most widely used procedures are ultrasound for DVT and the ventilation-perfusion scan or CT pulmonary angiography for pulmonary embolism.

12.2. Natural history and pathogenesis

VTE complicating IBD is associated with longer hospitalisation [11.7 vs 6.1 days].\textsuperscript{163} IBD-related mortality is increased when VTE occurs [17.0 vs 4.2 per 1000 hospitalisations for CD; 37.4 vs 9.9 per 1000 hospitalisations for UC; \(p < 0.0001\)].\textsuperscript{216} Recurrent VTE is increased in IBD patients, half of whom have active disease at recurrence.\textsuperscript{164, 33.4% [95% CI, 21.8%–45.0%]} recur within 5 years in IBD patients who had an unprovoked first VTE, compared with 21.7% [95% CI, 18.8%–24.6%] among patients without IBD [\(p = 0.01\)] (relative risk 2.5 [95% CI, 1.4–4.2]; \(p = 0.001\)].

Known inherited risk factors for VTE [factor V Leiden [FVL], factor II prothrombin, G20210A], methylenetetrahydrofolate reductase gene mutation [MTHFR, 677TT], plasminogen activator inhibitor type 1 [PAI-1] gene mutation, and factor XIII [val34leu]] occur with a similar frequency in IBD and the general population.\textsuperscript{216,217} Excess VTE in IBD patients is the result of interactions between acquired and inherited risk factors. The most important acquired risk factors are disease activity [relative incidence of VTE during disease flares compared with remission is 4.5], hospitalisation [6-fold higher risk in hospitalised compared with non-hospitalised patients], colonic disease, and recent surgery [the prevalence of VTE after surgery is 2.3 %].\textsuperscript{217} A large case-control study\textsuperscript{164} is illustrative; the relative risk of VTE was 4-fold for all IBD patients [2.6/1000 patient-years], with a 15-fold relative risk during a flare in IBD [9 episodes/1000 patient-years]. The absolute risk increased to 37.5/1000 patient-years in those hospitalised with a flare. Fibrulising or stenosing disease are also independently associated with greater risk.\textsuperscript{213} Prolonged immobilisation, central venous catheters, corticosteroids,\textsuperscript{172} oral contraceptives, and cigarette smoking have also been reported as risk factors. Hyperhomocysteinemia, a potential risk factor for VTE, can be secondary to folate and vitamin B\(_6\) deficiencies that are observed in some IBD patients. Young IBD patients with VTE usually have at least one of these risk factors. Treatment with anti-TNF decreases coagulation biomarkers and activates fibrinolysis,\textsuperscript{217} which could reduce risk of VTE. Other chronic inflammatory diseases [eg. rheumatoid arthritis] or other chronic bowel diseases [eg. coeliac disease] do not confer an excess risk of VTE.\textsuperscript{217} Perioperative independent risk factors have been reported as preoperative anaemia (OR 1.5 [95% CI, 1.1–2.0]), use of corticosteroids (OR 2.17 [95% CI, 1.7–2.8]), malnutrition (OR 1.41 [95% CI, 1.1–1.9]), and anaesthesia time > 231 min (OR 1.96 [95% CI, 1.5–2.6]).\textsuperscript{216}

12.3. Treatment

The treatment of VTE in IBD patients follows the same protocols as for non-IBD patients. Although low-molecular-weight heparin is most commonly used initially, low-dose unfractionated heparin or fondaparinux are acceptable alternatives. Long-term treatment usually comprises vitamin K antagonists [acenocoumarol, warfarin, fluindione, phenprocoumon] or the new, non-vitamin K antagonist oral anticoagulants such as dabigatran, rivaroxaban, apixaban, and edoxaban. There is no evidence on their use in the setting of IBD, but data from the general population have shown that apixaban 2.5 mg twice daily is associated with less bleeding episodes than either rivaroxaban 20 mg daily or dabigatran 150 mg twice daily.\textsuperscript{217} The duration of treatment depends on the balance between the risk of recurrence [previous history, risk factors] and the risk of treatment-induced bleeding.\textsuperscript{217} Clinicians should be aware that thio purines can reduce the effect of warfarin.

Indefinite anticoagulant therapy can be discussed with IBD patients who present with a VTE episode while in clinical remission without another provoking factor. Thromboprophylaxis should be considered for all inpatients with IBD. VTE occurs in about 2% of patients following hospitalisation for IBD, with incidences at 30, 60, 90, and 180 days of 3.7, 4.1, 5.4, and 9.4 per 1000 person-days, respectively.\textsuperscript{217} Pharmacological thromboprophylaxis during the index hospitalisation is associated with a significantly lower risk of post-hospitalisation VTE (HR 0.46 [95% CI, 0.22–0.97]).\textsuperscript{217} There is no evidence for prophylaxis of active disease in outpatients with IBD or for those flying, although high altitude has been associated with flares in disease.\textsuperscript{214} IBD patients undergoing surgery should also receive anticoagulant thromboprophylaxis during hospitalisation.
IBD-related bowel surgery confers an increased risk of VTE after surgery, more in UC than CD [3.3% vs 1.4%, \( p < 0.001 \)].

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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 statement is not only stored at the ECCO Office and the editorial office of JCC but 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 authors.

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**References**

For full References, please see the Supplementary Data at ECCO-JCC online.