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ECCO Topical Review

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ECCO Topical Review on Clinicopathological Spectrum and Differential Diagnosis of Inflammatory Bowel Disease

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Abstract

Introduction: Many diseases can imitate inflammatory bowel disease [IBD] clinically and pathologically. This review outlines the differential diagnosis of IBD and discusses morphological pointers and ancillary techniques that assist with the distinction between IBD and its mimics.
Methods: European Crohn's and Colitis Organisation [ECCO] Topical Reviews are the result of an expert consensus. For this review, ECCO announced an open call to its members and formed three working groups [WGs] to study clinical aspects, pathological considerations, and the value of ancillary techniques. All WGs performed a systematic literature search.
Results: Each WG produced a draft text and drew up provisional Current Practice Position [CPP] statements that highlighted the most important conclusions. Discussions and a preliminary voting round took place, with subsequent revision of CPP statements and text and a further meeting to agree on final statements.
Conclusions: Clinicians and pathologists encounter a wide variety of mimics of IBD, including infection, drug-induced disease, vascular disorders, diverticular disease, diversion proctocolitis,

radiation damage, and immune disorders. Reliable distinction requires a multidisciplinary approach.

Key Words: Inflammatory bowel diseases; ulcerative colitis; Crohn's disease; tuberculosis; parasitic infections; viral infections; bacterial infections; fungal infections; drug-induced abnormalities; immune checkpoint inhibitors; diverticulosis; vasculitis; ischaemic colitis; radiation-induced abnormalities; endoscopy; pathology; diagnostic imaging.

1. Introduction

The variety of diseases that can resemble IBD is wide. This is true for both incident and treated IBD and applies to both adult and paediatric IBD.[1–3] Distinction is often crucial for management, and an incorrect diagnosis can result in management delays or errors. Differentiation of IBD from other conditions may require not only standard clinical assessment but also endoscopy, histology, imaging, and other investigations. Factors such as patient age, previous surgery, and current drug therapy modify the approach to the investigations.

Although the diagnosis of new IBD depends initially on typical symptoms such as diarrhoea, rectal bleeding, and abdominal pain, these symptoms can have other causes.[4,5] Infective enterocolitis is an important differential diagnosis.[6] Endoscopy is an invaluable tool for the diagnosis of IBD and for its classification as ulcerative colitis [UC] or Crohn's disease [CD]. However, many diseases can produce an endoscopic picture similar to that of IBD.

Pathologists rely on a constellation of histological features to support or refute a suspected diagnosis of IBD, e.g. basal plasmacytosis, architectural changes, and granulomas.[2,7,8] Unfortunately, each individual feature of IBD can also be present in other circumstances, though not necessarily in the same combinations. When examining a resection specimen, there is usually an existing diagnosis of IBD. Consequently, pathological misdiagnosis is less likely. Additional investigations, including stool tests, imaging, and serology can also assist distinction. Newer molecular methods, including genetic testing, have a role in certain settings and particularly in a subgroup of the paediatric population.

2. Methods

European Crohn's and Colitis Organisation [ECCO] Topical Reviews are the product of expert consensus and aim to provide guidance where evidence is sparse. For this review, ECCO announced an open call. Three co-ordinators selected 12 experts and set up three Working Groups [WG] to explore, respectively, the clinical presentation of IBD and its mimics, pathological mimicry of IBD, and the value of ancillary techniques.

The WGs performed a systematic literature review using PubMed, Medline, the Cochrane database, and their own files. They produced a draft text including provisional Current Practice Position [CPP] statements. Discussions and a preliminary voting round took place, followed by revision of the CPP statements. All participants met again. Agreement on statements by ≥80% of participants led to their acceptance.

3. Infection

Current Practice Position 1

Several viral, bacterial, fungal, protozoan, and helminthic infections should be considered in the differential diagnosis of IBD. A detailed clinical history addressing intestinal and extraintestinal symptoms, travel history, sexual history, and conditions influencing immune status should be collected

3.1. Infections: general considerations

Many infections may mimic IBD [Figures 1 and 2]. Intestinal tuberculosis [ITB] causes symptoms such as diarrhoea, weight loss, and abdominal pain that may suggest CD.[9] *Salmonella*, *Shigella*, *Campylobacter*, and several viruses usually cause an acute self-limiting illness that may mimic new onset IBD.[10] Some agents, such as cytomegalovirus [CMV] or *Clostridioides difficile* may complicate pre-existing IBD.[11] A smaller number of agents can cause chronic gastrointestinal [GI] tract inflammation and long-lasting symptoms mimicking IBD [Table 1].

Non-specific symptoms are common to many of these entities. However, it can be useful to distinguish different clinical syndromes, including enteritis [diarrhoea and abdominal pain], colitis [diarrhoea, abdominal pain, and GI bleeding], or proctitis [anorectal pain, tenesmus, and urgency], particularly as different agents tend to affect different segments of the GI tract.[12] For example, *Yersinia* spp. usually affects the ileocaecal region,[13] whereas *Chlamydia trachomatis* or herpes simplex virus [HSV] can cause infectious proctitis.[14]

The investigation of extra-intestinal signs and symptoms is important. For instance, *Strongyloides stercoralis* or *Histoplasma capsulatum* may cause respiratory symptoms or pneumonia,[15,16] and lymphogranuloma venereum [LGV] or syphilis may be responsible for typical cutaneous findings.[17]

A travel history and sexual history are necessary. Increasing international travel increases the prevalence of diseases like amoebiasis,[18] schistosomiasis,[19] and strongyloidiasis.[20] There is a rising incidence of sexually transmitted infections, such as chlamydia, gonorrhoea, or syphilis, which can cause a proctitis resembling IBD.[12,21] Investigation of the status of the immune system is also important, as conditions such as HIV infection, steroid use, or pregnancy may result in severe or disseminated forms of IBD mimics including actinomycosis,[22] coccidioidomycosis,[10] and cryptosporidiosis.[21]

Certain histological features can help to distinguish IBD from common infections. Basal plasmacytosis and architectural changes favour IBD over infection. However, there are exceptions to the rules. Granulomas occur in CD but also in a wide variety of other conditions [Table 2].

Current Practice Position 2

Architectural disturbance and basal plasmacytosis favour IBD over infection

Current Practice Position 3

Granulomas alone cannot make the distinction between Crohn's disease and some types of infections. They should be assessed together with other histological features and with the clinical information

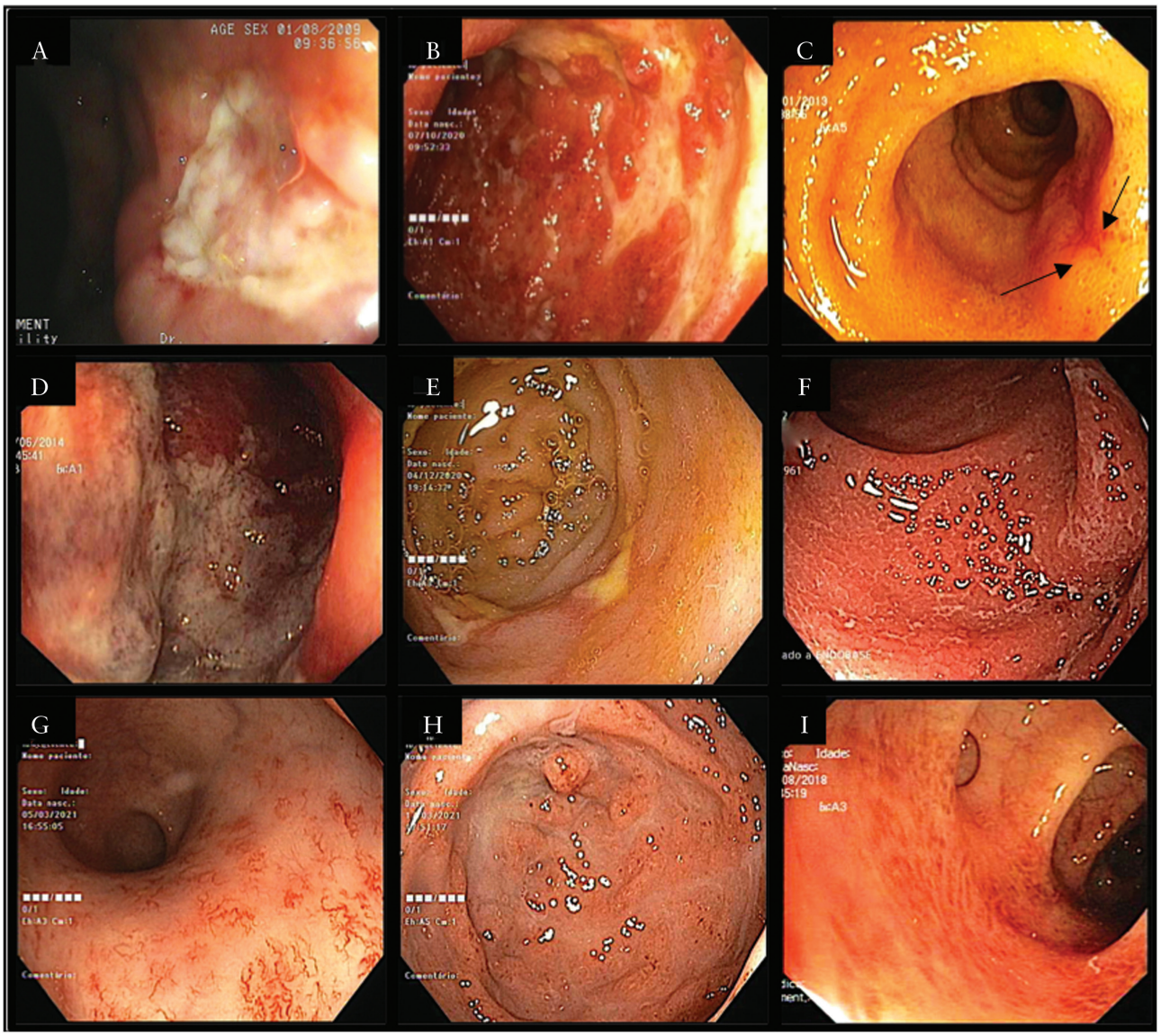

Figure 1. [Endoscopy.] A. A large ulcer with elevated borders and a fibrinous centre can be seen in this patient with amoebic colitis. B. Deep longitudinal ulcers in an intensely erythematous mucosa in a young male patient presenting with skin vasculitis and elevated IgA, suggesting intestinal involvement by IgA vasculitis. C. Round, shallow ulcers [arrows] in a normal background mucosa in a female patient with a diagnosis of Behçet's disease. D. An intensely oedematous and violaceous mucosa with exudate and confluent membrane is highly suggestive of ischaemic colitis. E. Superficial ulcers in the terminal ileum in a normal background mucosa in a patient regularly taking non-steroidal anti-inflammatory drugs [NSAIDs], suggesting NSAID ileitis. F. Erythematous mucosa with exudate, micro-erosions, and loss of vascular pattern in a patient receiving treatment with novilimumab [an immune checkpoint inhibitor]. G. Endoscopy of the rectum in a male patient who previously received pelvic radiation therapy for prostate cancer shows multiple non-confluent telangiectasia, suggestive of radiation proctitis. H. Endoscopy of the excluded rectum shows erythema, friability, oedema, and microerosions, compatible with diversion proctitis. I. Mild erythema and congestion may be seen in the interdiverticular mucosa without involvement of the diverticular orifices, which suggests diverticular colitis. Endoscopic aspects can be mild [as in the example here] or more severe with loss of submucosal vascular pattern, intense hyperaemia, diffuse ulceration, and reduced calibre of the colonic lumen. Endoscopy images published with the permission of Joana Torres [Hospital Beatriz Ângelo, Loures, Portugal], Luis Menchen [Hospital General Universitario 'Gregorio Marañón', Madrid, Spain], and Marilia Cravo [Hospital da Luz, Lisboa, Portugal].

3.2. Infections: tuberculosis

Current Practice Position 4

A combination of clinical history, endoscopy, biopsies, culture, and imaging can help to differentiate intestinal tuberculosis from Crohn's disease, but may not always be sufficient. Microbial techniques including staining, culture, and polymerase chain reaction [PCR] are widely used but lack sensitivity and have a low diagnostic yield. A negative interferon-γ release assay cannot rule out tuberculosis. A course of antituberculous therapy and longer-term follow up may be necessary in some instances

Tuberculosis [TB] is caused by *Mycobacterium tuberculosis* and is common in Asiatic and African regions.[23] TB is also increasingly important in Western countries due to immigration, immunosuppression, and resistance to anti-tuberculous drugs. ITB is the sixth most common extrapulmonary form and is a potentially serious illness.[9] Although mimicry of CD can be close, treatment is very different.

A definitive diagnosis of ITB is sometimes possible based on positive staining for acid-fast bacilli in tissue samples, mycobacterial culture, or PCR. Necrotising granulomas on histology or necrotic lymph nodes on imaging are almost diagnostic.[24] However, the gold-standard tests for *M. tuberculosis* have low sensitivity,[25–27] particularly in the GI tract. Therefore, differentiating ITB from other conditions is often a challenge. Diagnosis is a particular problem in TB-endemic countries. Furthermore, the

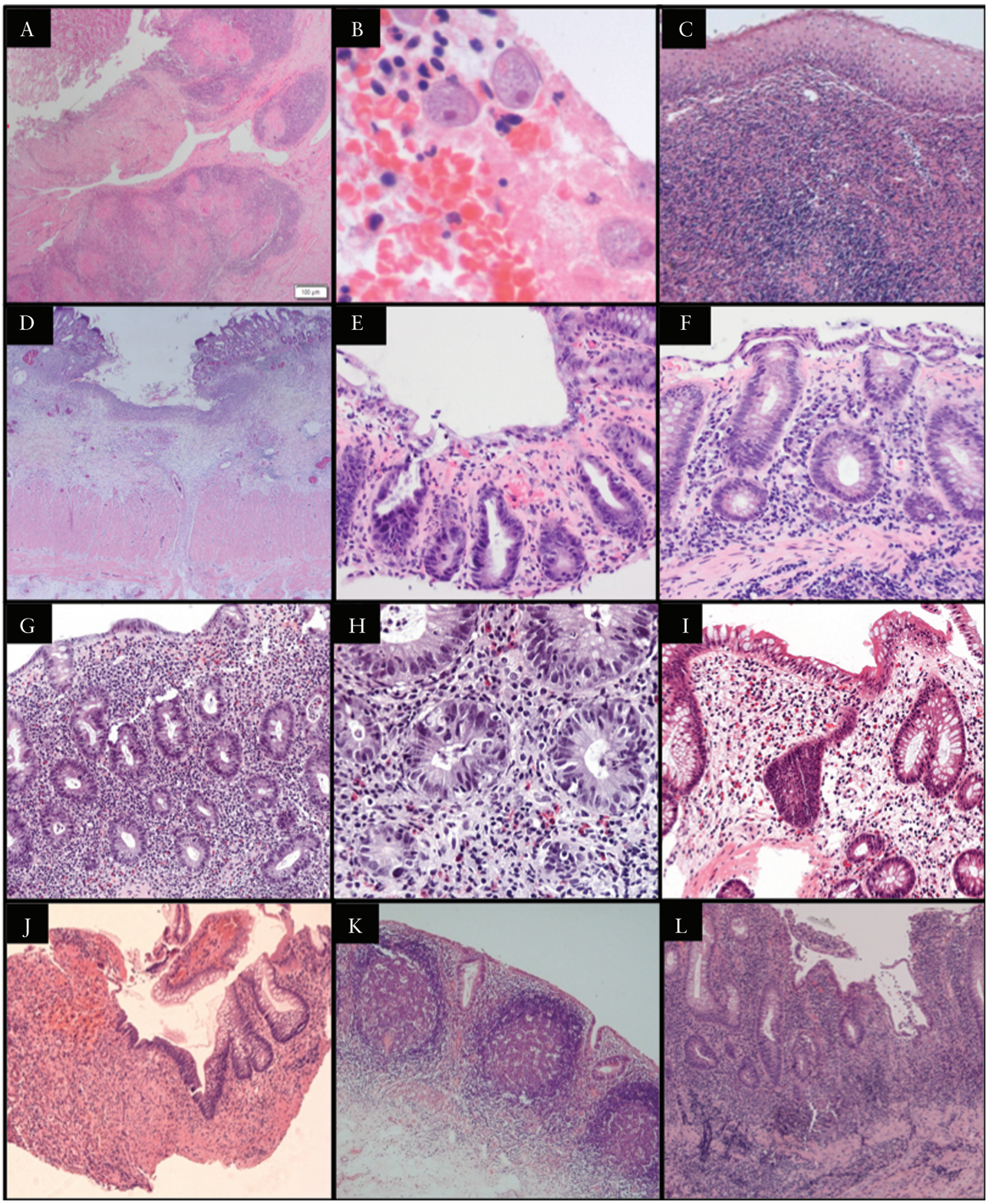

Figure 2. [Histology.] A. Histological assessment of a resected colonic mass from a 45-year old patient revealed numerous large confluent granulomas. Granulomas of this size and extent are unusual in CD and, together with central necrosis, allowed a histological diagnosis of tuberculosis. However, differentiation can be difficult, especially in a biopsy, as there is much overlap with CD and other infections. B. Amoebic colitis can sometimes resemble IBD in biopsies. Trophozoites are diagnostic if present. They are large [25–40 μm in diameter] and round or ovoid, with foamy pale cytoplasm that often contains ingested red blood cells, and have a small, round, pale purple, typically eccentric nucleus with a central karyosome. C. In the proctitis of lymphogranuloma venereum [LGV] or syphilis there is often a dense lymphoplasmacytic infiltrate. Unlike IBD, the inflammation often involves the anal mucosa, as in this example. D. A resection from a patient with suspected Behçet's disease showing an ulcer extending into the submucosa and undermining the adjacent mucosa, with otherwise relatively mild mucosal damage. The absence of transmural lymphoid aggregates, granulomas, and fibrosis might suggest a diagnosis other than

incidence of CD is rising in many of these areas. Current Asia-Pacific guidelines recommend empirical treatment for patients with diagnostic uncertainty.[28,29]

Some macroscopic features may help distinguish ITB from CD. ITB mainly involves the ileocaecal region, less often the remaining colon, and rarely the upper GI tract and anal region.[9] In contrast, CD can affect any part of the GI tract and is associated with perianal fistulae [52%] and with extra-intestinal manifestations, such as arthritis and erythema nodosum.[30] Endoscopically there are three different patterns of ITB, namely the ulcerative type [60%], the ulcerohypertrophic type [30%], and the hypertrophic type [10%]. There may be transverse, often circumferential ulcers, a patulous ileocaecal valve, a thickened and fibrotic wall, luminal narrowing, or a pseudotumour.[9] Features typical of CD are longitudinal ulcers, a cobblestone appearance, and inflammatory polyps.[31]

On histology, ITB usually produces granulomatous inflammation and other features that can resemble those of CD [Figure 2A]. A meta-analysis revealed that microgranulomas (odds ratio [OR] 3.56) and focally enhanced colitis [OR 3.65] favour a diagnosis of CD, whereas granulomas that are confluent [OR 0.04], multiple [OR 0.18], larger [OR 0.07], surrounded by a lymphocytic cuff [OR 0.15], and/or submucosal [0.17] are more likely in ITB [likelihood ratio 1.69–22]. Ulcers lined by epithelioid histiocytes strongly suggest TB.[27] Caseating necrosis and detectable acid-fast bacilli are diagnostic but are very rarely present in ITB.[32]

Additional methods, such as culture and molecular techniques, may detect mycobacteria, but these too are often non-contributory in the GI tract.[33] Interferon-γ release assays [IGRA] detect the release of interferon-γ after stimulation by the *M. tuberculosis* antigen and can help differentiate ITB from CD.[34] IGRAs have a sensitivity of 84% and a specificity of 86% for diagnosis of ITB[27,35,36] but cannot distinguish active from latent TB. By integrating clinical manifestations, endoscopic observations, and pathological findings, several prediction models are available online[27] which have sensitivities and specificities above 90%.[36] Clinical features are often unable to distinguish.[37,38] A summary is provided in Table 3.[27]

3.3. Infections: other bacteria

Bacterial food-borne infections, such as *Salmonella typhi*, *Shigella dysenteriae*, and *Shigella sonnei* involve the large bowel and ileum. Endoscopy reveals aphthoid and linear ulcers that may become deeply infiltrating. Acute infectious colitis lacks the histological features of IBD, but may be difficult to distinguish from UC in the acute phase because of crypt abscesses and cryptitis, and from CD in the resolving phase because of a predominantly mononuclear infiltrate and focality of cryptitis.[39] In long-standing inflammation, there may be mild crypt distortion. In shigellosis, severe crypt distortion may occasionally hinder distinction from IBD.[40]

Yersinia enterocolitica and *Yersinia pseudotuberculosis*, responsible for a food-borne gastroenteritis, are common enteropathogens in Western countries, mainly affect the ileocaecal region and appendix, and cause mesenteric lymph node enlargement. These Gram-negative coccobacilli may produce a thickened nodular mucosa with aphthoid or irregular-shaped ulcers and a congested serosal surface.[13,41,42] The appendix frequently perforates.[43] Suppurative or granulomatous inflammation are associated with lymphoid hyperplasia [mainly mucosal and submucosal]. *Y. enterocolitica* presents with hyperplastic Peyer's patches, superficial ulcers, necrosis, and palisading histiocytes. In contrast, *Y. pseudotuberculosis* produces mixed inflammation and granulomas with central necrosis and microabscesses.[41] Transmural lymphoid aggregates, fissuring ulcers, and skip lesions can resemble CD. CD is characterised macroscopically by a cobblestone pattern and creeping fat and microscopically may show crypt distortion, a thickened muscularis mucosae, and neuronal hyperplasia.[44] However, distinction may not be possible.

Actinomycoses, including *Actinomyces israelii*, are Gram-positive non acid-fast anaerobic microorganisms that involve the appendix and, less often, the right colon. The mucosa shows lymphoid hyperplasia, eventually with ulcers or fissures. Inflammation extends throughout the wall, inducing marked fibrosis, and may be associated with non-necrotising epithelioid granulomas that can resemble CD. Thorough sampling with Gram stain or silver stain may highlight colonies of filamentous bacteria. CD differs clinically from actinomycosis and extends beyond the appendix.[44,45]

The sexually transmitted diseases lymphogranuloma venereum [LGV] and syphilis, caused by *Chlamydia trachomatis* and *Treponema pallidum*, respectively, occur mainly in HIV-positive men who have sex with men [MSM] and present with a proctitis or proctocolitis. Endoscopically, there may be ulcers and, rarely, a mass lesion. Histologically, the mucosa shows intense chronic inflammation with numerous plasma cells and lymphoid aggregates, disproportionate to the mildness of the acute inflammation. In contrast with IBD, crypt distortion and basal plasmacytosis are minimal or absent and granulomas and Paneth cell metaplasia are rare. Diagnosis can sometimes be confirmed by molecular examination in LGV or by an immunohistochemical stain highlighting spirochaetes in syphilis.[46–49]

3.4. Infections: protozoa

Amoebiasis most commonly occurs in developing countries and is caused by *Entamoeba histiolytica*. Its prevalence is increasing

CD. The histological appearances are usually not specific. E. Biopsy appearances in ischaemia may be non-specific but are sometimes helpful. Here, there are characteristic changes including hyalinisation, crypt withering, small foci of haemorrhage, and mild acute inflammation. Classical histological features of IBD, particularly basal plasmacytosis, are absent. F. Immune checkpoint inhibitor colitis shows a wide variety of appearances histologically, sometimes with a mixed pattern that is not typical of IBD. In this example, the changes resemble those of collagenous colitis [including a subepithelial collagen band and detachment of surface epithelium]. G. In chronic or recurrent immune checkpoint inhibitor colitis, the histology can mimic IBD closely. In this example of anti-PD-1 colitis, there is chronic inflammation, mucin depletion, and neutrophil activity. Relatively little basal plasmacytosis and a significant increase in crypt intraepithelial lymphocytes are clues to drug aetiology. Nevertheless, a clinical history is necessary. H. An increase in crypt epithelial cell apoptoses may suggest drugs, as in this example of anti-PD-1 colitis, but is not specific. I. Colitis associated with mycophenolate mofetil. There is prominent distortion of crypts, resembling the architecture of UC. The lamina propria is less cellular than in typical untreated IBD. However, longstanding IBD can also have this appearance. J. A rectal biopsy 12 years after administration of radiotherapy for prostate cancer. There is crypt architectural distortion, potentially mimicking IBD, but the typical basal plasmacytosis of untreated IBD is not present. K. Diversion proctocolitis [DPC] can resemble IBD histologically, regardless of the original reason for surgery. Prominent lymphoid follicles, as in this example, are typical and might alert the pathologist to the possibility of DPC. However, this is not sufficient to make a diagnosis of DPC or to distinguish it reliably from IBD. L. A biopsy from the sigmoid colon in a 77-year old man with diverticulosis. Histologically, the mucosa shows diffuse chronic inflammation with architectural distortion, closely resembling UC. The rectal mucosa [not shown here] is histologically normal. On the basis of the clinical setting and anatomical distribution, diverticular colitis is much more likely than IBD in this case. Histology images published with the permission of Roger Feakins [Royal Free Hospital, London, UK] and Magali Svrcek [Saint-Antoine Hospital, Paris, France]. IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; PD-1, programmed cell death 1.

Table 1. Differential diagnosis of IBD: chronic infections.

Disease	Agent and route of transmission	Clinical manifestations	Clinical clues	Endoscopic findings	Pathological clues	Features overlapping IBD	Diagnostic methods
Yersiniosis[11,13,309]	*Yersinia enterocolitica* and *Yersinia pseudotuberculosis*; faecal-oral route [mainly undercooked pork or contaminated water]	Terminal ileitis, enteritis, mesenteric lymphadenitis, pseudoappendicitis	Higher risk in patients with iron-overload syndromes; preceding pharyngitis may be a presenting symptom	Terminal ileal and caecal ulcers; round or oval elevations of mucosa	Epithelioid granulomas	Erythema nodosum and reactive arthritis may be present	Stool culture
Actinomycosis[22,310,311]	*Actinomyces israelii* [90% of cases]; commensals of the oral cavity, GI, and urogenital tract [pathogenic when the mucosa barrier is breached]	Abdominal actinomycosis [20% of all actinomycoses]: appendix, caecum, and less frequently left colon	History of recent abdominal surgery, bowel perforation [mostly acute perforated appendicitis], neoplasia, poor oral hygiene, intrauterine contraceptive devices; more common in immunocompromised patients	Frequently with no visible mucosal changes on endoscopic studies; left colon obstructing mass may occur	Yellowish sulphur granules containing filamentous Gram-positive bacilli and inflammatory cells	Fistulisation of contiguous tissues in advanced disease [sometimes to the abdominal wall or perineum]	Culture of biopsy or pus or surgical specimen [most frequently]
Amoebiasis[18,312,313]	*Entamoeba histolytica*; faecal-oral transmission via ingestion of contaminated water or food	Amoebic colitis [predominantly caecum and right colon but can affect the entire colon, including the anal region]	Travellers or immigrants from endemic areas [Central and South America, Africa, Middle East, and Southern Asia]; MSM; immunosuppression, pregnant women and men with higher risk of invasive disease; fulminant colitis may develop after systemic steroid administration; fever and bloody stool absent in most cases	Localised inflammatory annular masses can develop in the caecum or ascending colon [amoebomas]; typical flask-shaped mucosal ulcers covered by shaggy yellow slough ['poached egg appearance'] may be seen but continuous mucosal UC-like inflammation can also be observed	Amoebic trophozoites with phagocytosed erythrocytes	Can rarely be associated with penetrating disease, causing enterocutaneous, rectovaginal, and enterovesical fistulae	Stool microscopy; stool antigen; colonic biopsy PCR or histology; serology antibody tests [useful in non-endemic regions]
Histoplasmosis[16,314,315]	*Histoplasma capsulatum*; inhalation of spores from soil	Terminal ileitis or colitis [in progressive disseminated histoplasmosis, which is an AIDS-defining disease]	Immigrants or travellers from endemic areas [Ohio and Mississippi valleys]; disseminated and severe disease more common in immunocompromised patients; previous history of pneumonia or respiratory symptoms; hepatosplenomegaly	Deep central ulcers on top of pseudopolyps, hyperaemia, friability, strictures, ulceration	Diffuse lymphohistiocytic infiltrates and nodules; fungi present	Colonic obstructing mass may occur; mucocutaneous ulcers in mouth; gastrointestinal bleeding or bowel perforation; arthritis and erythema nodosum may develop	Fungal blood or tissue culture; serology; urine and serum antigen; histological examination

Table 1. Continued

Disease	Agent and route of transmission	Clinical manifestations	Clinical clues	Endoscopic findings	Pathological clues	Features overlapping IBD	Diagnostic methods
Strongyloidiasis[15,20,316]	*Strongyloides stercoralis*; skin contact with contaminated soil [but faecal-oral, person-to-person, or sexual oro-anal transmission also possible]	Enteritis, colitis, proctitis	Immigrants, refugees, travellers, and military personnel from rural areas of tropical and subtropical regions; risk of severe disease in immunocompromised individuals [mostly steroid users]; dermatological [larva currens, per umbilical purpura] and respiratory symptoms; eosinophilia is common; Gram-negative bacteraemia may occur	Duodenal [oedema mucosal discoloration, erythema, subepithelial haemorrhages and megaduodenum] and colonic [oedema, loss of vascular pattern, aphthous ulcers, erosions, serpiginous ulcerations, xanthoma-like lesions with a skip pattern of inflammation and distal attenuation of the disease] changes may be found	Presence of organism; eosinophil-rich infiltrates	Hyperinfection may present with bowel obstruction and gastrointestinal bleeding	Microscopic stool evaluation; duodenal or colonic biopsies; PCR stool testing; serological tests
Schistosomiasis [bilharziasis][19,317,318]	*Schistosoma mansoni* and *Schistosoma japonicum* [mostly]; skin contact with contaminated water	Ileitis, appendicitis [rarely], colitis [more frequent]	Immigrants, refugees, travellers, and military personnel from rural areas of tropical and subtropical regions; eosinophilia is common	Mucosal oedema and erythema; pseudopolyposis, small superficial ulcers, schistosomal nodules [similar to pseudomembranous colitis]; distal colon more affected	Viable and nonviable eggs; eosinophilic infiltration	Bowel strictures or inflammatory masses may develop	Microscopic stool evaluation; rectal or intestinal biopsy; serology
Cryptosporidiosis[21,319]	*Cryptosporidium parvum* and *Cryptosporidium hominis*; faecal-oral via ingestion of infected food or water; person-to-person transmission via sexual contact	Terminal ileitis, colitis [AIDS-defining disease]	Self-limited illness in most immunocompetent individuals but severe and protracted disease in immunocompromised individuals; close contact with infected animals	Endoscopy is typically normal; duodenal oedema, nodularity, loss of mucosal folds and submucosal vasculature	*Cryptosporidium* appears basophilic and occurs either alone or in clusters on the brush border of the mucosal surface in duodenum; *Cryptosporidium* identified within crypt epithelial cells in colon	Articular and ocular manifestations may remain after initial infection	Microscopic stool or tissue evaluation; PCR stool testing; stool antigen
Coccidioidomycosis[10,315]	*Coccidioides immitis* and *Coccidioides posdasii*; inhalation of spores	Enteritis, colitis [AIDS-defining disease]	Endemic in Southwest USA; immunosuppression and pregnancy are major risk factors for disseminated disease	Multiple small ulcers	Coccidoidal spherules on biopsies	Articular and cutaneous manifestations may be present in disseminated disease	Duodenal or colonic biopsies; stool cultures; serology
Chlamydial proctitis[14,21]	*Chlamydia trachomatis* serovars D–K; anal receptive intercourse; contiguous spread to rectum from the cervix or vagina	Proctitis	HIV-positive patients; MSM	Nonspecific findings, such as friable erythematous mucosa with ulcerations	Massive lymphoplasmacytic lamina propria extension; florid follicular hyperplasia	Articular and ocular manifestations may be present	Rectal swabs for NAAT [genotyping by PCR];

Table 1. Continued

Disease	Agent and route of transmission	Clinical manifestations	Clinical clues	Endoscopic findings	Pathological clues	Features overlapping IBD	Diagnostic methods
Lymphogranuloma venereum proctitis[14,17]	*Chlamydia trachomatis* serovars L1–L3 [mostly serovar L2]; anal receptive intercourse; contiguous spread to rectum from the cervix or vagina	Proctitis with systemic symptoms [fever, myalgias, arthralgias, anorexia, malaise and weight loss]; proctocolitis	Unilateral painful inguinal or femoral lymphadenopathy or buboes [fluctuant and suppurative lymph nodes] and 'groove sign'; HIV-positive patients; MSM	Mucosal hyperaemia, mucopurulent discharge, friability and multiple ulcers; longstanding disease can cause fistulae, strictures, and a mass lesion	Massive lymphoplasmacytic lamina propria extension; abnormalities limited to the rectum and sigmoid colon; mild architectural distortion; minimal basal plasmacytosis; florid follicular hyperplasia	Articular and ocular manifestations may occur; anorectal abscesses, strictures and perianal fistulae may be present	Rectal swab for NAAT [genotyping by PCR]; immunofluorescence;
Gonorrhoeal proctitis[14,21]	*Neisseria gonorrhoeae*; anal-receptive intercourse or contiguous spread to rectum from the cervix or urethra	Proctitis	HIV-positive patients; MSM	Most patients have only mild mucosal erythema and oedema, and thick mucopurulent discharge or no endoscopic changes	50% have normal biopsies	Articular manifestations may be present	Gram stain, rectal swab for NAAT, culture of rectal swab
Syphilitic proctitis[14,21,320]	*Treponema pallidum*; anal receptive intercourse and oro-anal contact	Proctitis [may occur without antecedent or concurrent anorectal chancre]	Chancres [ulcerating papules below or above dental line]; constitutional symptoms and maculopapular rash on palms and soles in secondary syphilis; MSM	Loss of vascular pattern, ulceration, polypoid growths, occasionally mass lesions	Massive lymphoplasmacytic lamina propria extension; abnormalities limited to the rectum and sigmoid colon; mild architectural distortion; minimal basal plasmacytosis	Upper GI tract may be affected; granulomas may be found	Dark field microscopy; RPR, VDRL [confirmation with FTA-ABS or TP-PA]
HSV proctitis[321,322]	HSV-2 [HSV-1 in a minority of patients]; anal receptive intercourse	Proctitis; may present with fever, body aches, and lymphadenopathy in primary infection	Immunocompromised MSM; more likely than other forms of infectious proctitis to cause constipation, severe anorectal pain, difficulty urinating, impotence, sacral paraesthesias; multiple perianal skin and anal canal vesicles may be seen; HIV infection is the strongest risk factor	Friable mucosa, diffuse distal ulcerations, vesicular lesions; a large solitary ulcer may be seen	Multinucleated giant cells or intranuclear HSV inclusion bodies	Urinary symptoms may resemble those present in patients with entero- or colovesical fistulae	NAAT, viral culture

AIDS, acquired immunodeficiency syndrome; FTA-ABS, fluorescent treponemal antibody absorption test; GI, gastrointestinal; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IBD, inflammatory bowel disease; MSM, men who have sex with men; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction; RPR, rapid plasma reagin; TP-PA, *Treponema pallidum* particle agglutination; UC, ulcerative colitis; VDRL, venereal disease research laboratory.

Table 2. Granulomas in the gastrointestinal tract: differential diagnosis.

Infectious causes
Bacterial infections
• *Mycobacterium tuberculosis*
• *Mycobacterium avium intracellulare* complex
• *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*
• Salmonellosis
• Actinomycosis
• *Chlamydia trachomatis*
• *Treponema pallidum*
Worms
• Schistosomiasis
• *Enterobius vermicularis*
Fungi
• Histoplasmosis
Non-infectious causes
Intestinal inflammatory diseases
• CD
• [UC]
• Sarcoidosis
• Diverticular colitis
• Diversion proctocolitis
Foreign material
• Bowel preparation
• Barium
• Talc
• Pneumatosis coli
Immune-related disorders
• Chronic granulomatous disease
• Common variable immune deficiency [CVID]
• Cord colitis syndrome
Vascular disorders
• Behçet's disease [rarely]
• Churg-Strauss syndrome
• Giant cell arteritis
• Takayasu arteritis
• Granulomatosis with polyangiitis [formerly Wegener's granulomatosis]
Inherited disorder
• Hermansky-Pudlak syndrome
Drugs
• Immune checkpoint inhibitors
• Diclofenac
• NSAIDs [rarely]
Reaction to neoplasia

CD, Crohn's disease; UC, ulcerative colitis; NSAID, non-steroidal anti-inflammatory drug.

in wealthier countries due to an increase in travel and migration. Patients are asymptomatic or develop diarrhoea that is eventually bloody or mucoid. Cramps and tenesmus may also occur. The disease may become fulminant.[50] The large intestine, and in particular the caecum, may be involved. Endoscopy [Figure 1A] may reveal small aphthoid ulcers, larger irregular or serpiginous ulcers, flask-shaped lesions, and inflammatory polyps.

Histologically, the period-acid Schiff [PAS]-positive trophozoites, characterised by round, eccentric nuclei surrounded by a foamy cytoplasm and distinct cell membranes, may be identifiable on the surface of ulcers in necrotic material [Figure 2B]. The surrounding mucosa has an appearance ranging from normal to acute colitis to very severe inflammation. There may be a mild mononuclear infiltrate with some architectural disturbance, mimicking IBD. Basal plasmacytosis is uncommon. Granulomas, neural hyperplasia, and diffuse or transmural inflammation with lymphoid aggregates, as in CD, are unusual.[44,51]

3.5. Infections: immune deficiency

In immunocompromised patients, infections are diverse and include *Mycobacterium avium intracellulare* complex, LGV [Figure 2C], syphilis, viral infections, and fungal infections.

M. avium intracellulare complex occurs in immunocompromised patients and rarely in the immunocompetent. It can involve any part of the GI tract, most often the small intestine. Endoscopy reveals a normal mucosa or numerous yellow-white nodules. In immunocompetent hosts, biopsies show well-delineated, eventually necrotic, epithelioid granulomas, but in immunodeficient hosts the lamina propria shows expansion by sheets of pale macrophages containing numerous PAS diastase or acid-fast microorganisms.[52–54]

Cytomegalovirus [CMV] affects the whole GI tract and has a wide range of macroscopic appearances, including normal, erosions, large ulcers with a punched-out appearance, or deeply infiltrating ulcers causing a cobblestone pattern similar to CD.[55] Histologically, the appearances range from a mild neutrophil infiltrate with crypt apoptosis and dropout to a chronic lymphoplasmacytic infiltrate with architectural disarray, cryptitis, and crypt abscesses that can simulate IBD. Additionally, CMV infection may complicate existing IBD in the setting of corticosteroid use. Intranuclear 'owl's eye' inclusions are characteristic, are visible on routine haematoxylin and eosin [H&E] staining, and are highlighted by immunohistochemistry.[56,57]

Histoplasma capsulatum is a yeast infection that can disseminate throughout the body in immunosuppressed patients. There is a high prevalence of GI involvement [70–90%]. Any level may be involved, but the most common sites are the ileum and large intestine. Macroscopically, there is a nodular mucosa with variably sized ulcers and, rarely, a mass. Microscopically, there is a diffuse lymphohistiocytic infiltrate with some neutrophils and eosinophils. Uncommonly, giant cells and epithelioid granulomas are present, as in CD. There is expansion of macrophages due to the presence of 2–5 µm PAS-positive yeast forms.[58,59]

4. Vascular disorders

4.1. Vascular disorders: vasculitis

Gastrointestinal involvement occurs in approximately one-third of primary systemic vasculitides. The most frequent causes are immunoglobulin A vasculitis [Henoch-Schönlein purpura], antineutrophil cytoplasmic autoantibody [ANCA]-associated vasculitis, polyarteritis nodosa [PAN], Takayasu arteritis, and Behçet's disease.[60–64] Secondary vasculitis associated with rheumatoid arthritis and systemic lupus erythematosus [SLE] can also occur.[65,66] Rarely, IBD co-occurs with systemic vasculitis.[67]

Current Practice Position 5

The constellation of clinical symptoms and signs and multisystem manifestations are important for differentiating between gastrointestinal involvement by vasculitis and IBD

The clinicopathological features of vasculitis with GI involvement are mostly non-specific.[68] Gastrointestinal symptoms depend partly on anatomical location and partly on the size of affected vessels.[69–71] Young age at onset, multi-segment involvement, mucosal ulceration, and extra-intestinal involvement can result in mimicry of IBD. GI symptoms resembling those of IBD include acute or chronic abdominal pain and diarrhoea and [less frequently] bleeding, often accompanied by fever and constitutional symptoms.

Table 3. Features favouring intestinal tuberculosis [ITB] or Crohn's disease [CD] in a setting without definitive findings [adapted from Limsrivilai et al.[27]].

	Favours ITB	Favours CD
Clinical manifestations	Short disease duration	Long disease duration
	Fever	Diarrhoea
	Night sweats	Haematochezia
	Lung involvement	Perianal disease
	Ascites	Extra-intestinal manifestations
Endoscopy	Transverse ulcers	Longitudinal ulcers
	Patulous ileocaecal valve	Aphthous ulcers
		Cobblestone appearance
		Stricture
		Mucosal bridge
		Skip lesions
		Rectal involvement
		Sigmoid involvement
Pathology	Confluent granulomas	Absence of granulomas
	Large granulomas	Granulomas, if present, are smaller, non-confluent, and fewer than in ITB
	Multiple granulomas per section	Patchy mucosal chronic inflammation
	Serosal tubercles	Transmural lymphoid aggregates along inner and outer border of muscularis propria
CT enterography	Short segmental involvement	Wall stratification
		Comb sign
		Fibrofatty proliferation
Serology	Positive interferon-γ release assay	

Endoscopic findings in vasculitis [Figure 1B and C] are also non-specific and include erosions of the small and large bowel, deep ulceration, petechiae, nodularity, oedema, submucosal haemorrhage, strictures and, when severe, features suggestive of ischaemia.[72] Mucosal biopsies may be non-diagnostic, because the affected vessels are often located in the submucosa or deeper layers.[72]

Detailed assessment usually elicits the constellation of symptoms and signs that suggest vasculitis and that may point to a particular type [Table 4]. New onset hypertension, limb claudication, and asymmetrical, diminished, or absent arterial pulses are frequent in Takayasu arteritis.[63,67,73] Skin lesions, hypertension, renal insufficiency, neurological dysfunction, and abdominal pain are common in PAN, which is particularly likely in the setting of hepatitis B virus infection. Palpable purpura, haematuria, and arthritis are highly suggestive of IgA vasculitis,[74] which may cause deep longitudinal ulcerations of the terminal ileum mimicking the ulcers of CD [Figure 1B].[74,75] The presence of ear, nose, and throat complaints [rhinosinusitis, oral ulcers, cough, dyspnoea, and alveolar haemorrhage] together with rapidly progressing renal involvement are common in patients with granulomatosis with polyangiitis [formerly Wegener's granulomatosis]. The combination of asthma, allergic rhinitis, and peripheral eosinophilia in older adults suggests eosinophilic granulomatosis with polyangiitis [Churg-Strauss syndrome].

Recurrent oral and genital ulceration raises clinical suspicion for Behçet's disease.[76–78] Behçet's disease presents in childhood in up to 20% of cases, and GI involvement appears to be more frequent in children than adults.[79] GI involvement can be difficult to distinguish from CD, partly because the ileocaecal region is often involved [Figure 1C]. The pattern and type of ulceration can differ from those of CD [Table 5].[80] Histological changes may also resemble UC or CD. Prominent mucosal architectural distortion might occur adjacent to an ulcer in Behçet's disease but is otherwise unusual and loss of crypts is not a feature [Figure 2D]. Granulomas and transmural lymphoid aggregates favour CD. Nevertheless, there are cases with genuine overlap where a distinction is extremely difficult to make.[1,81–84]

Current Practice Position 6

The ancillary techniques to approach the diagnosis of vascular disorders include imaging, particularly abdominal computed tomography [CT] and CT angiography. For the diagnosis of vasculitis, serological tests are very useful although not always specific

The ancillary techniques to approach the diagnosis of vasculitis include imaging and serological, faecal, and molecular tests. There is an IgA leukocytoclastic vasculitis in Henoch-Schönlein purpura.[85,86] Serological tests are widely used although not always specific. In ANCA-associated vasculitis and PAN, ANCA and surrogate markers assist the diagnosis of vasculitis according to Watts' algorithm.[87] Anti-*Saccharomyces cerevisiae* antibodies are demonstrable in >40% of patients with Behçet's disease. In lupus enteritis, both antiphospholipid antibody and hypocomplementaemia occur frequently,[88] together with the classical SLE serology.[89] Anti-endothelial cell antibody may also be demonstrable in intestinal vasculitis.[81] Faecal calprotectin can help to confirm intestinal involvement by a known vasculitis, even in asymptomatic patients.[90–92] Genetic susceptibility,[93–95] different microRNA expression,[96] and serum amyloid A[97] have been observed in intestinal Behçet's disease. Moreover, soluble triggering receptor expressed on myeloid cells-1 [sTREM] has been proposed as a marker of disease activity in Behçet's disease.[98]

On CT examination, diffuse bowel wall enhancement, bowel dilation, ascites, or bowel perforation can occur in a vascular disorder.[71,89] Angiography may show signs of vascular involvement with microaneurysms, stenosis [mainly in medium-sized vasculitis like PAN], or both.[71] Evidence for the value of magnetic resonance

[MR] enterography is limited.[99] Cross-sectional imaging may show areas of bowel wall thickening with the target sign and engorgement of mesenteric vessels with the comb sign. Video-capsule endoscopy may show small bowel lesions such as erosions, ulcers, or petechiae, but is seldom indicated.

4.2. Vascular disorders: ischaemia

Acute ischaemic enterocolitis most commonly results from non-occlusive ischaemia. It can be idiopathic or a result of hypotension or aortic surgery. Typically, it affects elderly patients [mean age approximately 70 years].[100] Most older patients have multiple comorbidities, such as systemic hypertension, diabetes, chronic kidney disease, atrial fibrillation, previous cardiac/aortic surgery, chronic medication use, or another cardiovascular disease.[101,102] In younger subjects, ischaemia is more frequently the result of drug abuse [e.g., cocaine, ergotamine, oestrogen] or of a vasculitis.[76,103–106]

Abdominal pain, rectal bleeding, and bloody diarrhoea are the most frequent symptoms of ischaemia, usually with sudden onset.[101] Fever and weight loss can occur. Chronic disease and, rarely, intestinal strictures can develop.[100] Mimicry of IBD may be a result of similar symptoms or of variable degrees of bowel damage.[107]

Endoscopic findings, in the appropriate clinical setting, are highly suggestive of ischaemia [Figure 1D] and include petechial haemorrhages, oedema, fragile mucosa, segmental erythema, scattered erosions, longitudinal ulcerations, and sharply defined segments of involvement.[108] The left colon is most frequently involved. Isolated right colonic ischaemia occurs less frequently and has a poorer prognosis.[101]

Current Practice Position 8

Haemosiderin accumulation, hyalinisation of the lamina propria, mild-to-moderate inflammation, glandular dropout, and microthrombi may be useful for the differentiation of ischaemia from IBD

Biopsies may support the diagnosis of ischaemia [Figure 2E]. Histological findings range from oedema with vascular congestion or haemorrhage to coagulative necrosis and loss of crypts. There may be micro- and atrophic crypts lined by small irregular cells with eosinophilic cytoplasm, a dark nucleus, and prominent nucleoli in a hyalinised stroma. In acute phases, there may be haemosiderin accumulation in the lamina propria, sometimes accompanied by mild or moderate inflammation and microthrombi. These features assist differentiation from IBD.[109–111] A sharp line of demarcation between the abnormal and normal mucosa may be appreciable.

Current Practice Position 7

Long-standing ischaemic conditions can produce strictures and scarring with exuberant fibrosis, often segmental and patchy, that can pose problems for differential diagnosis with Crohn's disease

Long-standing ischaemia can cause strictures and scarring with exuberant diffuse fibrosis. In resections, transmural lymphoid aggregates and, very occasionally, giant cells or granulomas can resemble CD. The changes are also often segmental and patchy, frequently involving caecum, splenic flexure, or rectum. There is sometimes a resemblance to UC. Ischaemic damage can involve the mucosal layer with ulceration, and there may be haemorrhagic enterocolitis, ischaemic non-gangrenous colitis, or massive gangrenous colitis mimicking toxic megacolon of IBD.

Together with CT[112] and CT angiography, novel ultrasound techniques can be useful for detecting risk factors and for monitoring ischaemic enterocolitis.[113,114] Serum markers, such as arterial blood gas lactate among others, may have clinical utility and assist diagnosis.[115–117]

5. Drugs

Current Practice Position 9

Drug-induced enterocolitis must be included in the differential diagnosis of new onset IBD. Drugs and chemicals could also be considered as potential triggers of IBD flares

5.1. Drugs: general considerations

Numerous drugs and chemicals can cause small bowel and colonic toxicity that may resemble IBD.[118–120] Possible mechanisms include ischaemia secondary to: direct vasoconstriction (e.g., cocaine,[104] ergotamine,[121] and non-steroidal anti-inflammatory drugs [NSAIDs][122]); extrinsic compression by fibrosis [e.g., methysergide][123]; volume depletion [e.g., diuretics][124]; mesenteric thrombosis [e.g., oestrogens][125]; severe hypomotility [e.g,. drugs with serotoninergic and anticholinergic activity, such as clozapine][126,127]; hypersensitivity [e.g., alpha-methyldopa[128] and gold salts][129]; dysbiosis [e.g., *Clostridioides difficile* colitis after antibiotic treatment][130]; direct cytotoxicity [e.g., 5-fluorouracil[131] or mycophenolate][132]; and immune activation (e.g., immune checkpoint inhibitors [ICI]). Some drugs [e.g., rituximab] can also cause exacerbation of pre-existing IBD or even facilitate the onset of *de novo* IBD.[133–135]

Endoscopic findings of drug-induced enterocolitis are largely non-specific and include erythema, oedema, erosions and, occasionally, ulcers. The entire colon is affected in up to 27%.[136] ICI-induced colitis can mimic UC or CD [see below].

Current Practice Position 10

Pathological features of drug-induced injury are not specific. Awareness of the main patterns should help pathologists to make the correct diagnosis or at least to suggest the possibility of a drug-induced colitis or enteritis

Drug-induced enteritis and colitis can show many histological patterns. There may be features of lymphocytic colitis, collagenous colitis, ischaemia, pseudomembranous colitis, eosinophilic colitis, or IBD. Appearances are often not specific, and clinical correlation remains necessary for diagnosis. Awareness of the main patterns should help the pathologist to make or suggest the correct diagnosis.[137–142]

5.2. Drugs: non-steroidal anti-inflammatory drugs

NSAID-related damage can occur in up to 70% of patients using NSAIDs, but serious complications are rare.[143,144] NSAID injury can resemble IBD. NSAIDs can exacerbate IBD and other diseases, such as diverticulosis.[145–147] Macroscopic features of NSAID-related damage[143,145]

Table 4. Features that may help in the differential diagnosis between primary systemic vasculitis and inflammatory bowel disease [IBD].

Clinical entity[70]	Type of vasculitis	Demographics	Gastrointestinal involvement	Common clinical manifestations and clinical clues	Most common GI complaints	Diagnostic Methods
Takayasu arteritis[63,67,73,323]	Large vessel granulomatous vasculitis	More common in Asian and African persons More common in women [70–90%]	Rare [16%]	Fever, malaise, weight loss, arthralgia, claudication, chest pain, headache. New onset hypertension, vascular findings [diminished or absent pulses, arterial bruits], elevated inflammatory markers, concomitant neurological and respiratory symptoms	Post-prandial abdominal pain. Diarrhoea	Clinical and angiographic criteria
Polyarteritis nodosa[71,324,325]	Necrotising arteritis of medium or small arteries [without glomerulonephritis or vasculitis in arterioles, capillaries or venules]	Peak diagnosis around 6th decade of life. More common in men	25–40% of patients	Systemic symptoms common, skin lesions [livedo reticularis, purpura, nodules, ischaemia, and gangrene in severe cases], new onset hypertension, renal insufficiency due to ischaemia but not glomerulonephritis, neuropathy, multisystemic involvement	Abdominal pain due to ischaemia ['abdominal angina'] [small bowel more affected than large bowel]. GI bleeding; higher risk of colonic perforation during endoscopy	Angiographic findings [microaneurysms in renal, mesenteric, or cerebral territories]. Not associated with ANCA. Underlying hepatitis B or C virus infection [secondary PAN]
IgA vasculitis [Henoch-Schönlein][74]	Small vessel vasculitis [perivascular IgA deposition]	Children or young adults	May occur in up to 50% of patients	Palpable purpura of the extremities and buttocks, arthritis, haematuria	Abdominal pain, diarrhoea, terminal ileum may be involved mimicking CD. Elevated FCal may indicate GI involvement	Clinical criteria, elevated serum IgA, leukocytoclastic vasculitis with IgA deposition on biopsies
ANCA-associated vasculitis[71]	Type of necrotising vasculitis, with few or no immune deposits, predominantly affecting small vessels. Includes microscopic polyangiitis [MPA], granulomatosis with polyangiitis [GPA, formerly Wegener's granulomatosis], eosinophilic granulomatosis with polyangiitis [EGPA, Churg-Strauss syndrome]	Older adults, around 40–60 years	MPA: 20–50% GPA: 1–10% EGPA: 40–60%	MPA: alveolar haemorrhage and rapidly progressive necrotising glomerulonephritis. CSS: asthma, hypereosinophilia, and frequent cardiac involvement. GPA: lower and upper respiratory [pulmonary infiltrate or cavitation, epistaxis, chronic sinusitis, mastoiditis, otitis] and renal involvement [glomerulonephritis]	Can range from mild transient abdominal pain to peritonitis, bowel infarction, or haemorrhage	Granulomatous inflammation on biopsy of an artery or perivascular area [microscopic polyangiitis]; ANCA specific for myeloperoxidase [MPO-ANCA] or proteinase 3 [PR3-ANCA]; p-ANCA found in MPA and EGPA and p-ANCA more frequent in GPA
Behçet's disease[77,78,326,327]	Variable vessel vasculitis [small vessel vasculitis, arteritis, arterial aneurysms, and venous and arterial thromboangiitis and thrombosis may occur]	Around 20–40 years. Both sexes can be affected	Depends on series [excluding oral lesions]: can range from 4–38%	Recurrent oral and/or genital aphthous ulcers accompanied by skin lesions [pseudofolliculitis or erythema nodosum, dermographism], arthritis, uveitis, thrombophlebitis, gastrointestinal or central nervous system involvement	Abdominal pain, nausea, vomiting, diarrhoea and gastrointestinal bleeding and ulceration. Most commonly affected is ileocaecal region, but any part of the GI tract can be affected	Clinical criteria. No pathognomonic test, positive pathergy test

GI, gastrointestinal; ANCA, antineutrophil cytoplasmic autoantibody; PAN, polyarteritis nodosa; FCal, faecal calprotectin, CSS, Churg-Strauss syndrome.

include erythema, erosions, haemorrhages, and well-demarcated ulcers. Changes often have a patchy distribution and most commonly affect the ileocaecal region [Figure 1E]. A discrete ulcer, with normal surrounding mucosa, should raise suspicion of NSAIDs or other drugs.[140,144,145] Strictures can be present in the distal ileum and right colon, with prestenotic luminal dilation. Diaphragm disease is a rare but distinct entity that mostly affects the jejunum and ileum, rarely involves the proximal colon,[143,148] and is highly suggestive of NSAID injury.

Table 5. Features discriminating between intestinal Behçet's disease and Crohn's disease [CD][80,327–329] [adapted from Skef *et al.*[84]]

	CD	Behçet's disease
Geographical location	Northern Europe and North America. Increasing incidence in developing areas	Most frequent around the Mediterranean basin and in the Orient [ancient silk road]
Blood tests	ASCA positivity [although not diagnostic]	HLA B5 and HLA B51 [in approximately 50%]
Extra-intestinal manifestations	Common: arthralgia and arthritis; erythema nodosum, oral aphthoid ulcers may also be present. Perianal disease frequent	Common: mucocutaneous ulcers [++ oral and genital], neurological involvement, papulopustular lesions, pseudofolliculitis, uveitis more common in Behçet's disease. Perianal disease rare
Endoscopic lesions	Irregular, longitudinal, or serpiginous ulcers with cobblestone appearance; segmental or diffuse involvement	Round shape, focal distribution, and absence of aphthous and cobblestone lesions
Radiology	Stenosis, fistula, and/or abscesses frequent	Stenosis, fistula, and/or abscesses rare
Histology	Transmural chronic inflammatory infiltrate in resections, granulomas may be present	Variable vessel vasculitis occasionally demonstrable. Granulomas very rare

ASCA, anti-*Saccharomyces cerevisiae* antibodies; HLA, human leukocyte antigen.

Current Practice Position 11

Diaphragm disease strongly suggests NSAID injury. There is no other macroscopic or microscopic feature that reliably favours NSAID-related enterocolitis over IBD

Microscopic features of NSAID injury[143,145] are diverse and may include an increase in numbers of intraepithelial lymphocytes, eosinophils, and crypt epithelial cell apoptoses. There may be mild crypt distortion, erosions, ulcers, fibrosis and, in the small bowel, pyloric gland metaplasia and villous atrophy.[149] Granulomas are very rare. Severe crypt architectural distortion, marked inflammation, basal plasmacytosis, and granulomas favour IBD or another cause. Classic transmural lymphoid aggregates strongly favour CD over NSAID injury.

5.3. Drugs: immune checkpoint inhibitors and inhibitors of phosphatidylinositol 3-kinase

Current Practice Position 12

The current gold standard for the diagnosis of immune checkpoint inhibitor [ICI] enterocolitis is endoscopy with biopsy. Investigation should include stool tests to exclude infections. Currently, no routine biomarker appears to be specific for immune checkpoint inhibitor-related enterocolitis

5.3.1. Immune checkpoint inhibitors: general considerations

Several monoclonal antibodies targeting immune checkpoint molecules are available for the treatment of advanced neoplasms.[150] These include ipilimumab (an anti-cytotoxic T lymphocyte-associated antigen 4 [CTLA-4] antibody), nivolumab and pembrolizumab (targeting programmed cell death 1 [PD-1]), and atezolizumab, durvalumab, and avelumab [anti-PD-ligand 1 antibodies]. These ICIs induce immune activation and robust anti-tumour T cell activity and can greatly improve survival. Phosphatidylinositol 3-kinase [PI3K] inhibitors share features with ICIs.

Immune-mediated adverse events, including an enterocolitis that can resemble IBD, are common following administration of ICIs and of PI3K inhibitors and may be severe.[151–159] The median time of onset is approximately 50 days after administration.[154] Colitides caused by different ICIs have some differences but are generally difficult to distinguish.[160–162] Diarrhoea occurs in one-third, and the incidence of ICI-associated enterocolitis, a serious complication that can be fatal,[155,157,163] ranges from 0.7–21%.[155,162,164,165] Severe diarrhoea and endoscopically proven colitis are more likely to be secondary to ipilimumab than to anti-PD-1 and anti-PD-L1 antibodies.[154,157,165,166] Other factors that increase the risk of enterocolitis are a combination of two ICIs, concurrent NSAID use, and melanoma [rather than another malignancy].[154,157,162,166]

ICIs may trigger a flare of quiescent IBD or lead to a first IBD presentation in patients with underlying genetic susceptibility.[161] Immune-mediated, drug-induced enterocolitis also includes paradoxical IBD that may occur in patients with spondyloarthropathies.[167–170]

5.3.2. Immune checkpoint inhibitors: macroscopic changes

Any part of the GI tract can be involved in ICI gastroenteritis. In lower GI tract disease, the inflammatory process usually affects the large bowel exclusively and the rectum is usually involved. There may be pancolitis [23% to >40%], left-sided colitis [31–43%], and less often ileitis [11–14%],[171–175] with both ileal and colonic involvement in <20%.[164,173,176,177] Macroscopically, the mucosa can show erythema, erosions, and ulcers. The distribution may be diffuse [one-half to two-thirds of patients] or patchy [one-third to one-half] [Figure 1F].[178] Endoscopic ulcers are present in up to a third and predict a poorer outcome.[163,173,176,177] Severe endoscopic abnormalities, pancolitis, and histological activity may predict a requirement for biologic treatment. Early endoscopic evaluation of ICI-associated diarrhoea is critical,[163] as mortality reaches 5%.[154] Full colonoscopy is recommended for the index procedure as the distribution is often discontinuous.[153]

ICI-related colitis often resembles IBD clinically and pathologically, especially when chronic or recurrent. Macroscopically, diffuse disease may resemble UC and discontinuous involvement may mimic CD. Distal distribution or pancolitis may suggest UC and ileitis might resemble CD.

5.3.3. Immune checkpoint inhibitors: histology

Microscopic features of ICI colitis are diverse and include mixed inflammation of the lamina propria [lymphocytes, plasma cells, and eosinophils], cryptitis, crypt abscesses, crypt destruction/rupture, and granulomas. Crypt architectural distortion, if present, is usually mild. Other changes include Paneth cell metaplasia, crypt atrophy/dropout, lymphocytic crypt injury, and apoptosis at the base of crypts, including apoptotic microabscesses.[171–173,175,179] Occasionally there is a microscopic colitis-like picture [Figure 2F–H].

There may be close histological resemblance to IBD. If anti-PD-1 colitis recurs [sometimes several months after cessation of therapy], there may be chronic features such as basal lymphoplasmacytosis, crypt architectural irregularity, and Paneth cell metaplasia. Apoptosis and lymphocyte-mediated epithelial damage at the base of crypts favour ICI colitis, whereas severe inflammation, severe crypt distortion, and basal plasmacytosis favour UC. However, there is overlap.[172,180]

Enterocolitis may also occur after PI3K inhibitor administration, typically resulting in intraepithelial lymphocytosis, epithelial cell apoptosis, cryptitis, and crypt abscesses.[181–183] Again, there may be close resemblance to IBD histologically.[172]

5.3.4. Immune checkpoint inhibitors: ancillary tests

A CT scan is a possible alternative for diagnosing enterocolitis secondary to CTLA-4 inhibition, with a sensitivity of 85.2%, specificity of 75.0%, positive predictive value of 95.8%, and negative predictive value of 42.9%.[184,185] In a 'real-life' heterogeneous population study, the performance of CT for diagnosis of ICI enterocolitis appeared moderate to poor.[185] However, CT remains important for excluding extraluminal complications, such as perforation and abscess formation.

The role of faecal calprotectin as a diagnostic marker in this setting remains unclear.[178,186] Serum antibodies against the enteric flora and perinuclear anti-neutrophil cytoplasmic antibodies that are frequent in IBD may occur in a minority of patients with anti-CTLA-4-induced enterocolitis.[186] A retrospective study suggested that faecal lactoferrin results may help inform prioritisation of endoscopy.[187,188]

No routine biomarker reliably predicts the development of ICI-related enterocolitis. One study identified a whole-blood mRNA signature [a 16-gene signature, including mainly interleukins and chemokine genes] that was predictive of diarrhoea and colitis in patients treated with tremelimumab.[189] Baseline microbiota composition may predict colitis induced by anti-CTLA-4.[190,191] Specifically, symbiotic gut microbiota with high proportions of Firmicutes, such as *Faecalibacterium prausnitzii* L2-6, butyrate-producing bacterium L2-21, and *Gemmiger formicilis* ATCC 27749, are associated with an enhanced anti-tumour response to ICI and with a higher risk of anti-CTLA-4 enterocolitis.[190] In contrast, Bacteroides are more highly represented in patients who remain colitis free.[191] In a phase 1 trial, there was a positive correlation between elevated baseline serum IL-17 levels and the risk of diarrhoea and severe colitis.[152,174,192]

5.4. Drugs: mycophenolate

There are two common preparations of mycophenolic acid: mycophenolate mofetil [MMF] and mycophenolate sodium.[193] Gastrointestinal side effects are less frequent in the latter.[194] Macroscopic features[195–199] of MMF colitis include diffuse or segmental erythema, erosions, and ulcers, typically with rectal sparing. Endoscopy may be normal. Mimicry of IBD occurs in 36–81.8%.[196,197]

Current Practice Position 13

The presence of dilated crypts filled with eosinophils or containing an increased number of apoptotic bodies favours mycophenolate mofetil-related colitis over IBD in the appropriate clinical setting

Histological features[197–201] include focal architectural changes, increased endocrine cells in shrunken crypts, dilated crypts containing eosinophils, and an increase in crypt epithelial cell apoptotic bodies.[197] The lamina propria usually appears empty but may contain a mixed inflammatory cell infiltrate. Architectural distortion can be present in both IBD and MMF-related colitis, but IBD typically has more intense inflammation [Figure 2I]. The number of crypt epithelial cell apoptoses is typically higher in MMF colitis than in IBD [usually more than 10 apoptotic cells/10 crypts] but there is overlap.[197] Granulomas and pyloric gland metaplasia are very uncommon in MMF colitis.[199,202]

6. Paediatric onset mimics of IBD

Current Practice Position 14

In paediatric patients with onset of IBD symptoms below 6 years of age, and especially below 2 years of age, a monogenic form of IBD and/or an underlying primary immune deficiency should be considered

Current Practice Position 15

In paediatric patients with onset of IBD symptoms above 6 years of age, in combination with aggressive, refractory, or atypical clinical presentations, specific comorbidities, or family history, a monogenic form of IBD and/or an underlying primary immune deficiency should be considered

Current Practice Position 17

Genetic testing should be considered in children with suspected monogenic disorders. However, routine genetic testing for all children with a new diagnosis of IBD is not recommended

About 10–15% of all IBD patients present before the age of 18 years.[203] Paediatric onset IBD has some distinct phenotypic differences in comparison with adult IBD. As in adults, the differential diagnosis of paediatric onset IBD includes infectious, drug-induced, and immunological causes. However, some infants and young children with IBD-type presentations have diseases associated with a single-gene variant [i.e., a monogenic IBD-like disorder].[204–208] It is important to identify these disorders, as these patients often have a higher morbidity than those with classical IBD and the management may differ, sometimes profoundly.[208,209]

Monogenic IBD-like disorders include primary immunodeficiencies and intestinal epithelial cell defects. The associated genes usually differ from the genetic variants found in genome-wide association studies of IBD and may be involved in intestinal epithelial barrier function, phagocyte bacterial killing, hyperimmune or autoimmune inflammatory disorders, and the function of the adaptive immune system.[210–212] Some primary immune deficiencies may present in older childhood and, rarely, in adulthood.

Interleukin-10 [IL-10] deficiency is probably the best-known cause of a monogenic IBD-like disorder and is a severe primary immune deficiency that presents at a very young age with extensive

perianal disease and severe enterocolitis. The cause is a loss-of-function mutation in either IL-10RA or IL-10RB, probably resulting in absence of negative-feedback signalling mediated by IL-10, which in turn perturbs homeostasis of the intestinal immune system.[213]

Chronic granulomatous disease [CGD] is a primary immune deficiency characterised by impaired phagocytosis by intestinal granulocytes and defective bacterial clearing. Neutrophils are deficient in neutrophil extracellular traps, autophagy, and apoptosis. Hyperactivation of NF-κB and the inflammasome in CGD phagocytes leads to long-lasting production of pro-inflammatory cytokines and inflammatory manifestations. CGD presents with a diverse clinical spectrum, ranging from subtle manifestations to severe infections to a monogenic IBD-like disorder. Non-specific diarrhoea is common. There is frequently a discrepancy between the paucity of symptoms and the severity of endoscopic changes [particularly extensive colonic involvement]. Life-threatening infections and hyperinflammation occasionally develop.[214]

XIAP deficiency is a rare primary immunodeficiency caused by mutations in the XIAP [BIRC4] gene. The estimated incidence is 1–2 cases per million live births.[215] Delays in diagnosis can have serious consequences. One patient with a long-standing incorrect diagnosis of IBD had multiple bowel resections.[216]

Current Practice Position 16

There are no pathognomonic histological characteristics that can differentiate IBD-like monogenic disorders from IBD in paediatric age groups. The correct diagnosis rests on the use of genetic studies. Some histological features may alert the pathologist to the possibility of monogenic disorders

Histology cannot differentiate IBD-like monogenic disorders reliably from classic IBD.[217] Indeed, there is much overlap. However, there may be features such as epithelial shedding, epithelial tufting [disorganisation and crowding of small groups of surface epithelial cells resulting in tufts of extruding epithelium],[218] and florid epithelial cell apoptosis that may alert the pathologist to the possibility of a monogenic disorder.[208,219] Defects of enterocyte differentiation and polarisation can cause congenital microvillous inclusion disease and congenital tufting enteropathy, in which histology may again suggest the correct diagnosis.

CGD may mimic CD histologically in up to 40%.[217] In contrast with typical CD, the changes frequently include multiple granulomas, sometimes necrotising, with or without active colitis, and mucosal accumulation of characteristic pale yellow/brown macrophages.[220]

If there is clinical suspicion of an underlying primary immune deficiency or a monogenic form of IBD, referral to a specialist centre for testing is appropriate. Recurrent severe or atypical infections may suggest primary immunodeficiency. A family member with a monogenic disorder, consanguinity, or multiple family members with early onset IBD may point to a monogenic IBD-like disorder.

The approach differs slightly between younger and older children. Those presenting with IBD before 6 years of age should be considered for testing for monogenic causes of their very early onset IBD [VEO-IBD].[221–223] Nevertheless, there remains a significant polygenic component to most cases of VEO-IBD,[224] with a monogenic cause in a minority.[225] In one centre, a monogenic cause was identified in 3% of those younger than 18 years of age.[204,223] In patients over 6 years of age, an underlying genetic condition should be considered in the appropriate setting and particularly if there is refractory disease, specific comorbidity, or a suspected family history.[208,219,226,227]

Next-generation sequencing techniques are an option, and whole-exome sequencing may be useful.[204,219,226,228] An important limitation of widespread genetic testing is availability, particularly of expertise to interpret the results.[229] Accordingly, it is advisable to limit such testing to specialist centres with adequate laboratory facilities and sufficient clinical, immunological, and genetic expertise.[207]

6.1. Autoimmune enteropathy

Current Practice Position 18

Autoimmune enteropathy is rare and can cause crypt-destructive enterocolitis. However, marked villous atrophy [in the small bowel], absence of goblet cells, absence of Paneth cells, and extensive basal crypt apoptosis may assist with its distinction from IBD

Autoimmune enteropathy [AIE] is a frequent cause of infantile intractable diarrhoea.[230] The entire GI tract is often involved, but the histopathological changes are most severe in the small bowel. There is much variation. Some cases, especially in older children or adults, show milder degrees of intestinal damage concomitant with crypt-destructive colitis and gastritis.[231] However, there is marked villous atrophy in the small bowel and absence of goblet and Paneth cells with extensive basal crypt apoptosis, which may help to differentiate AIE from IBD.

7. Radiation damage

Abdominal and pelvic radiotherapy may lead to acute and chronic intestinal injury. After conventional radiotherapy, 2–5% of patients develop chronic small bowel damage,[232] and the risk of chronic radiation coloproctitis reaches 30%.[233] Rectal and sigmoid involvement are the most common.[234] The latent period between treatment and development of chronic damage is often up to 24 months, but the disease may become evident and progressive many years later.[234,235]

Endoscopic findings of acute radiation injury include oedema, erythema, friability, and ulcers [Figure 1G].[236] Chronic radiation coloproctitis leads to mucosal atrophy and telangiectasia.[237] Strictures, perforation, and fistulae are less common.[238–240] Distal colorectal distribution and the presence of vascular changes may resemble IBD. Acute radiation colitis [hours to days] is less often a diagnostic challenge.[2]

Current Practice Position 19

The histological features that may help differentiate chronic radiation colitis from IBD, such as stromal and vascular changes, are less apparent in a biopsy than in a resection specimen

Current Practice Position 20

Basal plasmacytosis, a histological feature characteristic of IBD, is usually not present in radiation colitis or diversion colitis

Histological features of radiation colitis that are shared with IBD include crypt distortion, Paneth cell metaplasia [rarely], and chronic inflammation [Figure 2J]. Features favouring radiation damage are fibrosis, stromal hyalinisation, vascular ectasia, and vascular myo-intimal hyperplasia. Basal plasmacytosis favours IBD but can sometimes occur in radiation colitis. Differentiation in a mucosal biopsy may be challenging. In the submucosa, fibroblasts may show cytonuclear atypia and the vascular changes are usually more marked than in the mucosa. Therefore, diagnostic clues are often more easy to detect in a resection than in a biopsy. Clinical history is important.

Current Practice Position 21

In the appropriate clinical setting, CT and MR enterography may support a diagnosis of radiation damage and its potential complications

Imaging techniques, such as MR enterography, in patients with radiation damage can show mural thickening and stenosis and also bowel angulation due to adhesions and retraction of the mesentery.[241,242] Videocapsule can be useful,[243–245] particularly when stenosis and sub-obstructive symptoms are not present. Multi-slice spiral CT can show mural thickening, fibrotic changes, or other complications.[246,247]

8. Diversion proctocolitis

Diversion proctocolitis [DPC] occurs during the first year after surgery in the defunctioned segment of large bowel after its exclusion from the faecal stream [e.g., after ileostomy or colostomy]. DPC can occur in any disease setting, including IBD, diverticular disease, motility disorders, or colon cancer, and seems to subside after restoration of intestinal continuity.[248,249] Endoscopic and histological inflammation occur in up to 55% and 72% of diverted segments, respectively,[250] and the disease is often subclinical.[251]

Endoscopy in DPC shows non-specific inflammatory changes, mucosal exudates, nodularity, and aphthoid ulcers [Figure 1H].[252–254] In patients without pre-existing IBD, the proximal 'in-continuity' colon shows no signs of inflammation.[254] Regardless of the underlying reason for diversion, the appearances can mimic new IBD. Usually, the clinical setting allows diagnosis. Diagnosis of IBD in the diverted colon in patients without a previous IBD diagnosis is not advisable.

Common histological features of DPC are crypt distortion, a mucosal lymphoplasmacytic infiltrate, cryptitis, and ulceration. These can also occur in IBD.[255] Cryptolytic or suture-associated granulomas may be present. Non-cryptolytic granulomas rarely occur. Prominent mucosal and submucosal lymphoid hyperplasia with germinal centres are characteristic but not specific [Figure 2K].

9. Diverticular colitis/segmental colitis associated with diverticulosis

Diverticular colitis, or segmental colitis associated with diverticulosis [SCAD], refers to inflammation that is usually between or close to diverticula. Diverticular colitis affects around 1.2% of patients with diverticular disease and is most frequent in the elderly.[3,256,257] Symptoms include abdominal pain, tenesmus, haematochezia, and diarrhoea.[257–259] Endoscopic patterns range from mild to severe inflammation and include reddish round lesions, loss of the submucosal vascular pattern, oedema, erosions, and [when severe] ulceration [Figure 1I].[260,261] The typical location of inflammation in the inter-diverticular mucosa, without involving the diverticular orifices and with rectal sparing, should prompt the diagnosis.

Current Practice Position 22

Diverticular colitis is difficult to distinguish from IBD on the basis of histology

The histology of diverticular colitis is sometimes similar to that of IBD [Figure 2L].[262] Examination and biopsy of the rectum separately from the colon will assist differentiation from UC. An IBD history, or evidence of IBD elsewhere in the GI tract, is necessary before making a diagnosis of IBD in this setting.[263,264] In resection specimens, diverticular disease may cause fistulae, granulomas, and transmural inflammation and mimicry of CD. However, the inter-relationship between diverticular disease and IBD may be complex.[265]

10. Hidradenitis suppurativa

Current Practice Position 23

Perianal Crohn's disease and hidradenitis suppurativa share several clinical features. The presence of abscesses at other sites, a severe disease at onset, and sinus tracts/fistulae not communicating with the bowel are suggestive of hidradenitis suppurativa

Hidradenitis suppurativa [HS] is a chronic inflammatory skin disease caused by follicular occlusion and secondary infection in areas rich in apocrine sweat glands, such as the axillae and genital area. HS occurs more frequently in patients with CD than in controls.[266] In severe cases, HS can manifest with subcutaneous nodules, recurrent abscess formation, fistulae, and sinus tracts,[267,268] which can make differentiation from perianal CD challenging. Furthermore, histological features of HS include suppuration and granulomatous inflammation that again can cause confusion with CD. Pelvic magnetic resonance imaging [MRI] may help to differentiate between the two entities.[269] The presence of abscesses at other sites, such as the groin and axillae, and severe disease at onset rather than a gradual worsening, are suggestive of HS. Furthermore, fistulas in HS rarely extend to the anal canal and are generally simple, whereas those of CD are often complex.

11. Other pathological mimics of IBD

Other entities that can mimic IBD histologically include microscopic colitis,[270] sarcoidosis, inflammatory 'cap' polyposis,[271] idiopathic myo-intimal hyperplasia of mesenteric veins,[272] mucosal prolapse,[2] endometriosis,[273,274] a mass lesion,[275] and neoplasia.[276–278] Common variable immune deficiency [CVID] is a potential clinical and pathological mimic, but careful histological examination of mucosal biopsies will usually lead to the correct diagnosis, as plasma cells are absent or very sparse.

12. Ancilllary investigations: further roles

Current Practice Position 24

Serological and faecal biomarkers are useful for determining disease activity, predicting risk of relapse, and potentially predicting therapy response in IBD patients, but are not helpful for differential diagnosis

Additional tests may help differentiate IBD from other causes of inflammation. The choice of investigations depends heavily on the clinical setting. Standard blood inflammatory markers, C-reactive protein and faecal biomarker, and faecal calprotectin are not specific for differentiating between IBD and other causes of colitis.[279]

Current Practice Position 25

The diagnostic utility of -omics technologies in IBD is still in a very early phase of validation, and the applicability of these technologies in routine practice is currently uncertain

'Omics' technologies involve objective identification of gene products, including genes [genomics], mRNA [transcriptomics], proteins [proteomics], and metabolites [metabolomics] in a biological sample. An integrated approach to 'omics' has improved the understanding of complex physiological and pathological disease processes, including IBD aetiopathogenesis.[280–283] 'Omics' also has the potential to introduce novel biomarkers that could influence diagnosis and management.[284,285] There may be differences between IBD and non-IBD individuals, e.g. the enteric virome in CD and UC patients was different from that of healthy individuals in one study.[286] Faecal gut microbiome data also have the potential to distinguish between IBD and non-IBD and between CD and UC.[287] However, there is often considerable overlap. Furthermore, the gut microbiome and virome can vary with diet and geography. Häsler *et al.* studied the transition of intestinal homeostasis to dysbiosis by integrating multiple levels of data, namely the mucosal transcriptomic post-transcriptional alterations and the mucosal microbiome of patients with UC and CD in comparison with healthy individuals.[288] Wasinger *et al.* reported a panel of protein markers that were progressed into the 'validation' stage. Phosphoprotein 24 [SPP24] and α-1 microglobulin could differentiate between IBD patients and healthy controls, and guanylin and secretogranin-1 differentiated between UC and CD.[289] These technologies are at an early stage of evaluation and need further standardisation and validation.[280]

13. Conclusion

Current Practice Position 26

Reliable distinction between IBD and its mimics requires constant awareness by clinicians and pathologists of the wide range of differential diagnoses of IBD. Close communication between clinicians and pathologists is essential

Current Practice Position 27

Mimics of IBD include infection, diverticular colitis, diversion proctocolitis, vascular disorders, drug-induced injury, and immune disorders

Current Practice Position 28

Distinction between IBD and its mimics requires comprehensive clinical assessment, including a full history with duration of symptoms. Investigations may include routine blood tests, endoscopic examination, histopathology, microbiological tests, serology, imaging, and faecal and serum biomarkers

This review highlights the wide range of differential diagnoses of IBD. Infection and drugs are among the more common considerations.[6] Most of the common symptoms of new IBD can also occur in other diseases.[4,5] Existing and past medical history is always important. Sometimes the patient is not even aware of these details, such as unknown HIV positivity or radiotherapy several decades earlier.[49]

Endoscopic examination is often crucial for accurate diagnosis and is a standard investigation for IBD. Several conditions [e.g., ICI colitis, LGV/syphilitic proctitis, and Behçet's disease] can have endoscopic appearances similar to those of IBD.[46,49,82,290,291]

In colorectal biopsies, histological features supporting IBD include basal plasmacytosis, architectural changes, and granulomas.[2,5,292–298] A combination of changes is more informative than a single feature. Histologically, some enterocolitides resemble IBD particularly closely, such as diverticular colitis, diversion proctocolitis, LGV/syphilis, other chronic infections,[46,49] and ICI-induced colitis.[172,180] TB, yersiniosis, and Behçet's disease can resemble the ileocolitis of CD. Many other entities share some histological features with IBD [Table 6]. Accurate interpretation often requires full clinicopathological correlation, and submission of the endoscopy report with the sample may assist interpretation. Documentation of whether the patient has suspected new IBD or treated IBD is especially important.[299,300]

In resections, the diagnosis of IBD is usually already apparent before pathological assessment. However, there are exceptions. Severe acute or fulminant colitis without a pre-existing history of intestinal disease is most often secondary to IBD but can have other causes.[301–303] In resections and on imaging, diverticular disease may resemble CD.

Awareness of the mimics of IBD is important for many reasons, partly because of profoundly different responses to treatment in some settings. For example, treatment of an infection with immunosuppressive IBD-type therapy may cause clinical deterioration, and many other IBD mimics do not respond to IBD medications or may respond temporarily [e.g., CVID].[304–307]

Paediatric IBD shares many features with adult IBD. There are several disorders in children, including monogenic IBD-like illnesses, that resemble IBD.[208] Few clinical or histological features can make the distinction reliably. Additional genetic tests and newer tests are often necessary.

Ancillary investigative techniques [e.g., stool tests, imaging, and serological markers] may be helpful. Faecal calprotectin assists with

Table 6. Summary of selected pathological mimics of inflammatory bowel disease [IBD].

Mimic	Risk of clinical mimicry	Risk of histological mimicry	IBD-like features	Findings supporting correct diagnosis	References
Diverticular disease	+	+++	Histological features of diverticular colitis can resemble IBD, including crypt distortion. Resections can show CD-like changes	Presence of diverticula. Older patient with sigmoid colon disease only	3,265,330–333
Diversion proctocolitis	+	+++	Often superimposed on pre-existing IBD. Appearances often resemble IBD on histology. Diffuse chronic inflammation	Clinical history of surgery	255,334–337
Tuberculosis	+++	++	Ileocaecal disease. Granulomas, usually non-necrotising and usually lacking demonstrable acid-fast bacilli when in GI tract. Can mimic CD clinically	Tuberculous granulomas more likely to be numerous, large [>400 μm], confluent. See Table 2	48,338,339
Yersinia	++	++	Can mimic CD clinically, granulomas, ileocaecal	Yersinia may show central necrosis of granulomas and perigranulomatous lymphoid cuff histologically	48,338
LGV/syphilis	++	+++	Can mimic CD or UC. Most often involve rectum	Less likely than IBD to have basal plasmacytosis, crypt distortion, Paneth cell metaplasia histologically. Absent or mild neutrophil activity. Mucosal eosinophils rare compared with IBD. Prominent submucosal plasma cells and endothelial swelling. Clinical history: typically HIV-positive and MSM	49,340–342
Amoebic colitis	+++	+++	Clinical features may closely resemble UC or CD. May have crypt distortion and basal plasmacytosis	Trophozoites useful if present, but sometimes absent	48
Mass lesion	+/-	+	Occasionally IBD-like histology in a biopsy	Mild histological changes. Granulomas uncommon. Imaging/endoscopic information essential	275
Radiation colitis [chronic]	+	++	Crypt changes and mucin depletion can occur	Basal plasma cells uncommon. Clinical history essential	3,343–345
Ischaemic colitis [chronic]	+	+/-	Crypt atrophy and distortion can occur	Fibrosis, hyalinisation, withering of crypts. No basal plasma cells. Endoscopy, imaging	3,343–345
Mucosal prolapse	++	+	Solitary rectal ulcer may suggest rectal UC. Crypt distortion may mimic IBD	Angulation of crypts, vertical smooth muscle fibres, fibrosis. Clinical setting	
Common variable immune deficiency [CVID]	+	++	Crypt distortion, mucin depletion and lamina propria hypercellularity can occur	Absence or depletion of plasma cells usual. Almost never shows basal plasmacytosis. Clinical history important but may not be known	305
Autoimmune enteropathy	+	+	May resemble IBD histologically	Crypt changes and basal plasmacytosis rare. Epithelial cell apoptoses may be increased. Clinical setting [intractable diarrhoea in a child]. Multiple GI sites	346–348
Monogenic IBD-like disorders	+++	+++	Very similar to IBD, with clinical and histological overlap	Genetic tests necessary to distinguish	208
Drugs, immune checkpoint inhibitors	+++	+++	Can closely resemble IBD macroscopically and histologically, especially if chronic or recurrent	Variable histology. Clinical history necessary	172,180
Drugs, NSAIDs	+/-	+/-	IBD-like changes rare	Clinical history	
Drugs, mycophenolate mofetil	+/-	+	May cause crypt distortion, crypt atrophy, chronic inflammation, crypt abscesses. and cryptitis	Crypt architectural changes usually mild. Crypts may be dilated. Eosinophils may be numerous. Empty lamina propria is typical. No basal plasmacytosis	
Behçet's disease	+++	+++	Ileocaecal disease with ulcers. Occasional CD-like picture. Crypt distortion adjacent to ulcers	No basal plasmacytosis or granulomas. Crypt loss rare. Little or no mucin depletion. Vasculitis occasionally apparent on histology. Additional tests	349
Sarcoidosis	+	++	Granulomas	Rarely affects GI tract. Architectural changes and basal plasmacytosis of IBD are rare. Clinical picture; other organs involved. Tests, e.g,. imaging, serology	

CD, Crohn's disease; UC, ulcerative colitis; GI, gastrointestinal; MSM, men who have sex with men; NSAID, non-steroidal anti-inflammatory drug; LGV, lymphogranuloma venereum.

monitoring the development of active inflammation in IBD. Its role in the assessment of ICI colitis is still unclear.[308] The established panel of techniques has recently been enriched with high-throughput molecular techniques, including next-generation sequencing and exome sequencing, which are of particular interest for recently individualised entities such as monogenic IBD-like disorders in young children. Molecular tests, including differential gene expression and proteomic profiles, have also been proposed in infections and notably in ITB.

An important factor affecting the accuracy of distinction between IBD and its mimics is constant awareness by clinical teams and pathologists of the possibility of alternative disorders. If a clinical, histological, or other feature is not typical of IBD, caution is appropriate before making a diagnosis of IBD.

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