Differential Diagnosis of Inflammatory Bowel Disease

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A diagnosis of inflammatory bowel disease (IBD) is usually suspected in patients with chronic digestive symptoms, especially diarrhea (with or without blood in the stools), abdominal pain, and poor weight gain. Numerous other diseases can have similar symptoms. For some of them, laboratory investigations, endoscopic and even histological features may be difficult to distinguish from those of ulcerative colitis (UC) or Crohn disease (CD).

In the short term, the most important challenge is to rule out an infectious disease. In the long term, the differential diagnosis with other chronic diseases, such as eosinophilic gastroenteropathy, vasculitis, lymphoma, or immunodeficiency syndromes, may cause some diagnostic difficulties.

In some cases, the possibility of IBD, mostly CD, is considered in a child presenting with abdominal mass, isolated esophagogastroduodenal, or perineal involvement.

Acute Onset Diarrhea

In 10 to 20% of adults with IBD, patients present with apparently transient diarrhea, abdominal cramps, and low-grade fever [1]. In this acute onset disease, the diagnoses to be considered are mostly intestinal infection, food allergy, and acute appendicitis.

Intestinal Infection

In the case of acute diarrhea, patients are thought to have *viral gastroenteritis* particularly if they appear to recover promptly. However, prolonged diarrhea, right lower quadrant tenderness, or a slow recovery should alert the physician to the possibility of early IBD. A *bacterial or parasitic infection* of the intestine can also be responsible for prolonged symptoms. Stool sample should, therefore, be collected for culture and toxin assays that can identify one of the numerous pathogens responsible for intestinal infection (Table 17.1). In the last years, development of multiplex gastrointestinal pathogen panel tests allows to simultaneously

Table 17.1 Laboratory tests used to detect enteropathogens

Laboratory test	Organism suggested or identified
Microscopic stool examination	
• Fecal leukocytes	Invasive or cytotoxin-producing bacteria
• Trophozoites, cysts, oocysts, or spores	*Giardia lamblia*, *Entameoba histolytica*, *Schistosoma mansoni*
• Spiral or S-shaped gram-negative bacilli	*Campylobacter*
Stool culture	
• Standard	*Escherichia coli*, *Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*
• Specific selective medium	*Clostridium difficile*, *E coli O157:H7*
(to be specified to the laboratory)	*Aeromonas*, *Plesiomonas shigelloïdes*, *Klebsiella oxytoca*, *Vibrio parahemolyticus*
Stool cytotoxicity assay	*Clostridium difficile* (A or B toxin)
Stool Multiplex gastrointestinal pathogen panel tests (PCR)	*Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*, *E coli*, *Klebsiella oxytoca*, *Clostridium difficile*
	Adenovirus, *Astrovirus*, *Norovirus*, *Rotavirus*, *Sapovirus*
	Cryptosporidium, *Cyclospora*, *Entameoba histolytica*, *Giardia lamblia*
Culture of colonic biopsy sample	*Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*, *Klebsiella oxytoca*, *E coli O157:H7*
PCR on colonic biopsy sample	*Mycobacterium tuberculosis*, *Yersinia Adenovirus*, *Cytomegalovirus*
Circulating antibodies	*Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*, *Entameoba histolytica*

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identify common bacterial, viral and parasitic pathogens using molecular testing, with 100% sensitivity and 100% negative predictive value [2]. However, these tests also generate considerable additional positive results of uncertain clinical importance [3]. According to the age of the patient, the severity of symptoms and the type of bacteria, an appropriate antibiotic treatment may then be initiated. When no pathogen is present in the stools, imaging such as an abdominal ultrasound is usually performed. It can show enlarged mesenteric lymph nodes and thickening of the colonic and/or ileal wall, but these findings can be seen in infectious diseases as well as in IBD. In this setting, colonoscopy is useful, enabling the visualization of colonic lesions and collection of biopsy samples for histology and culture. The endoscopist should describe the lesions precisely without directly stating a final diagnosis of IBD. Besides *Clostridium difficile,* which is responsible for the typical pseudomembranous colitis, infection with numerous bacteria or parasites may lead to colonic lesions that can be very similar to those of UC or CD [4] (Table 17.2). Moreover, bacterial overgrowth or intestinal infection is part of initial manifestations in 10–20% cases of IBD. When symptoms are severe, it may be justified to propose a short-course empiric treatment with broad-spectrum antibiotics active against enteric pathogens (e.g., ceftriaxone or ciprofloxacin—usually after 15 years of age, and metronidazole).

If laboratory tests and evolution of symptoms do not confirm the hypothesis of infection, the diagnosis can be changed to IBD based on histological findings. Acute inflammatory changes of cryptitis, and crypt abscesses with neutrophilic infiltration, are not specific and are seen in both entities. The more discriminatory findings in favor of a first manifestation of IBD are the presence of glandular bifurcations and distortions, an infiltration of the mucosa with plasmocytes, and the presence of granulomata [5, 6]. However, these findings are rarely seen when endoscopy is performed at an early stage, and acute episodes of colitis may remain initially unclassified. Half of these patients will relapse in the following 3 years, leading to a diagnosis of IBD, usually UC [7]. When the diagnosis is uncertain, one should avoid starting long-lasting anti-inflammatory/immunosuppressive treatment and be cautious when giving information to the family.

Table 17.2 Main infectious agents responsible for IBD-like lesions during endoscopy

Microorganism	Possible Ileal involvement	Crohn-like aspect	UC-like aspect
Aeromonas	N	+	++
Campylobacter	Y	++	+
Clostridium difficile	N	+	+
Eschericchia coli	N	+	+
Klebsiella oxytoca	N	+	+
Mycobacterium tuberculosis	Y	+++	+
Plesiomonas shigelloides	N	+	+++
Salmonella enteritidis	Y	+	++
Shigella dysenteriae	Y	+	+++
Vibrio parahemolyticus	N	+	+
Yersinia enterocolitica	Y	+++	+
Entamoeba histolytica	N	+	+++
Cytomegalovirus	Y	+	+++

N = no; Y = yes

Food Allergy

Food proteins, usually milk or soy, may produce an allergic colitis which is typically encountered in infants under the age of 2 with a family history of atopy [8–10]. Rectosigmoidoscopy usually shows mucosal erythema and nodularity [11], but lesions may include aphthous ulcerations that mimic CD. The diagnosis of allergy is suspected if an eosinophilic infiltration of the mucosa is present on histology [12]. Allergy skin tests using a panel of the main allergens responsible for food allergy in children can be used to direct the exclusion of the offending protein. A rapid disappearance of symptoms will then confirm the diagnosis [12].

Acute Appendicitis

Acute appendicitis may cause some diarrhea, associated with the classic right lower quadrant pain and tenderness. If clinically warranted, then this diagnosis may be confirmed by ultrasound examination and/or computed tomography of the abdomen. In some rare cases, CD is discovered because of ileal involvement during operation [13, 14] or at the histological examination of the appendix [15, 16]. One should be aware of the possibility of CD in cases of ileitis associated to appendicitis because appendicectomy may lead to complications such as fistula, abscess, and peritonitis.

Chronic or Recurrent Intestinal Symptoms

Chronic or recurrent intestinal symptoms represent the most frequent presentation of IBD in the pediatric population and include symptoms such as abdominal pain and diarrhea lasting up to several months or years, especially in CD. This long delay until the diagnosis may be explained by the frequency in the general population of these non-specific symptoms, as up to 10% of children between 7 and 11 years old seek medical attention for recurrent abdominal pain [17]. A

periumbilical location of pain is typical in functional abdominal pain, but it is also present in most children with IBD. In patients with uncomplicated abdominal pain, constipation, lactose intolerance, peptic disease, food allergy, pathology of the urinary tract, or psychosocial causes should be considered and eliminated. The presence of fever, anorexia, weight loss or growth disturbance, perineal involvement, or blood in the stools suggests the possibility of IBD. This suspicion should be strengthened by laboratory investigations showing anemia and increased inflammatory markers (C-reactive protein, erythrocyte sedimentation rate), ultrasound examination of the abdomen showing a thickening of the intestinal wall, and/or elevated fecal calprotectin [18]. However, these features are not specific to IBD and further investigations are useful to eliminate other diseases (Table 17.3).

Intestinal Infection

Even in case of chronic digestive manifestations, an infectious etiology remains the most frequent differential diagnosis to be considered [4, 19]. It is, therefore, important to collect stools for bacterial and parasitic pathogens at the initial evaluation of a patient with suspected IBD. Contrary to acute presentation, an anti-microbial treatment is generally not considered until laboratory tests have confirmed a specific infectious disease. Depending on the pathogen, the part of the gut involved and the symptoms may vary, leading to consideration of either CD or UC (Table 17.2).

Table 17.3 Useful investigations for differential diagnosis of IBD in children with chronic diarrhea

Blood	Polynuclear count and morphologic features
	Lymphocyte count
	FACS enumeration of T and B lymphocytes
	Serum electrophoresis
	IgG, A, M
	Total haemolytic complement
	C_3, C_4 concentrations
	Anti-Neutrophil Cytoplasm antibody
	Anti-Saccharomyces Cervisea antibody
	Anti-Transglutaminase antibody
	Specific IgE against food allergens
	Anti-bacteria antibody (*Shigella*, *Salmonella*, *Campylobacter, Yersinia, Entameoba histolytica)*
Stools	Fecal leukocytes
	Microscopic examination
	Standard and specific medium culture
	Clostridium difficile cytotoxin assay
Skin tests for	Tuberculosis
	Food allergens
Imaging of the abdomen	US examination
	CT-scan or MRI
Endoscopy	Oesogastroduodenoscopy
	Biopsy for histology
	Ileo-colonoscopy
	Biopsy for histology, bacterial culture, PCR

Infection with *Yersinia enterocolitica* is usually associated with a mild illness in children [20] but subacute and chronic ileitis or ileocolitis has been reported [20, 21] and may resemble CD [22]. This can also be associated with erythema nodosum and polyarthritis. Endoscopic features include aphthoid lesions of the cecum and ileum with round or oval elevations with ulcerations. Ulcers are mostly uniform in size and shape, in contrast to CD [23]. Histological findings of Yersinia infection are not pathognomonic and usually are only indicative of acute and/or chronic inflammation. US examination or MRI show mucosal thickening and nodular pattern of the terminal ileum and colon that can mimic CD, but also enlarged mesenteric lymph nodes [24]. In contrast to CD, fistula formation and fibrotic stenosis are not observed. Stool or biopsy sample cultures may require a specific enrichment medium, are time consuming and not always positive. Identification and characterization of pathogenic Yersinia enterocolitica isolates by PCR in stools or in paraffin-embedded tissue block [25]. The diagnosis can also be made with the identification of serum antibodies (Western blot) against Yersinia outer protein antigens (YOP antigens), the concurrent presence of both IgG and IgA antibodies indicating an ongoing infection [26]. Infection with enteropathogenic and enteroaggregative *Escherichia coli* (EPEC, EAEC) may be responsible for chronic diarrhea in children, especially when they live or travel in developing countries [27, 28].

Infection with *Clostridium difficile* leads to digestive disease ranging from self-limited diarrheal syndrome, to severe pseudomembranous colitis [29]. Sometimes, sustained symptoms lead to consideration of the possibility of IBD. *Clostridium difficile* infection must be sought in children receiving antibiotics, especially beta-lactams, although it may occur without prior antibiotic therapy. Rectosigmoidoscopy, performed with care and minimal insufflation, reveals the presence of typical yellow-white pseudomembranes in approximately one third of patients [29] and infection is confirmed by the presence of the toxin A or B in stool or by polymerase chain reaction. Nevertheless, *Clostridium difficile* infection can occasionally occur in patients with UC or CD, even without the use of antibiotics, and stool toxin positivity has been reported in 5 to 25% of IBD patients with relapse, mostly after antibiotic exposure [30, 31]. Reductions in gut microbial diversity as well as an increase in pro-inflammatory species have been identified in IBD patients, a dysbiosis that may play a role in increasing *Clostridum difficile* infection risk in IBD patients. Due to an overlap in symptomatology, diagnosis and treatment of *Clostridum difficile* infection are also challenging in the IBD population, and it is recommended that stool assay for

Clostridium difficile is obtained in children with IBD during acute relapses [32, 33].

Giardia intestinalis infection can be associated with chronic diarrhea, abdominal pain, and weight loss [34] which may occasionally lead one to consider the possibility of IBD. Giardia is found in most countries in the world, the prevalence being highest in developing countries. Trophozoites or cysts of *Giardia intestinalis* can be found in fresh stool specimens, or rectal biopsies. In some cases, it may be necessary to examine duodenal aspirations or biopsies. Jejunal morphology may be normal, although partial or even total villous atrophy has been reported [35, 36]. Failure to eradicate giardiasis can be due to hypogammaglobinemia or deficit in secretory IgA.

Entamoeba histolytica infection occurs mostly in developing countries. Infection may be asymptomatic or lead to a dysenteric syndrome. Demonstration of *Entamoeba histolytica* trophozoites and cysts in stools remains the mainstay of diagnosis. Chronic amoebic colitis could lead to clinical, radiologic, and endoscopic findings that can be indistinguishable from those of IBD [37, 38]. However, this differentiation is important because amoebiasis can become fulminant if the patient is treated with immunosuppressive agents for a presumed IBD [39]. In these chronic manifestations, the parasite can be difficult to find in stools samples or in rectal biopsies, even using a concentration technique. The presence of high titers of antibodies in the serum may then be helpful in the diagnosis of chronic amoebiasis.

Intestinal tuberculosis accounts for 2% of tuberculosis worldwide and remains a challenging diagnosis in developing countries, because treatments used for CD may adversely affect tuberculosis [40]. Intestinal tuberculosis can affect any part of the intestine but more frequently involves the ileocecal region, isolated colonic location being present in only 10–25% of cases. Symptoms can be very similar to those of CD; these include diarrhea, abdominal pain, fever, weight loss, abdominal mass of the right iliac fossa, and even suppurative perineal lesions. The presence of intramural swelling, mesenteric thickness, stricture or fistula on US examination, or MRI can be encountered in both diseases [41], although the absence or minimal asymmetric thickening of colonic wall and the presence of enlarged necrotic lymph nodes favor the diagnosis of tuberculosis [41–44]. Nodules, ulcers, and strictures can be seen at ileocolonoscopy, or possibly at enteroscopy in the case of isolated jejunal lesions [45–47], but these lesions can be indistinguishable from those of CD. Usually, intestinal tuberculosis has less than four segments involved, a patulous ileocecal valve, transverse ulcers (longitudinal in CD) and more scars [48]. The characteristics of histologic lesions may also be helpful, needing to perform multiple biopsies [49]: in tuberculosis, granulomata are typically bigger, often confluent, located beneath the ulcerations, and absent in non-inflamed mucosa, and half of them contain caseum. Tuberculin skin test is positive in only 70–80% of patients with intestinal tuberculosis. The diagnosis may be facilitated by the presence of active pulmonary tuberculosis (but this is present in only 20% of cases), ascites, or large lymphadenopathy on imaging [40, 42]. Unfortunately, acido-alcoolo-resistant bacilli are very rarely present on direct examination of intestinal biopsies, and culture requires at least 4 weeks and is positive in only 40% of cases. Tissue PCR assays for *Mycobacterium tuberculosis* on intestinal biopsies are faster and show an accuracy of more than 80% for the diagnosis of intestinal tuberculosis [50]. Amplification of insertion element IS6110 that is specific for *M. tuberculosis,* in the fecal samples [51] and the Quantiferon-TB gold, a blood test using an interferon-γ-release assay, look to be promising tools [52] but their diagnostic value for the diagnosis of intestinal tuberculosis remains to be evaluated. Combination of Interferon-gamma releasing assay and anti-Saccharomyces cerevisiae antibody has a high specificity for the diagnosis of ITB [53]. New prediction models using of a CD prediction score combining colonoscopy, laboratory, and radiologic factors, can also be useful for calculating the probability of either CD or ITB at initial evaluation [54]. In cases of persistent doubt, empiric treatment with antituberculosis drugs has been proposed in countries where the prevalence of tuberculosis is high, reconsidering diagnosis of CD if the patient's condition does not improve [55]. Nevertheless, this approach is not recommended by others who advise to make every effort to reach an accurate diagnosis before starting specific therapy [42].

Primary intestinal infection with *cytomegalovirus* (CMV) can occur in immunocompromised children but is exceptional in immunocompetent children [56]. Endoscopy reveals ulcerative and hemorrhagic colitis, and histological examination of the biopsy will confirm the infection with CMV by finding typical intra-nuclear inclusions in the colonic mucosa, associated with immunostaining with a specific antibody. PCR of colonic tissue can also be used to detect viral DNA in the colon, although the significance of a positive result remains unclear in the absence of histological features of CMV disease. CMV colitis is rare in CD or mild-moderate UC [57, 58]. In patients with severe and/or refractory UC, local reactivation of CMV can be detected in inflamed colonic tissue in about 30% of cases but does not influence the outcome in most studies [58]. Nevertheless, treatment with ganciclovir has allowed some patients with severe colitis to avoid colectomy despite poor response to conventional IBD therapies [59]. It is recommended to test for CMV reactivation via PCR and/or immunochemistry on colonic biopsies in patients with severe colitis refractory to immunosuppressive therapy and treat with ganciclovir when CMV is detected [33, 60, 61].

Celiac Disease

Celiac disease is easily recognized in the classic mode of presentation of children who present with chronic diarrhea, anorexia, failure to thrive, and abdominal distension. Presentation is often less typical in older children who complain of abdominal pain, chronic diarrhea, anorexia, short stature, or iron-resistant anemia—symptoms that may also suggest IBD. In this situation, laboratory investigations should include specific antibodies against tissue transglutaminase, endomysium, or deamidated gliadin peptides. If these antibodies are positive, the diagnosis of celiac disease will be further confirmed by duodenal biopsy showing villous atrophy with increased number of intra-epithelial lymphocytes [62].

Eosinophilic Gastroenteropathy

Eosinophilic gastroenteropathy is a rare condition characterized by infiltration of the gastrointestinal tract with eosinophils [63]. Most common symptoms are vomiting, abdominal pain, and growth failure. Diarrhea associated with rectal bleeding is present in 23% of cases, especially in infants**,** and symptoms of protein-losing enteropathy are present in 33–100% of cases [64, 65]. Endoscopic examination may show nodularity, erythema, friability, erosions, and ulcerations in the upper digestive tract and/or in the colon [11, 66]. The diagnosis is strongly suggested by a context of food allergy or the association with hypereosinophilia in the blood, which is present in 70–100% of cases [65]. The presence of excessive eosinophils in the digestive mucosa will confirm the diagnosis although it may also be encountered in CD. Gastric biopsies may demonstrate eosinophilic gastroenteropathy more consistently, most patients having more than 10 eosinophils per high power field in the antral or duodenal mucosa [67]. Allergic skin tests or serum-specific IgE against main food allergens are useful to guide dietary recommendations [64].

Primary or Acquired Immunodeficiency Diseases

The importance of the intestine as an immune barrier is highlighted by the proximity of gut-associated lymphoid tissue to the luminal surface of the gastrointestinal tract, an external environment which is rich in microbial pathogens and dietary antigens. Significant gastrointestinal disorders, leading to chronic diarrhea, malabsorption, and failure to thrive, are frequently present in primary [68] or acquired immunodeficiency diseases [69]. In the recent years, advances in technology, such as whole-exome sequencing and targeted sequencing panels, allowed exploring young patients with IBD-like manifestations [70], and led to identify a significant number of monogenic diseases [71–73], affecting the epithelial barrier, the inflammatory response, or the immune response (Table 17.4). These diseases should be sought after, especially in cases of very early (<6 years) or infantile (<2 years) onset symptoms, and often present with a distinct phenotype, i.e., indeterminate pancolitis or severe ulcerative or fistulizing perineal disease [70]. Although the frontier between these monogenic diseases (still currently being discovered) and classic IBD is vague, the precise characterization of the genetic defect is of importance because therapeutic options may be different in some cases, like bone marrow transplantation, for example. This emphasizes the importance of a close collaboration between pediatric gastroenterologists, immunologists, and specialists in immunodeficiency syndromes for early efficient medical care and for active research to discover involved genes.

The most frequent manifestations of immunodeficiency syndromes are recurrent, persistent, and severe or unusual infections [74]. Disturbance of the immune system in the gut may also lead to auto-immune diseases, excessive production of IgE, or malignancies [75, 76].

Immunodeficient patients may present with chronic non-specific enterocolitis, characterized at small bowel biopsy by subtotal villous atrophy with acute and chronic inflammatory cell infiltration of the lamina propria [77–79]. This chronic non-specific enteropathy is not responsive to a gluten-free diet and occurs in several immunodeficiency disorders, affecting humoral response (X-linked agammaglobulinemia, IgA deficiency, common variable immunodeficiency), T-cell function (Wiskott-Aldrich syndrome, Acquired Immuno Deficiency Syndrome), or both (combined immunodeficiency). In some cases, strictures of the intestine may develop [77–79]. In these patients, it is important to rule out infection with opportunistic bacteria or parasites, and also with more common pathogens, such as rotavirus, adenovirus, and picornavirus [74]. In rare patients, the cause of the chronic enterocolitis is a disease affecting the epithelial barrier (Table 17.4).

Enterocolitis that resembles CD is mostly associated with neutropenia or defects of phagocytic function. Patients with chronic granulomatous disease may present with chronic colitis, perirectal abscesses and fistulae, and antral narrowing [80, 81]. The similarity with CD also includes endoscopic appearance, radiographic abnormalities, and even histologic features showing granulomata and giant cells in the digestive mucosa. Nevertheless, a paucity of neutrophils, an increased number of eosinophils, eosinophilic crypt abscesses, pigmented macrophages, and nuclear debris suggest chronic granulomatous disease [82]. Patients with Leukocyte Adhesion Molecule Deficiency, a rare disorder of phagocytic function, also present with oral and perineal involvement that may be mistaken for CD. These manifestations include stomatitis with pharyngitis, gingivitis with peridontis, ischiorectal abcesses, and distal ileocolitis [83]. Other disorders of neutrophils, such as congenital neutropenia, glycogen stor-

Table 17.4 Gastrointestinal manifestations in genetic defects associated with immunodeficiency syndromes

Disease	Gastrointestinal manifestations	Gene
Epithelial barrier function defects		
Dystrophic epidermolysis bullosa	Moderate to severe colitis	*COL7A1*
Kindler syndrome	Haemorrhagic UC-like colitis	*FERMT1*
X linked ectodermal dysplasia	Atypical CD-like enterocolitis, villous atrophy and epithelial cell shedding	*IKBKG*
ADAM-17 deficiency	First week of life non-bloody later bloody diarrhoea	*ADAM17*
Familial diarrhea	Partially neonatal onset of familial watery diarrhea. CD developed in adult age	*GUCY2C*
Neonatal inflammatory skin and bowel disease TTC7A deficiency Kindler syndrome Epithelial NADPH oxidases defect	IBD-like enterocolitis Colitis Colitis Colitis	*EGFR* *TTC7A* *FERMT1* *NOX1, DUOX2*
Phagocyte defects bacterial killing		
Chronic granulomatous disease	Stomatitis, perineal absesses, IBD like enterocolitis	*CYBB, CYBA, NCF1, NCF2, NCF4, LACC1*
Glycogen storage disease type 1b	Perioral and perianal lesions, CD-like ileocolitis	*SLC37A4*
Congenital neutropenia	Stomatitis, CD-like colitis	*G6PC3*
Leucocyte adhesion deficiency 1	Stomatitis, ileocolitis, perianal abscess, fistulas, CD-like colitis	*ITGB2*
Hyper- and autoinflammatory disorders		
Mevalonate kinase deficiency	IBD-like enterocolitis	*MVK*
Phospholipase Cγ2 defects	UC-like colitis	*PLCG2*
Familial Mediterranean fever	UC-like colitis	*MEFV*
Familial haemophagocytic lymphohistiocytosis	IBD-like enterocolitis	*STXBP2*
X linked lymphoproliferative syndrome 2	CD-like enterocolitis, fistulising perianal disease	*XIAP*
X linked lymphoproliferative syndrome 1	IBD-like enterocolitis, gastritis	*SH2D1A*
Hermansky–Pudlak syndrome Multisystem autoimmune disease	CD-like enterocolitis, perineal lesions	*HPS1, HPS4, HPS6* *STAT3*
B cell and antibody defects		
Common variable immunodeficiency	Persistent intestinal infections, food allergies, autoimmune diseases, malignancies (gastric cancer, lymphoma), CD-like colitis	*ICOS, LRBA*
Agammaglobulinaemia	Persistent intestinal infections, gastritis, malignancies (gastric cancer, lymphoma), CD-like colitis	*BTK, PIK3R1*
Severe combined immunodeficiency	Severe persistent opportunistic infections, IBD-like enterocolitis	*ZAP70, RAG2, IL2RG, LIG4, ADA, CD3γ*
IL-21 deficiency Hyper-IgM syndrome	Severe early onset colitis Oral ulcers, IBD-like	*IL21* *CD40LG, AICDA*
Wiskott–Aldrich syndrome	UC-like colitis	*WAS, WIPF1*
Omenn syndrome	Stomatitis, IBD-like enterocolitis	*DCLRE1C, DCLRE1X*
Hyper IgE syndrome	buccal granulomatous disease, UC-like colitis.	*DOCK8*
Trichohepatoenteric syndrome	Intractable diarrhoea, colitis	*SKIV2L, TTC37*
Regulatory T cells defects		
IPEX, IPEX-like Autoimmune lymphoproliferative syndrome type 5	Autoimmune enteropathy, colitis Enteropathy	*FOXP3, IL2RA, STAT1* *CTLA4*
CD122 deficiency DEF6 deficiency RIPK1 IL-10 signalling defects	Enteropathy Enteropathy IBD-like Stomatits, perianal abscesses and fistula, CD-like ulcerative colitis.	*IL2RB* *DEF6* *RIPK1* *IL10RA, IL10RB, IL10*
NOD2 signaling defects Anhidrotic ectodermodysplasia	IBD Colitis	*NOD2, TRIM22* *IKBKG*

Gene names were used according to HUGO gene nomenclature
CD Crohn disease, *IBD* Inflammatory bowel disease, *IPEX* X linked immune dysregulation, polyendocrinopathy, enteropathy, *UC* Ulcerative colitis

age disease type 1b, and the Hermansky–Pudlack syndrome [84], are responsible for CD-like enterocolitis. The same presentation may be caused by T- or B-cell defects, IgA deficiency, and acquired immunodeficiency syndrome [68, 85].

Severe ulcerative or fistulizing perineal disease occurring in a very young child is suggestive of IL-10-signaling pathway defect [86–88] or X-linked lymphoproliferative syndrome 2 [89, 90] and may also be encountered in phagocytic defects or Hermansky–Pudlack syndrome.

Auto-immune enteropathy is characterized by severe persistent diarrhea associated with circulating auto-antibody against gut epithelial cell and/or another auto-immune disorder [91, 92]. An additional consideration is X-linked familial disease which includes polyendocrinopathy (IPEX syndrome) [93–95]. Although the colon is frequently involved [93, 96, 97], the lesions are predominant in the small intestine, with inflammatory cell infiltration of the mucosa, and subtotal or total villous atrophy [93, 94, 97], leading to secretory, and protracted diarrhea in the first months of life [98, 99]. Nevertheless, antibodies to colonic epithelial cells have been also found in patients with UC [100], and 10% of IBD patients suffer from one or more auto-immune diseases [101], leading to some diagnostic difficulties in the older child.

Intestinal Neoplasm

Patients with *intestinal lymphoma* often present with chronic digestive symptoms, such as abdominal pain, distension, and/or diarrhea. Lesions are usually located in the small bowel although some cases may involve the colon [102, 103]. Ultrasound examination shows a thickening of the intestinal wall, and/or narrowing of the lumen of the gut which can be very similar to CD [104]. Extent of the lesions is more precisely seen with a MRI of the abdomen, and upper digestive endoscopy and/or ileocolonoscopy are mandatory to provide histologic confirmation. Nevertheless, if the lesions are limited to part of the small intestine, the biopsy may require an enteroscopy or even a surgical procedure, by laparoscopy or laparotomy. Predisposing conditions for intestinal lymphoma in children include inherited or acquired immunodeficiency syndromes, immunosuppressive therapy, and Epstein-Barr Virus infection [105]. In developing countries, Mediterranean lymphoma is characterized by the proliferation of IgA-secreting B lymphocytes. The diagnosis is usually suspected because of the presence of alpha heavy chain in the serum [106].

Vasculitis Disorders

Henoch–Schoenlein purpura is a frequent vasculitis, involving the gut, skin, joints, and kidney. Diagnosis is easily made in a child presenting with typical skin purpura, but gastrointestinal symptoms, i.e., colicky abdominal pain and bleeding, may precede the skin rash by a number of days. In some cases, isolated duodenojejunitis without purpura may occur [107], and terminal ileitis mimicking Crohn disease has been described [108, 109].

In other less frequent systemic vasculitides, such as polyarteritis nodosa [110, 111], Wegener granulomatosis [112], Behçet's disease [113, 114], and lupus arteriosus [115], intestinal involvement can lead to chronic abdominal pain associated with bleeding. Endoscopic and histological findings may be very similar to CD, even with the presence of granuloma. Extra-digestive manifestations, especially neurological, respiratory, renal, and cutaneous lesions suggest systemic vasculitis [116] (Table 17.5). On the other hand, extra-intestinal vasculitis can complicate IBD, involving the retina, brain, skin, muscle, joints, and lung [117–122]. The

Table 17.5 Extra-digestive manifestations and useful investigations for the diagnosis of systemic vasculitis in children with digestive symptoms resembling Crohn disease

Vasculitis	Extra-digestive manifestations	Investigations
Periarteritis nodosa	Multiple neuritis	Skin, muscle biopsy
	Myositis	Angiography
	Arterial hypertension	
	Skin ulcerations and gangrene	
Wegener granulomatosis	Epistaxis, sinusitis, otitis, hearing loss	Thoracic CT-scan
	Stridor, hoarseness	c-ANCA
	Cough, wheezing, dyspnea, hemoptysis	Nasal mucosa biopsy
	Necrotizing glomerulonephritis	
	Skin ulcerations and gangrene	
	Conjunctivitis, uveitis, optic neuritis	
	Pseudotumor cerebri	
Behcet's disease	Serious buccal aphtous	HLA-B5
	Genital ulcers	
	Uveitis	
	Thrombophlebitis	
	Menigoencephalitis	
Lupus arteriosus	Typical facial erythema	Antinuclear antibody
	Myocarditis, pericarditis, endocarditis	Anti-DNA antibody
	Pleuropneumonitis	
	Glomerulonephritis	
	Thrombophlebitis	
	Hemolytic anemia and thrombopenia	
	Keratoconjunctivitis, retinitis	

differentiation between primary systemic vasculitis and IBD can be clinically challenging but is important because their treatment and outcome are different [123]. The confirmation of the vasculitic process is more often evident on extra-intestinal biopsies (skin, muscle, kidney) than on intestinal biopsies and on angiography showing aneurysms and caliber variation of visceral arteries [110].

Abdominal Mass

The discovery of an abdominal mass has been found to reveal ileocolic CD in some adults and children [124–126]. Ultrasound examination and MRI of the abdomen are first-line investigations which will exclude extra-digestive malignant tumors, such as lymphoma, sarcoma, nephroblastoma, or neuroblastoma. When the mass is developed from the digestive tract, glandular lymphoma or adenocarcinoma of the colon, although rare in children, can be suspected [127–129]. Radiologic findings may be very similar in some benign lesions, like leiomyoma, pseudoinflammatory tumor, or tuberculosis [130, 131]. Nevertheless, surgical exploration is generally required, leading to correct diagnosis after histologic examination of the excised tumor. Intestinal tuberculosis may be a challenging diagnosis because histologic findings may be very similar to those of CD, although granulomata are typically larger and contain caseum in the case of tuberculosis [49]. Polymerase chain reaction for *Mycobacterium tuberculosis* should be systematically performed [50, 51].

Isolated Esophagogastroduodenal Involvement

Esophagogastroduodenal involvement is present in 25–40% of children with CD, usually discovered during upper digestive endoscopy with systematic biopsies, performed at initial work-up [132–136]. More rarely, patients may present with symptoms suggestive of peptic disease, including epigastric burning pain and early satiety, these often being relieved by antacids or antisecretory treatment [137, 138]. Endoscopy can show heterogeneous lesions, but a bamboo-joint like appearance is suggestive of CD [133, 137, 139–141]. Uncommonly, CD patients present with an isolated gastric or duodenal ulcer [134]. In the case of long-lasting symptoms or altered growth rate, the possibility of CD should be kept in mind and a biopsy of the edge of the ulcer looking for the presence of granulomata should be performed [133, 137]. The differential diagnosis for upper gastrointestinal CD includes *Helicobacter pylori* infection, peptic ulcer disease, viral gastritis, eosinophilic GI disease, Wegener's granulomatosis, sarcoidosis, carcinoma, gastric lymphoma, and tuberculosis [142].

Isolated Perineal Disease

Skin tags, anal fissures, and perianal fistulae or abcesses are frequent in infants who are in diapers and/or have a history of constipation with hard stools.

Such perianal lesions also occur in half of patients with CD, mostly in the context of colonic inflammation [143]. These lesions may precede other manifestations of intestinal disease in about one third of these patients [144]. In adolescents, perianal lesions can be severe [145, 146], hidden, and unrecognized for several months. The diagnosis of CD should then be considered in the case of extensive or refractory perianal lesions occurring in children. Confirmation of diagnosis will be obtained by MRI showing abscesses and fistulae and their relationship to the elevators [147], the presence of granuloma on biopsies of perianal lesions that required surgery, and/or colonoscopy that will show colitis [144, 146]. Severe ulcerative or fistulizing perineal disease occurring in a very young child is suggestive of monogenic diseases such as IL-10-signaling pathway defect [86–88], X-linked lymphoproliferative syndrome 2 [89, 90], phagocytic defects [80], or Hermansky–Pudlack syndrome [84]. More rarely, perineal lesions can occur after trauma or sexual abuse [148, 149].

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