Review Article

Inflammatory bowel disease:clinical features and manifestations beyond the bowel

Abstract. Inflammatory bowel disease(IBD)encompassesaspectrumof diseases, withCrohn's disease(CD)andulcerativecolitis(UC) representing the two broadest subtypes of IBD. Multiple extraintestinal manifestations (EIMs) are more frequent in (IBD); 5% –50% of the patients might be affected. The most often implicated sites of manifestations are musculoskeletal and dermatological structures.However,while some symptoms like peripheral arthritis and erythema nodosum correlate with IBD progression, others have their own course of disease like axial arthropathy, gangrenosis of the pioderma and primary sclerosic cholangitis. This review would provide a summary of the most frequent EIMs and their prevalence.

Key words: Ulcerative colitis, Crohn's disease, Inflammatory bowel disease

1. Introduction

Inflammatory bowel disease (IBD) is a chronic diseasewhich relapses immune-mediated. The two major IBD subtypes are ulcerative colitis and Crohn's disease [1].Ulcerative colitis is a chronic, idiopathic inflammatory condition that affects the colon, most frequently affecting adults between 30 and 40 years of age with disabilities [2, 3] .It is characterized by relapse and remittance of inflammation in mucosal tissues, starting in the rectum and spreading to proximal colon segments.UC marked by cycles of recovery and cycles of recurrent, the latter, frequently presenting with a combination of abdominal pain vomiting, rectal bleeding,weight lossand malaise, is responsible for the vast majority of the disease burden and reduced quality of life [4, 5].

The risk for UC newly diagnosed patients is between 10% and 35% for five years and ultimately the long-term risk of colorectal cancer is enhanced by extensive and persistent inflammatory activity [6]. The control of symptoms such as increased frequency of bowel movement and rectal hemorrhage was a controlled problem[5]. The introduction of standardized clinical scores, such as the Truelove and Witts criteria[7] and the Mayo score[5], allowed for a more accurate evaluation of the disease and, while they are sometimes used in clinical trials[8, 9], have not yet been validated. This strategy, aimed at regulating and alleviating the effects of inflammation, did not target the inflammatory activity itself.

In comparison, there is a major correlation between clinical IBD and other disorders, such as irritable bowel syndrome (IBS) or infectious diarrhea [10], And some authors recorded a long-term recovery of UC patients with IBS-like symptoms (abdominal pain, elevated stool frequency) two to three times more frequency than controls [14]. In contrast, others observed high stool frequency in up to 27% of patients with full endoscopic and histological healing, indicating a potential explanation for non-inflammatory functional intestinal damage [15]. Finally, in a systematic study of clinical trials, clinical recovery during the placebo reached up to 15% [16]. However, there is growing evidence that clinical improvement without mucosal healing (MH) is

not associated with reduced hospitalization or colectomy rates over the years [17, 18].Inflammatory markers such as erythrocyte sedimentation rate, fecal marker calprotectin and serum markers C-reactive protein are other desirable choices for tracking UC patients[11].

Further studies are required to explain adequate surveillance strategies and cut-off rates before it is widely used in clinical practice.Mucosal inflammation is a central component of both UC and CD but, unlike Crohn's disease, a transmural disease with both strict and penetrating phenotypes, the development of the disease is limited to the UC mucosa [12]. Therefore, it is no surprise that MH will prove an appealing target when addressing UC patients regardless of the severity of the disorder, inflammatory biomarkers or clinical presentation. Extensive research has been published over the past decade supporting the value of histological healing[13, 14]as it has shown excellent correlation with reduced risk of relapse[15]and hospitalization [16]. In some studies, histological healing may be involved in the definition of MH in addition to the endoscopic findings [16].

The therapy is aimed at inducing and sustaining clinical and endoscopic remission.Current treatment choice for UC includes aminosalicylates, such as corticosteroids (including systemic corticosteroids such as hydrocortisone or prednisolone, and topical corticosteroids such as budesonide), mesalamine (5-aminosalicylic acid; 5-ASA) in both oral and rectal formulations, sulfasalazine,thiopurines (6-mercaptopurine and azathioprine), calcineurin inhibitors (tacrolimus and cyclosporine), anti-tumor necrosis factor (TNF)-a drugs (including infliximab, adalimumab, and golimumab), methotrexate andmore recently, the anti-integrin drug vedolizumab[16].This review summarizesthe most common EIMs and itsclinical features and their prevalence and suggested management

2. Extraintestinal manifestations

UC and CD also cause extraintestinal manifestations (Table. 1), as seen in 25 to 40 % of patients with IBD [45]. Almost every organ may be affected, but the primary manifestations are symptoms affecting the skin, eyes, joints and liver. Having one extraintestinal manifestation raises the likelihood that another will develop [46].

The treatment of underlying gut inflammation leads to the symptoms of concurrent disease activity such as erythema nodosum, episcleritis peripheral and arthritis. IBD can be associated with a specific disease, for example, IBD is closely correlated with primary sclerosing cholangitis (PSC); 75% of PSC patients have UC and 5 %to 10 % have CD. Nevertheless, only 5% of UC patients and 2% of CD patients develop PSC, respectively. [47]. IBD patients are suffering from persistent diarrhea, usually with mucous and blood. For UC, symptom period may vary and appear to be more indolent, lasting weeks to months [17-19].

Extraintestinal manifestations in 21% -47% of patients with IBD are reported.[1]. Most extraintestinal manifestations are not well known for pathogenesis. In recent years, however, significant advances in the genetic basis of IBD have occurred with the advent of genomewide interaction studies. In particular, 99 susceptibility loci or genes have been reported to date (47 in ulcerative colitis and 71 in Crohn's disease)[20].

Many organs may be involved withextraintestinal manifestations in IBD patients. Extraintestinal symptoms injoints,skin, hair have been correlated with the level of bowel

inflammation, but cardiothoracic and gastrointestinal (hepatobiliary) desorption generally did nothave that correlation. [1].

2.1 IBD Manifestations of gastrointestinal

Pancreatic and hepatobiliary damageconsider the most severe extraintestinal manifestationsin IBD patients. While the relations between many liver disorders and IBD are well known, other associations are far more.[21].

2.1.1 Primary Sclerosing Cholangitis

In the IBD setting, PSC is the most common hepatobiliary manifestation [20]. PSC symptoms are progressive inflammation in the biliary tree, obliterative fibrosis and death, resulting in biliary fibrosis, cirrhosis and probable hepatic failure[22]. The PSC-IBD relationship was first identified by Smith and Loe in 1965[23].

Table 1. Extraintestinal Manifestations of IBD

Gastrointestinal	Primary sclerosing cholangitis (PSC) PSC–autoimmune "hepatitis overlap syndrome" Drug-induced hepatitis Hepatic steatosis Hepatic abscess Portal vein thrombosis Pancreatitis Immunoglobulin G4 (IgG4)–associated cholangitis Primary biliary cirrhosis Cholelithiasis Autoimmune pancreatitis
Urinary	Enterourinary fistulas Obstructive uropathy Nephrolithiasis
Musculoskeletal	Arthritis: ankylosing spondylitis, isolated joint involvement Hypertrophic osteoarthropathy: clubbing, periostitis Other: aseptic necrosis, polymyositis
Pulmonary	Large airways disease Pneumonia

Cardiac	Congestive heart failure
Ocular system	Uveitis/iritis, episcleritis, scleromalacia, corneal ulcers, retinalvascular disease Conjunctivitis Orbital pseudotumor
Dermatologic/Oral system	Reactive lesions: erythema nodosum, pyoderma gangrenosum, aphthous ulcers, necrotizing vasculitis Specific lesions: fissures, fistulas, oral Crohn disease, drug rashes Nutritional deficiencies: acrodermatitis enteropathica, purpura,glossitis, hair loss, brittle nails Associated diseases: vitiligo, psoriasis, amyloidosis
Hematologic	Anemia, hyperhomocysteinemia
Metabolic system	Growth retardation in children and adolescents, delayed sexual maturation, osteopenia/osteoporosis

2.1.2 PSC–Autoimmune (Hepatitis Overlap Syndrome)

In IBD patients, especially in ulcerative colitis patients, an association between autoimmune hepatitis and PSC has been reported. Several case reports of IBD patients who were initially diagnosed with autoimmune hepatitis later established PSC histological evidence [24].

2.1.3 Cholangiocarcinoma

The emergence ofcholangiocarcinoma, a crippling malignancy with an exceedingly poor prognosis, is a feared complication of PSC. Though cholangiocarcinoma does not result directly from IBD, the literature has well established a significantrelation between cholangiocarcinoma and PSC [1].PSC patients tend to show cholangiocarcinoma earlier than intermittent cholangiocarcinoma[25].With a lifetime incidence of 5%-15%, PSC patients have a substantially higher chance of cholangiocarcinoma progress[26].

2.1.4 Drug-induced Hepatitis

Although hepatobiliary disorders described above share common IBD pathogenesis; many medicines used to treat IBD can cause liver toxicity. A variety of medications have been involved, includingsulfasalazine,cyclosporine, thiopurines,methotrexate as well as certolizumab,adalimumab and infliximabas the biologic agents. Influenza-like symptoms andincreased liver enzymesin hepatotoxicity conditionusually resolve after the drug treatment has been discontinued [27].

2.1.5 Hepatic Steatosis

The most hepatobiliary complication of IBD is hepatic steatosis, or fatty liver[28]. Agroup of researchers reported that 35% of the 511 IBD patients had a fatty liver disorder[29]. In published studies,fatty liver disease has beenshown amassive variability in its prevalence (13% to 100%) [1]. The level of fatty liver infiltration and the severity of colitis were found to be associated with

ulcerative colitis patients.[30]. In IBD patients, the protein deficiency, corticosteroid therapy and chronic malnutrition, may lead fatty liver condition whilethe exact causesare somewhat unclear, [1].

2.1.6 Hepatic Abscess

The frequency of pyogenic liver abscesses in patients with IBD is slightly greater than in the general population[28]. Researchers indicated that the loss of barrier integrity of the intestine mucosamay lead toliver damage by an infectious agent through mesenteric veins[1]. In addition, portal vein associated- thrombosis can alsooccur in the portal pyelophlebitis condition[31].

2.1.7 Portal vein thrombosis

In IBD patients, a thrombosis disorder is commonly observed at the portal vein [28].The levels of platelets, fibrinogen and factor V and VIII have been increased in patients with IBD, with antithrombin III being lowered, both of which may raise the risk of thrombosis. The IBD patients who have just undergone abdominal surgeryare more likely to develop portal vein thrombosis[32]. In patients with ulcerative colitis following restorative proctocolectomy, the portal vein thrombosis with a high incidence has been recorded [33].

2.1.8 IBD and Pancreatic manifestations

Concerning IBD-associatedpancreatic manifestationsin autopsies, in 1950, Ball et al. [34]receded on pancreatic features accompanied by UC detected for the first time. In 1956, Chapin et al. [35]described that histological changes in the pancreas with regional enteritis were mainly interlobar and periductal fibrosis and swelling of the acinar cells[36].Subsequently, in US and Europe, researches on IBD, especially pancreatitis associated CD, have been recorded progressively since the 1970s[37-39].

Pancreatic disorders related with IBD involve, pancreatic cancer (PC) acute pancreatitis (AP), chronic pancreatitis (CP), increasing of pancreatic enzymesandexocrine pancreatic insufficiency (EPI[40].More details about pancreatic manifestations accompanied by IBDis shown inFig. 1.

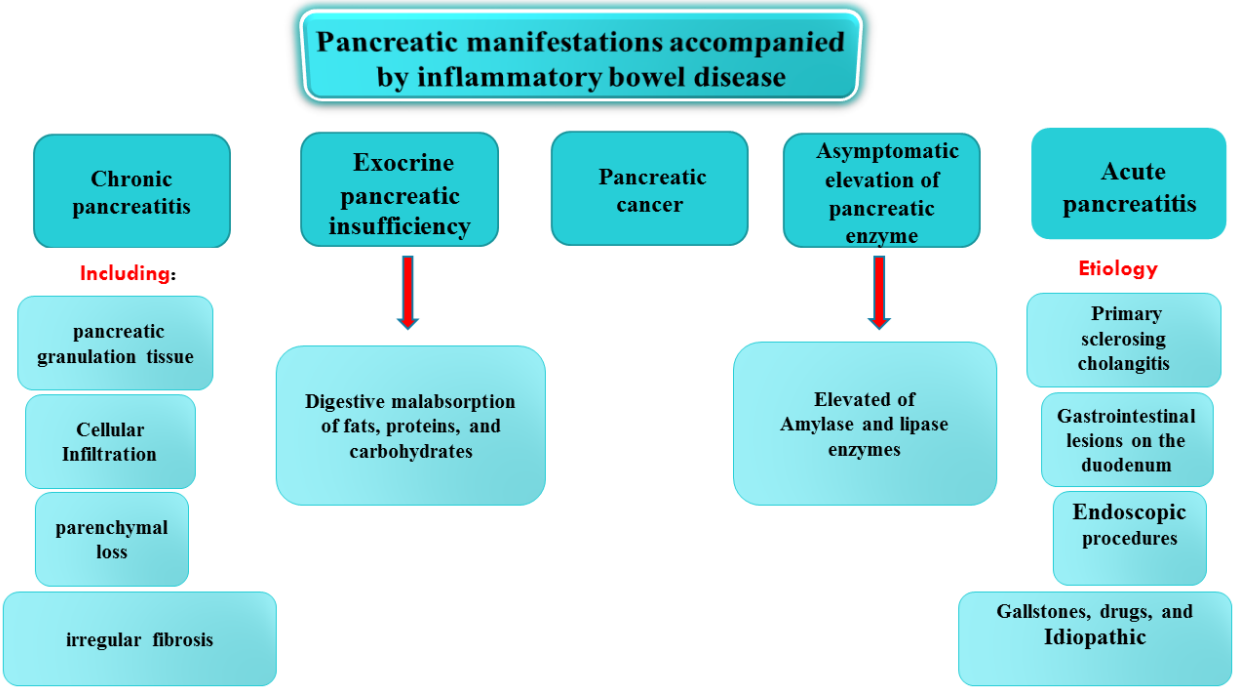

Figure 1. Pancreatic manifestations accompanied by IBD.

2.1.9 Other diseases associated with IBD

IgG4-associated cholangitis. It was identified in individuals with diseasesassociated with IgG4with autoimmune pancreatitis, a relation between ulcerative colitis and cholangitis associated with IgG4 has beenobserved[41].

Primary biliary cirrhosis. It is a characteristic autoimmune disorder of the hepatic tissue that arises through the progressive degradation of the inflammatory bile ducts and the obliteration of plasma cells and lymphocytes toward the portal way. The literature indicates a correlation between IBD and primary biliary cirrhosis but has not yet been widely recognized [42].

Cholelithiasis. Gallstones are commonly found in IBD patients. IBD progression and its pathophysiological changes may lead to gallstone development. A substantial correlation has been identified between cholelithiasis abnormality and Crohn's disease, with 13% and 34% as a prevalence rate[43]. The link between ulcerative colitis and cholelithiasis is uncertain, because, in ulcerative colitis patients,there does not seem to be a substantially elevated incidence of gallstones relative to the general population[29].

Autoimmune Pancreatitis.A correlation between autoimmune pancreatitisand IBD have proposed by some researchers, while to date, the preciseassociation is not well-defined. It has been shown that IBD-associated pancreatitis has similar clinical, morphological, and histological characteristics to the same detected featuresin autoimmune pancreatitis[43].

3. Urinary manifestations of IBD

In the IBD setting, the majority ofdifferent urinary complications have been reported in patients with Crohn's disease, with an incidence rate of 4% -23%.The complications are clearly

appearing in people with serious or chronic illness. Urinary conditions can be directly or indirectly associated with the development of the disease[44].

3.1 Enterourinary Fistulas

These disorders are the most comfortable urinary form inpatientswithIBD, a colovesical fistulas are the famous type of fistula. While,in Crohn's disease,gastrointestinal tract-confined fistulas are relatively common, fistulas between the urinary system and the gastrointestinal tract are much less common and severe complications, with an incidence rate of 2%-3.5% [44]. Most patients with a well-known history of IBD are in their 4th or 5th decade. The incidence rate is high in males, due to the position of the adnexa and uterus in women between the intestines and the bladder[45].

3.2 Obstructive Uropathy

Calculus obstructive uropathy is occurring in 1.9% – 6% of Crohn disease patients, is oftenignored urologic complication of Crohn disease [44]. Transmural bowel inflammation may lead to hydroureteronephrosis which followed by ureteral compression, fibrosis, or encasement and the right collecting ductsusually involved. [46].

3.3 Nephrolithiasis

IBD patients are 10–100 times more susceptiblethan other patients inthe hospital to develop nephrolithiasis, with 12 % as an incidence rate in patients withCrohn's disease [44]. Adults with Crohn's disease are at higher risk relative to patients with ulcerative colitis than children[47].

4. IBD and musculoskeletal manifestations

There are multiple musculoskeletal forms of IBD;almost 53% of patients have musculoskeletal system-related pain[48].The most common sites involved in IBD arthropathy are axial and peripheral[49].

4.1 IBD-related Spondyloarthropathy

This disease involves psoriatic arthritis, idiopathic ankylosing spondylitis, undifferentiated spondyloarthropathyand reactive arthritis. Spondyloarthropathy associated with IBD is divided into peripheral and axial arthropathy. Symptoms of axial type include back pain, sacroiliitis that triggers inflammation and spondylitis, whereas peripheral arthritis includes self-limiting nondeforming arthritis which develops and decreases with intestinal flares [50].

4.2 IBD and arthropathy manifestations

Arthropathy is common among IBD patients, and this condition is known as spondylarthritis (SpA).The SpA is further graded, based on the primary signs, as axial and peripheral[51]. A diagnosis of axial SpA is made using sacroiliitis radiographic findings consistent with symptoms of low back inflammatory pain. Radiological findings of sacroiliitis are significant in about 15%-27% of IBD patients,[52-54]while, progressive ankylosing spondylitis (AS)

with syndesmophytes occurs in only about 3%-10% of patients.In addition, in Crohn's disease (CD) and AS patients, HLA-B27 is found in approximately 25%–75% of cases, whereas in those with isolated sacroiliitis, HLA-B27 is found in only 7%–15% of cases. HLA-B27 Positivity in IBD patients suggests that these patients are at a higher risk of developing AS;[55]however, since HLA-B27 positivity in idiopathic AS patients is significantly lower, it cannot be regarded as a diagnostic marker [52, 56].

5. IBD and pulmonarymanifestations

Black et al.[57], in their analysis of population research, found that patients with IBD have pulmonary symptoms more often than the general population. Raj et al.[58]observed a four-fold rise in the incidence of IBD in their patients with airway disease in a 10-year retrospective study. The prevalence of disease-related pulmonary symptoms is highly variable and the symptoms continuum is broad. The pathogenesis of pulmonary findings associated with IBD is uncertain, but may be associated with an embryological origin of the intestinal mucosa and respiratory, a reaction with intestinal epithelium and lung antigen exposure, and/or an intestinal inflammatory mediator [59].

6. IBD and cardiac manifestations

To date, the link between cardiovascular disorders and IBD has not been completely explained. Researchers have indicated that patients with IBD have a higher risk of stroke,myocardial infarctionand cardiovascular mortality in recent years, particularly during the active stageof the disease. [60]. The findings of Danish nationwide cohort studyrecorded high incidence of heart failure in patients with IBD that was highly associated with active bowel disease periods[61]. Other studies have proposed, however, that there is no correlation between increased cardiovascular disease incidence andIBD. Furthermore, a meta-analysis of 11 trials showed no increase in mortality ofcardiovascular patients between the control group the and IBD group [62].

7. IBD and ocular systemmanifestations

According to the findings ofthe population studyin the IBD setting,researchers have reported that the prevalence of ocular extraintestinal symptoms is between 4 % and 12 %[63]. The most common eye findings include inflammatory disorders affecting various areas of the globe, ranging from episcleritisandconjunctivitis to more serious conditions such as anterior uveitis and scleritis [64]. Vision may be permanently compromised with scleritis, or anterior uveitis, while it is possible to detect unusual orbital extraintestinal manifestations of IBD with images[59].

8. IBD Skin diseases manifestations

8.1 Erythema nodosum (EN**)**

EN is distinguished by the appearance of subcutaneous nodules raised, tender, purple, or violet (1–5 cm in diameter), which makes it simple to diagnose. The extensor surface of the extremities, particularly the anterior tibial areas, are the most commonly affected areas, and occasionally, the trunk or upper extremities are also involved. Also, EN is associated with other

systemic symptoms such as arthralgia and fatigue. This can be clinically treated by removing the metastatic CD, and usually no biopsy is performed.

EN is the most common dermatological manifestation in patients with IBD and is more frequent in women and CD patients (4%-15% CD vs. 3%-10% CD cases).[65, 66].EN is associated with IBD activity and flares in general but not with its severity[67].Because of its connection with disease operation, management of the underlying IBD is the cornerstone of therapy. However, treatment with systemic corticosteroids may be needed in extreme cases, while treatment with infliximab, azathioprine or adalimumab may be required in resistant cases or those with repeated relapses[68, 69].

8.2Pyoderma gangrenosum

PG is characterized by the formation of a skin pustule that quickly becomes a violent-edged burrowing ulcer, around 2–20 cm in diameter. PG occurs most often on the shins and adjacent to the stomas, though it can occur anywhere on the body, including genitals.It initially occurs as a single or multiple erythematous papule(s)/pustule(s), but subsequent dermis necrosis contributes to the production of deep excavating chronic ulcerations.

For PG, the histopathological findings are non-specific, and hence their diagnosis is made dependent on the characteristic findings of the lesions after excluding other possible skin diseasesbased on the typical findings of the lesions. In some cases, a biopsy from the periphery of the lesion may be required to exclude specific skindiseases. Therefore, a high index of suspicion is requiredto avoid misdiagnosis of PG[55].

CONCLUSIONS

EIMs are moderately common through the IBD course not only limited to the gut,and in some cases, these EIM can be much more crippling than intestinal disease, which can occur long before IBD is diagnosed. Careful screening for EIMs in these patients and early appropriate diagnosis are imperative to reduce the overall morbidity. Increasing evidence suggests that IBD and associated extraintestinal disorders are not isolated diseases but share common mechanistic and pathophysiologic pathways, many of which remain elusive to date. In numerous cases, controlling the IBDactivity can also help in limiting the EIM; however, the further controlled trials remain the keys to development of the early differentiated diagnosis approach and promising treatment policies.

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Conflicts of Interest

The authors declare that theyhave no conflictof interest.

References

[1] Navaneethan U, Shen B: Hepatopancreatobiliary manifestations and complications associated with inflammatory bowel disease. Inflammatory bowel diseases 2010, 16:1598-619.

[2] Torres J, Billioud V, Sachar DB, Peyrin-Biroulet L, Colombel J-F: Ulcerative colitis as a progressive disease: the forgotten evidence. Inflammatory bowel diseases 2012, 18:1356-63.

[3] Hoivik ML, Moum B, Solberg IC, Henriksen M, Cvancarova M, Bernklev T: Work disability in inflammatory bowel disease patients 10 years after disease onset: results from the IBSEN Study. Gut 2013, 62:368-75.

[4] Levesque BG, Sandborn WJ, Ruel J, Feagan BG, Sands BE, Colombel J-F: Converging goals of treatment of inflammatory bowel disease from clinical trials and practice. Gastroenterology 2015, 148:37-51. e1.

[5] Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel J-F, Allez M, D'Haens G, D'Hoore A, Mantzaris G, Novacek G: Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. Journal of Crohn's and Colitis 2012, 6:991-1030.

[6] Van Assche G, Dignass A, Bokemeyer B, Danese S, Gionchetti P, Moser G, Beaugerie L, Gomollón F, Häuser W, Herrlinger K: Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. Journal of Crohn's and Colitis 2013, 7:1-33.

[7] Truelove S: Corisone in ulcerative colitis. Final report on a therapeutic trial. Br Med J 1955, 2:104-8.

[8] Colombel JF, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, Marano CW, Strauss R, Oddens BJ, Feagan BG: Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology 2011, 141:1194-201.

[9] Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH: Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. Inflammatory bowel diseases 2008, 14:1660-6.

[10] Peyrin-Biroulet L, Sandborn W, Sands B, Reinisch W, Bemelman W, Bryant R, d'Haens G, Dotan I, Dubinsky M, Feagan B: Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. American Journal of Gastroenterology 2015, 110:1324-38.

[11] Yoon JY, Park SJ, Hong SP, Kim TI, Kim WH, Cheon JH: Correlations of C-reactive protein levels and erythrocyte sedimentation rates with endoscopic activity indices in patients with ulcerative colitis. Digestive diseases and sciences 2014, 59:829-37.

[12] Dignass A, Eliakim R, Magro F, Maaser C, Chowers Y, Geboes K, Mantzaris G, Reinisch W, Colombel J-F, Vermeire S: Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. Journal of Crohn's and Colitis 2012, 6:965-90.

[13] Bessissow T, Lemmens B, Ferrante M, Bisschops R, Van Steen K, Geboes K, Van Assche G, Vermeire S, Rutgeerts P, De Hertogh G: Prognostic value of serologic and histologic markers on clinical relapse in ulcerative colitis patients with mucosal healing. American Journal of Gastroenterology 2012, 107:1684-92.

[14] Peyrin–Biroulet L, Bressenot A, Kampman W: Histologic remission: the ultimate therapeutic goal in ulcerative colitis? Clinical Gastroenterology and Hepatology 2014, 12:929-34. e2.

[15] Bitton A, Peppercorn MA, Antonioli DA, Niles JL, Shah S, Bousvaros A, Ransil B, Wild G, Cohen A, Edwardes MDD: Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. Gastroenterology 2001, 120:13-20.

[16] Bryant RV, Burger DC, Delo J, Walsh AJ, Thomas S, von Herbay A, Buchel OC, White L, Brain O, Keshav S: Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up. Gut 2016, 65:408-14.

[17] Kornbluth A, Sachar DB, Gastroenterology PPCotACo: Ulcerative colitis practice guidelines in adults: American college of gastroenterology, practice parameters committee. American Journal of Gastroenterology 2010, 105:501-23.

[18] Sawczenko A, Sandhu B: Presenting features of inflammatory bowel disease in Great Britain and Ireland. Archives of disease in childhood 2003, 88:995-1000.

[19] Cummings JF, Keshav S, Travis SP: Medical management of Crohn's disease. Bmj 2008, 336:1062-6.
[20] Bernstein CN, Blanchard JF, Rawsthorne P, Yu N: The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. The American journal of gastroenterology 2001, 96:1116-22.
[21] Olpin JD, Sjoberg BP, Stilwill SE, Jensen LE, Rezvani M, Shaaban AM: Beyond the bowel: extraintestinal manifestations of inflammatory bowel disease. Radiographics 2017, 37:1135-60.
[22] Zhang W, Nuki G, Moskowitz R, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt K, Croft P, Doherty M: OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis and cartilage 2010, 18:476-99.
[23] Smith MP, Loe RH: Sclerosing cholangitis: review of recent case reports and associated diseases and four new cases. The American Journal of Surgery 1965, 110:239-46.
[24] Floreani A, Rizzotto ER, Ferrara F, Carderi I, Caroli D, Blasone L, Baldo V: Clinical course and outcome of autoimmune hepatitis/primary sclerosing cholangitis overlap syndrome. American Journal of Gastroenterology 2005, 100:1516-22.
[25] Broome U, Olsson R, Lööf L, Bodemar G, Hultcrantz R, Danielsson A, Prytz H, Sandberg-Gertzen H, Wallerstedt S, Lindberg G: Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. Gut 1996, 38:610-5.
[26] Walker SL, McCormick PA: Diagnosing cholangiocarcinoma in primary sclerosing cholangitis: an "evidence based radiology" review. Abdominal imaging 2008, 33:14-7.
[27] Roenigk HH, Auerbach R, Maibach H, Weinstein G, Lebwohl M: Methotrexate in psoriasis: consensus conference. Journal of the American Academy of Dermatology 1998, 38:478-85.
[28] Restellini S, Chazouillères O, Frossard JL: Hepatic manifestations of inflammatory bowel diseases. Liver International 2017, 37:475-89.
[29] Bargiggia S, Maconi G, Elli M, Molteni P, Ardizzone S, Parente F, Todaro I, Greco S, Manzionna G, Porro GB: Sonographic prevalence of liver steatosis and biliary tract stones in patients with inflammatory bowel disease: study of 511 subjects at a single center. Journal of clinical gastroenterology 2003, 36:417-20.
[30] Riegler G, D'INCÀ R, Sturniolo G, Corrao G, Blanco CDV, Di Leo V, Carratù R, Ingrosso M, Pelli M, Morini S: Hepatobiliary alterations in patients with inflammatory bowel disease: a multicenter study. Scandinavian journal of gastroenterology 1998, 33:93-8.
[31] Vakil N, Hayne G, Sharma A, Hardy DJ, Slutsky A: Liver abscess in Crohn's disease. American Journal of Gastroenterology 1994, 89.
[32] Jackson L, O'Gorman P, O'connell J, Cronin C, Cotter K, Shanahan F: Thrombosis in inflammatory bowel disease: clinical setting, procoagulant profile and factor V Leiden. QJM: monthly journal of the Association of Physicians 1997, 90:183-8.
[33] Baker ME, Remzi F, Einstein D, Oncel M, Herts B, Remer E, Fazio V: CT depiction of portal vein thrombi after creation of ileal pouch–anal anastomosis. Radiology 2003, 227:73-9.
[34] Ball WP: Pancreatic lesions associated with chronic ulcerative colitis. Arch Pathol 1950, 50:347-58.
[35] Chapin LE, Scudamore HH, Baggenstoss AH, Bargen JA: Regional enteritis: associated visceral changes. Gastroenterology 1956, 30:404-15.
[36] Frey CF: Acute pancreatitis as a complication of ulcerative colitis and collagen disease. University of Michigan Medical Center journal 1967, 33:18-21.
[37] Legge DA, Hoffman HN, Carlson HC: Pancreatitis as a complication of regional enteritis of the duodenum. Gastroenterology 1971, 61:834-7.
[38] Meltzer SJ, Korelitz BI: Pancreatitis and duodenopancreatic reflux in Crohn's disease. Case report and review of the literature. Journal of clinical gastroenterology 1988, 10:555-8.
[39] Seyrig J-A, Jian R, Modigliani R, Golfain D, Florent C, Messing B, Bitoun A: Idiopathic pancreatitis associated with inflammatory bowel disease. Digestive diseases and sciences 1985, 30:1121-6.
[40] Iida T, Wagatsuma K, Hirayama D, Yokoyama Y, Nakase H: The Etiology of Pancreatic Manifestations in Patients with Inflammatory Bowel Disease. Journal of clinical medicine 2019, 8:916.

[41] Dastis SN, Latinne D, Sempoux C, Geubel AP: Ulcerative colitis associated with IgG4 cholangitis: similar features in two HLA identical siblings. Journal of hepatology 2009, 51:601-5.
[42] Tada F, Abe M, Nunoi H, Azemoto N, Mashiba T, Furukawa S, Kumagi T, Murakami H, Ikeda Y, Matsuura B: Ulcerative colitis complicated with primary biliary cirrhosis. Internal medicine 2011, 50:2323-7.
[43] Navaneethan U, Shen B: Hepatopancreatobiliary manifestations and complications associated with inflammatory bowel disease. Inflammatory bowel diseases 2010, 16:1598-619.
[44] Tonolini M, Villa C, Campari A, Ravelli A, Bianco R, Cornalba G: Common and unusual urogenital Crohn's disease complications: spectrum of cross-sectional imaging findings. Abdominal imaging 2013, 38:32-41.
[45] Talamini M, Broe P, Cameron JL: Urinary fistulas in Crohn's disease. Surgery, gynecology & obstetrics 1982, 154:553-6.
[46] Ruffolo C, Angriman I, Scarpa M, Polese L, Pagano D, Barollo M, Bertin M, D'Amico DF: Urologic complications in Crohn's disease: suspicion criteria. Hepato-gastroenterology 2006, 53:357-60.
[47] McLeod RS, Churchill DN: Urolithiasis complicating inflammatory bowel disease. The Journal of urology 1992, 148:974-8.
[48] Levine JS, Burakoff R: Extraintestinal manifestations of inflammatory bowel disease. Gastroenterology & hepatology 2011, 7:235.
[49] Arvikar SL, Fisher MC: Inflammatory bowel disease associated arthropathy. Current reviews in musculoskeletal medicine 2011, 4:123-31.
[50] Brakenhoff LK, van der Heijde DM, Hommes DW, Huizinga TW, Fidder HH: The joint—gut axis in inflammatory bowel diseases. Journal of Crohn's and Colitis 2010, 4:257-68.
[51] Rudwaleit M, Van Der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, Braun J, Chou C, Collantes-Estevez E, Dougados M: The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Annals of the rheumatic diseases 2009, 68:777-83.
[52] Chan J, Sari I, Salonen D, Silverberg MS, Haroon N, Inman RD: Prevalence of sacroiliitis in inflammatory bowel disease using a standardized computed tomography scoring system. Arthritis care & research 2018, 70:807-10.
[53] Leclerc‐Jacob S, Lux G, Rat A, Laurent V, Blum A, Chary‐Valckenaere I, Peyrin‐Biroulet L, Loeuille D: The prevalence of inflammatory sacroiliitis assessed on magnetic resonance imaging of inflammatory bowel disease: a retrospective study performed on 186 patients. Alimentary pharmacology & therapeutics 2014, 39:957-62.
[54] Peeters H, Vander Cruyssen B, Mielants H, De Vlam K, Vermeire S, Louis E, Rutgeerts P, Belaiche J, De Vos M: Clinical and genetic factors associated with sacroiliitis in Crohn's disease. Journal of gastroenterology and hepatology 2008, 23:132-7.
[55] Harbord M, Annese V, Vavricka SR, Allez M, Barreiro-de Acosta M, Boberg KM, Burisch J, De Vos M, De Vries A-M, Dick AD: The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. Journal of Crohn's and Colitis 2016, 10:239-54.
[56] Orchard T, Holt H, Bradbury L, Hammersma J, McNally E, Jewell D, Wordsworth B: The prevalence, clinical features and association of HLA‐B27 in sacroiliitis associated with established Crohn's disease. Alimentary pharmacology & therapeutics 2009, 29:193-7.
[57] Black H, Mendoza M, Murin S: Thoracic manifestations of inflammatory bowel disease. Chest 2007, 131:524-32.
[58] Raj A, Birring S, Green R, Grant A, de Caestecker J, Pavord I: Prevalence of inflammatory bowel disease in patients with airways disease. Respiratory medicine 2008, 102:780-5.
[59] Katsanos A, Asproudis I, Katsanos KH, Dastiridou AI, Aspiotis M, Tsianos EV: Orbital and optic nerve complications of inflammatory bowel disease. Journal of Crohn's and Colitis 2013, 7:683-93.
[60] Kristensen SL, Ahlehoff O, Lindhardsen J, Erichsen R, Jensen GV, Torp-Pedersen C, Nielsen OH, Gislason GH, Hansen PR: Disease activity in inflammatory bowel disease is associated with increased risk

of myocardial infarction, stroke and cardiovascular death–a Danish nationwide cohort study. PloS one 2013, 8.
[61] Kristensen SL, Ahlehoff O, Lindhardsen J, Erichsen R, Lamberts M, Khalid U, Nielsen OH, Torp-Pedersen C, Gislason GH, Hansen PR: Inflammatory bowel disease is associated with an increased risk of hospitalization for heart failure: a Danish Nationwide Cohort study. Circulation: Heart Failure 2014, 7:717-22.
[62] Dorn SD, Sandler RS: Inflammatory bowel disease is not a risk factor for cardiovascular disease mortality: results from a systematic review and meta-analysis. American Journal of Gastroenterology 2007, 102:662-7.
[63] Das KM: Relationship of extraintestinal involvements in inflammatory bowel disease (new insights into autoimmune pathogenesis). Digestive diseases and sciences 1999, 44:1-13.
[64] Rothfuss KS, Stange EF, Herrlinger KR: Extraintestinal manifestations and complications in inflammatory bowel diseases. World journal of gastroenterology: WJG 2006, 12:4819.
[65] Chowaniec M, Starba A, Wiland P: Erythema nodosum–review of the literature. Reumatologia 2016, 54:79.
[66] Freeman HJ: Erythema nodosum and pyoderma gangrenosum in 50 patients with Crohn's disease. Canadian Journal of Gastroenterology and Hepatology 2005, 19:603-6.
[67] Trost L, McDonnell J: Important cutaneous manifestations of inflammatory bowel disease. Postgraduate medical journal 2005, 81:580-5.
[68] Clayton T, Walker B, Stables G: Treatment of chronic erythema nodosum with infliximab. Clinical and Experimental Dermatology: Viewpoints in dermatology 2006, 31:823-4.
[69] Ortego‐Centeno N, Callejas‐Rubio J, Sanchez‐Cano D, Caballero‐Morales T: Refractory chronic erythema nodosum successfully treated with adalimumab. Journal of the European Academy of Dermatology and Venereology 2007, 21:408-10.