Classification of Inflammatory Bowel Disease in Children

15

Athos Bousvaros

Introduction

The correct phenotyping and classification of children with inflammatory bowel disease remains problematic, especially for the child with IBD limited to the colon. In a child presenting with bloody diarrhea and endoscopic evidence of colitis, even an experienced clinician may have trouble distinguishing acute self-limited colitis (ASLC) from inflammatory bowel disease, or ulcerative colitis from Crohn disease. This chapter will review, in sequence: the diagnostic evaluation of IBD; the differentiation of ASLC from IBD; the differentiation of ulcerative colitis from Crohn disease; the classification of ulcerative colitis into subtypes; and the classification and phenotyping of Crohn disease. The reader is also referred to additional papers that discuss these issues in more detail: the recommendations for diagnosing written by the ESPGHAN IBD working group, and the recommendations for differentiating between UC and CD by the Montreal and Paris working groups [1–3]. Much of the information in this chapter is derived from a Clinical Report on Differentiating CD from UC prepared by the author and his colleagues for the North American Society for Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) [4]. The most significant changes since the priori edition of this textbook include the development of the Paris Classification for phenotyping children with IBD, and the development of additional serologic and imaging methods to aid in diagnosis.

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Diagnostic Evaluation of Inflammatory Bowel Disease

Discussed elsewhere in the book, the diagnostic evaluation of inflammatory bowel disease involves both gathering evidence to support the diagnosis of CD or UC, and also gathering data to exclude other confounding conditions (e.g. tuberculosis, *Clostridium difficile* infection). Initially, a clinician must suspect the diagnosis of IBD on the basis of history, examination, and preliminary laboratory testing (hematocrit, erythrocyte sedimentation rate, albumin), and then exclude other intercurrent illnesses. At that point, the physician has a choice of a wide variety of diagnostic modalities to help the clinician in determining whether or not a patient has IBD (Table 15.1). The standard evaluation of an inflammatory bowel disease patient, however, consists of two primary tests: colonoscopy with biopsy, and small intestinal imaging (with either barium upper GI series with small bowel follow-through, magnetic resonance imaging [MRI], or computed tomography). Many clinicians also choose to perform an esophagogastroduodenoscopy with biopsy at the time of diagnosis also, because it frequently provides useful clinical information as to the disease type and severity. This chapter discusses how to appropriately interpret endoscopic, histologic, and imaging findings, focusing predominantly on endoscopy and histology. Other diagnostic markers (including genetics and serology) will also be reviewed. While these markers have limited utility in the diagnosis of IBD, endoscopy and histology remain "the gold standard."

Distinguishing Acute Self-Limited Colitis from IBD Involving the Colon

It is now recognized that our current culture methods are capable of identifying only a small subset of microorganisms that inhabit the intestine, and we cannot reliably culture all pathogens from a stool sample. In addition, a small number of documented cases of infectious colitis last longer than 30

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Table 15.1 Tests currently utilized in the diagnosis of IBD

Blood or serum
Complete blood count
Serum albumin
Erythrocyte sedimentation rate
C-reactive protein
Serologies
Anti-neutrophil cytoplasmic antibody
Anti-*Saccharomyces cerevisiae* antibody
Antibodies to outer membrane porin
Antibodies to flagellin
NOD2 genetics (principally used in research studies)
Radiographic studies
Barium contrast radiography
Abdominal computed tomography
Abdominal magnetic resonance imaging
Radionuclide scintigraphy with Tc99 labeled white blood cells
Endoscopy and histology
Upper endoscopy with biopsies
Colonoscopy with biopsies
Video capsule endoscopy

days [5, 6]. Therefore, not every patient with bloody diarrhea and negative stool cultures has inflammatory bowel disease as the cause of their colitis. Epidemiologists utilize strict criteria (e.g., bloody diarrhea for over 6 weeks, or greater than two episodes of colitis within a 6-month period) to determine if a patient has ulcerative colitis [7, 8]. However, the practicing clinician does not wish to wait 6 weeks or longer to determine whether or not to treat the patient for IBD. Thus, in children with bloody diarrhea and negative stool cultures, performance of colonoscopy with random biopsies for histology early in the course of suspected IBD is important. Certain clinical and laboratory parameters (including chronic history of gastrointestinal complaints, growth failure, perianal tags, abnormal liver function tests, family history of IBD, and iron deficiency anemia) strengthen the argument for early colonoscopy in the individual patient. In contrast, other findings (fever, positive fecal leukocytes or calprotectin) can be seen in both IBD and infection [9]. It is also important to remember that a patient may have laboratory finding suggestive of infection, and also have new onset IBD. The new, ultrasensitive *C. difficile* PCR test has been particularly problematic in this regard, as the test is so sensitive it may not be able to differentiate between *C. difficile* colonization and *C. difficile* infection in the IBD patient [10].

Studies suggest that colonoscopy with careful examination of biopsy samples will allow differentiation between ASLC and IBD. In a cohort of 114 adults with acute colitis of less than 5 days duration, Mantzaris et al. performed colonoscopy at disease onset and subsequent flexible sigmoidoscopies at 1, 3, 6, and 18–24 months after initial illness. At 12 months after the onset of illness, a total colonoscopy was performed. Ultimately 68 patients were diagnosed with ASLC, and 46 patients were diagnosed with IBD (42 UC, 4 Crohn ileocolitis). Patients with UC had a significantly higher prevalence of diffuse erythema (100% vs. 25%), granularity (100% vs. 8%), and friability (100% vs. 12%) than patients with ASLC; in contrast, patients with self-limited colitis had a significantly higher prevalence of patchy erythema and microaphthoid lesion [11]. Histologic features identified reported in chronic inflammatory bowel disease but not in ASLC include: basal plasmacytosis, basal lymphoid aggregates, crypt branching, crypt atrophy, and the presence of Paneth cells in the left colon [6, 11–13]. Other findings, such as focal crypt destruction or superficial aphthous lesions, do not reliably differentiate between ASLC and IBD [14]. In one pediatric study, 8 of 29 patients with focal active colitis (cryptitis with an adjacent increase in lamina propria macrophages and T lymphocytes) were ultimately diagnosed with Crohn disease [15]. In another more recent study of focal active colitis in 90 adults, medications (NSAIDs) and infection were the most common causes, but 15% of patients who initially presented with focal active colitis on biopsy went on to develop IBD [16].

In summary, in a patient with bloody diarrhea and negative stool cultures, the performance of colonoscopy with random biopsies throughout the colon may provide the clinician and pathologist with evidence that proves or disproves the diagnosis of inflammatory bowel disease. Endoscopic findings suggesting IBD include erythema, granularity, and friability, and histologic evidence supporting an IBD diagnosis include crypt distortion, crypt branching, and basal lymphoplasmacytic infiltrate. While the patient with focal active colitis on biopsy has a 15–25% chance of developing IBD over time, this histologic finding alone is not enough to make a diagnosis.

Distinguishing Ulcerative Colitis from Crohn Disease

Endoscopy and Biopsy

It is usually straightforward in most patients to differentiate UC from CD on colonoscopy. In most cases of Crohn disease, the inflammation is limited to the ileum, cecum, and ascending colon. In contrast, classic ulcerative colitis typically begins in the rectum, extends proximally, is in a diffuse continuous distribution, and does not involve the small bowel. Even if Crohn disease is limited to the colon, the endoscopic appearance will help differentiate the two diseases; Crohn disease is characterized by aphthae, deep fissures, and cobblestoning, while UC is characterized by superficial inflammation, granularity, and friability (Fig. 15.1a, b). Evidence of ileal stenosis or ulceration, perianal

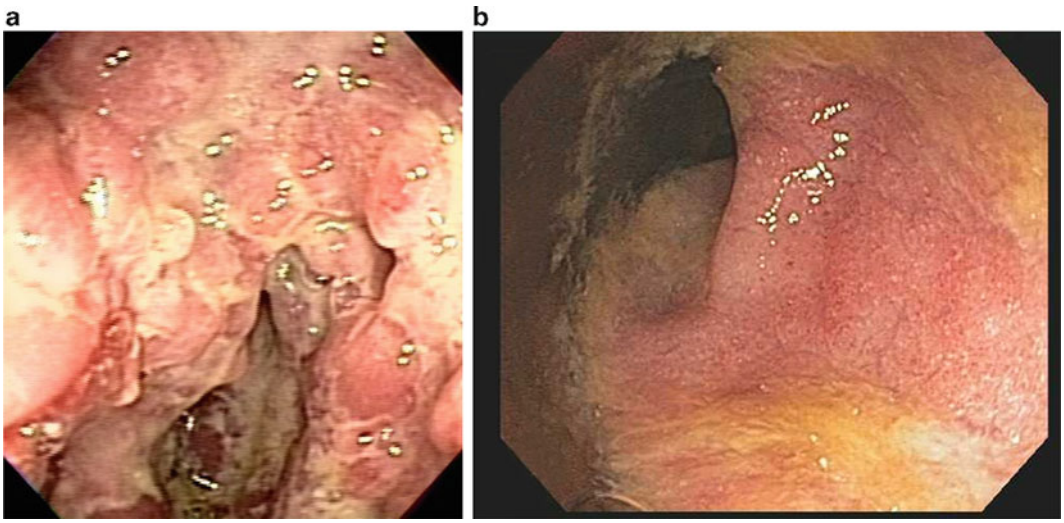

Fig. 15.1 (**a**) Crohn disease of the colon—note the deep fissuring ulcers and discontinuous inflammation. (**b**) Ulcerative colitis—granularity, friability, and loss of vascular pattern

Table 15.2 Endoscopy and histology in inflammatory bowel disease—the Porto criteria

	Crohn disease	Ulcerative colitis
Endoscopy (and visualization of oral and perianal regions)	Ulcers (aphthous, linear, or stellate)	Ulcers
	Cobblestoning	Erythema
	Skip lesions	Loss of vascular pattern
	Strictures	Granularity
	Fistulas	Spontaneous bleeding
	Abnormalities in oral or perianal regions	Pseudopolyps
	Segmental distribution	Continuous with variable proximal extension from rectum
Histology	Submucosal or transmural involvement	Mucosal involvement
	Ulcers: crypt distortion	Crypt distortion
	Crypt abscess	Crypt abscess
	Granulomas (non-caseating, non-mucin)	Goblet cell depletion
	Focal changes (within biopsy)	Mucin granulomas (rare)
	Patchy distribution (biopsies)	Continuous distribution

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Table 15.3 Nonclassical findings at presentation in UC patients, which do not exclude the diagnosis of UC

1.	Clinical
	Small anal fissures or skin tags (<5 mm in size)
	Oral ulcers
	Growth impairment
	Diarrhea without macroscopic or microscopic blood
2.	Endoscopic
	Gastritis without aphthae
	"Backwash ileitis"—ileal erythema without linear ulceration
	Periappendiceal inflammation in a patient without pancolitis
	Rectal inflammation less severe than in the more proximal colon (relative rectal sparing)
3.	Histologic
	Microscopic ileitis without granuloma
	Microscopic gastritis without granuloma
	"Relative rectal sparing" (histologic inflammation less severe in the rectum).
	"Patchiness" (normal colonic mucosa in between two areas of colonic inflammation)

disease, or granulomatous inflammation also helps establish the diagnosis of Crohn disease. Clinical, endoscopic, and histologic features that assist the clinician in differentiating these two conditions were summarized by the ESPGHAN Porto working group, and are given in Table 15.2 [1].

However, a subset of patients with IBD involving the colon will have certain "non-classical" features that may make the clinician less certain as to whether the patient has ulcerative colitis or Crohn disease. These are summarized in Table 15.3; all of these findings have been reported in ulcerative colitis. While it may be tempting to give a patient a diagnosis of "indeterminate colitis" if a patient has any of these atypical features, such a diagnosis makes it more difficult to enter such a patient into clinical trials or epidemiologic registries. Therefore, the author of this chapter suggests that a physician classify such a patient as ulcerative colitis, document the non-classical finding, and follow up the

patient to see if the finding resolves or evolves over time. Some of these non-classical findings (ileitis, gastritis, periappendiceal inflammation, rectal sparing, and "patchy" histology) are discussed in more detail below.

"Backwash Ileitis" vs. Crohn of the Ileum

The term "backwash ileitis" was originally used to describe an abnormal appearance of the terminal ileum observed radiologically or endoscopically in patients with ulcerative pancolitis. The term derives from the original contention that the ileitis resulted as a reaction to "the reflux of colonic contents into the terminal ileum." Currently such ileitis in UC is considered to be primary ileal mucosal inflammation. The prevalence of backwash ileitis in both children and adults has been evaluated in several studies. The most comprehensive study in adults was performed by Heuschen et al., who evaluated 590 adults with UC undergoing colonic resection. In this study 107 of 476 patients with pancolitis (22%) had evidence of backwash at colectomy; in contrast, backwash ileal inflammation was not seen in any patients with left sided ulcerative colitis [17]. The prevalence of backwash is similar in children [18].

In backwash ileitis, radiographic studies of the terminal ileum demonstrate a normal caliber ileum without stenosis or cobblestoning; however, a rough "sandpaper" appearance may be present in the terminal ileum [17, 19, 20]. At endoscopy a patient with backwash ileitis has a normal ileocecal valve without signs of stricture, stenosis, or ulceration. In backwash ileitis, normal lymphoid nodules may be present, but no linear ulcerations, deep fissures, or areas of cobblestoning are seen.

The histology of backwash ileitis, and what specific features differentiate this entity from CD of the ileum, remain unclear. Studies suggest that changes seen in "backwash ileitis" are usually mild, consisting of villous atrophy, increased mononuclear cells, and scattered crypt abscesses [21]. In contrast, Crohn disease of the ileum may be characterized by: "discrete transmural lymphoid aggregates," "segmental bowel involvement," or "non-necrotizing granulomas" [22].

Some investigators have automatically classified a patient as having Crohn disease or indeterminate colitis if there is any histologic inflammation on an ileal biopsy [23, 24]. This approach is probably overly conservative. Two recent case–control studies compared patients with backwash ileitis and matched controls, and suggest no difference in long term pouch outcomes after colectomy [22, 25]. In the larger study, prevalence of pouchitis (about 35%) was comparable in both the backwash and non-backwash group, as was the prevalence of fistulae around the pouch (around 10%) [22]. In the opinion of the NASGHAN working group, identification of nonspecific or microscopic ileitis in a patient with typical features of UC does not warrant a change of diagnosis, unless there are specific features suggesting Crohn disease (e.g., linear ulcers, cobblestoning, or granulomas). Rather, if nonspecific ileitis is identified, and the patient has ulcerative colitis involving the entire colon, the term "UC with backwash ileitis" is more appropriate. Suggested standard descriptions of ileal inflammation are provided in Table 15.4.

Table 15.4 Ileitis—suggested descriptions

1.	Normal ileum—an ileum that is both *macroscopically* and *microscopically* normal, without features of inflammation. Lymphoid nodularity of the terminal ileal Peyer's patches should be considered a normal finding
2.	Histologic backwash ileitis (microscopic inflammation of the ileum)—active ileitis (focal or diffuse) with or without features of chronicity identified on histologic examination, with an endoscopically *normal* ileum
3.	Endoscopic and histologic backwash ileitis—endoscopic erythema and granularity of the terminal ileum, confirmed upon histology with findings of active or chronic ileitis
4.	Crohn disease of the ileum—linear ulceration, cobblestoning, and narrowing of the ileum, often associated with ulceration of the ileocecal valve. These findings may be demonstrated either by endoscopy of the terminal ileum, or by barium upper GI with small bowel follow-through contrast study. The histology may be normal (due to the focal nature of the inflammation), or demonstrate acute and chronic ileitis. The presence of noncaseating granulomas on ileal biopsy automatically classifies a patient as having CD of the ileum

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Gastritis in Patients with Inflammatory Bowel Disease

Esophagogastroduodenoscopy (EGD) is increasingly being performed as part of the initial evaluation in children with suspected inflammatory bowel disease, especially if a child is under anesthesia. Performing an EGD in a child adds very little time to the initial diagnostic evaluation, and may identify gastric pathology that requires additional medical treatment (e.g., proton pump inhibitors or immunomodulators). The Porto working group of ESPGHAN has recommended routine upper endoscopy at initial presentation to aid in the diagnosis of pediatric IBD [1]. However, in certain patients, the endoscopic or histologic findings seen on EGD may raise uncertainty as to whether the patient has CD or UC.

It is now well documented that patients with both CD and UC may have upper GI tract inflammation, and that the prevalence of inflammation seen in the esophagus, stomach, and duodenum is comparable in both CD and UC. Both nonspecific gastritis and focally enhanced gastritis (defined as perifoveolar or periglandular mononuclear or neutrophilic

infiltrate around gastric crypts) may be identified in the gastric biopsies of patients with IBD. A large epidemiologic study of both adults and children determined that 25% of IBD patients have gastritis, and approximately 13% have duodenitis, with this upper tract inflammation being more common in younger patients [26]. Focal gastritis is more common in the gastric biopsies of patients with Crohn disease than patients with ulcerative colitis [1, 27, 28]. In a retrospective study of 238 children with UGI biopsies, focal gastritis was present in 5/24 (20.8%) of patients with UC, but it was more common in CD patients (28/43 or 65.1%) compared to 2.3% of controls without IBD and one of 39 with *Helicobacter pylori* [29].

The most useful histologic finding on upper endoscopy in the IBD patient is the identification of granulomas on routine biopsy of the esophagus, stomach, or duodenum. The performance of such biopsies in IBD patients at initial diagnosis will identify non-caseating granulomas in 12–28% of patients, which will establish the formal diagnosis of Crohn disease [27, 30–33]. In one study by Kundhal et al., 39 children with ulcerative or indeterminate colitis and normal barium small bowel radiographs underwent upper endoscopy. Granulomas were present on antral biopsy in five patients (14%), thus changing the diagnosis to CD [31]. In a review of duodenal, antral and esophageal biopsies from children with CD and UC in whom *H. pylori* infection had been excluded, Tobin noted granulomas in 40% of patients. While the majority of these were identified in the stomach, granulomas could also be identified in the esophagus or duodenum [33]. While granulomas may also be seen in other conditions, including *H. pylori* disease and sarcoidosis, the identification of upper GI tract granulomas on upper endoscopy strongly suggests Crohn disease in a child with IBD.

Periappendiceal Inflammation in Ulcerative Colitis

The finding of right colonic inflammation in a patient with disease limited to the left colon suggests a skip area, which should suggest Crohn disease. However, patients with UC that does not extend to the cecum may have an inflamed distal (left) colon, a normal transverse and ascending colon, and evidence of periappendiceal and cecal inflammation (a.k.a. a "cecal patch"). The finding of a "cecal patch" was well documented on studies of colectomy specimens, which demonstrate appendiceal involvement as a "skip lesion" that can be seen in UC [34–38]. More recently, prospective and retrospective studies of colonoscopy and histology have confirmed that periappendiceal inflammation is common in UC [38–44]. In a recent large series involving adults and children, 29 of 369 (7.9%) of UC patients (in whom the disease did not involve the entire colon) had evidence of cecal inflammation [45]. In one study examining resected appendices in patients with CD and UC, appendiceal inflammation was noted in both groups, and the inflammation was of comparable severity [46]. In summary, mild periappendiceal inflammation can occur in both CD and UC. In CD, this appendiceal inflammation usually occurs in conjunction with more extensive inflammation of the ileum and cecum, with a more normal distal colon. In contrast, in UC, the appendiceal inflammation is usually seen with pancolitis, but can be seen as an isolated "cecal patch" in patients with left sided UC or proctitis.

Rectal Sparing and Patchiness

The classic definition of ulcerative colitis requires diffuse continuous disease that begins in the rectum and extends proximally, to some point higher up in the colon, without "skip areas." "Rectal sparing," where the rectum is not inflamed (absolute rectal sparing), or inflamed less severely than the more proximal colon (relative rectal sparing) was thought to be suggestive of Crohn disease. Recent studies emphasize that colonic inflammation may be less severe in children than in adults with new onset UC, leading to relative or absolute rectal sparing. Three studies have directly compared new onset UC in children to adult-onset UC, and all of these suggested less severe and less diffuse architectural abnormalities in children. Two of these studies demonstrated a higher prevalence of rectal sparing in children compared to adults [47–49].

The term "patchiness" refers areas of normal mucosa (either endoscopically or histologically) between two areas of colonic inflammation. As with rectal sparing, the finding of histologic "patchiness" was originally thought to be suggestive of a Crohn disease skip area. However, a number of studies suggest that rectal sparing and patchiness can be seen in ASLC, new onset untreated ulcerative colitis in children, and medically treated ulcerative colitis in adults [48–51]. In the study by Glickman et al., 16% of children with new onset treatment naïve UC had patchy chronic colitis, compared to no adults. In contrast, patchy disease can be seen in adults at the time of colectomy, and such a finding does not necessarily warrant a change in diagnosis from UC to CD [52]. The precise reason why the histology of new onset UC differs between children and adults remains unclear, though it may be a function of younger age and shorter duration [49].

It is important to emphasize the effects of treatment on a patient with either CD or UC. Certain treatments, particularly immunomodulators and infliximab, are highly effective at inducing mucosal healing. Even milder medical

therapies such as aminosalicylates may cause attenuation of inflammation, resulting in patchiness [50, 53]. Therefore, the best opportunity to distinguish CD from UC is at the time of the initial endoscopic evaluation.

Radiographic Imaging Studies in the Differentiation of UC from CD

The role of barium radiography in differentiating between CD and UC is well established, and most of the initial epidemiologic studies that classified these two diseases utilized the findings on barium radiography to assist in the differentiation of these two conditions. In Crohn disease of the ileum, the terminal ileum, ileocecal valve, and cecum demonstrate various degrees of narrowing, ulceration, and stenosis [54]. In contrast, in UC with backwash ileitis the terminal ileum has a granular appearance, the ileocecal valve is wide open, and the cecum is normal caliber. Some authors have questioned the utility of barium radiography in otherwise healthy patients with a normal ileoscopy, it is unclear how often the findings of a barium study change the diagnosis [54].

While at one time, experts recommended that all children with IBD undergo an upper GI with small bowel follow through at the time of initial diagnosis, newer imaging modalities are currently replacing the barium meal at many centers. The expertise and the use of non-barium imaging modalities (ultrasound, nuclear medicine, computed tomography, and MRI studies) in the differentiation of CD from UC vary greatly from center to center. All of these modalities have been utilized in the diagnosis of IBD patients, with good results [19, 55–57]. However, the benefits in diagnosis must be weighed against the study's cost and the radiation exposure to the patient [58].

The most appealing of these newer modalities is MRI, because MRI generally provides reasonable quality images without exposure to radiation. Of the above modalities, MRI scan of the bowel offers the potential benefit of accurate anatomic localization without radiation. Recent studies suggest that MRI can differentiate between CD of the ileum and backwash ileitis by evaluating bowel wall thickness of the ileum [19, 56]. A prospective study in children comparing MRI to CT scan suggested comparable sensitivity and specificity for detecting small bowel findings such as bowel wall thickening, mesenteric inflammation, fistula, and abscess [59]. However, in this clinician's experience, MRI is highly operator dependent, and nonspecific abnormalities such as "jejunal enhancement" may mislead the radiologist and clinician. Thus, I recommended not changing a patient's diagnosis from UC to Crohn disease simply on the basis of a jejunal MRI finding alone. To have pancolonic "UC-like disease" and true jejunal inflammation is extremely rare. If an MRI demonstrates a nonspecific abnormality in the mid small bowel, such a finding should be confirmed by some sort of other modality (either another type of imaging study or enteroscopy).

Serologic and Genetic Testing

A number of serum markers of variable sensitivity and specificity are currently available as a "diagnostic panel for inflammatory bowel disease." Serology is discussed in greater detail elsewhere in this book (Chap. 18). The utility of serology in differentiating between CD and UC is highly controversial, and there remains doubt if this test has utility in routine clinical pediatric practice [60, 61]. The anti neutrophil cytoplasmic antibody (pANCA) is identified in approximately 75% of patients with ulcerative colitis, and up to 20% of patients with Crohn disease [62–64]. In contrast, antibodies to *Saccharomyces cerevisiae* antibody (ASCA) are present in 40–80% of patients with Crohn disease, are rarely if ever seen in UC, and are preferentially associated with ileocecal Crohn disease.

As previously discussed, the current gold standard for diagnosis of CD and UC is based on endoscopy and histology, not on serology. However, there is increasing evidence, that serologic markers may be predictive of pouch complications, including Crohn disease of the pouch. Coukos et al. identified two markers (ASCA and CBir) as predictive of the risk of pouchitis, pouch fistulae, or need for pouch takedown [65]. In a second study, Melmed et al. identified family history of Crohn disease and positive ASCA serology as risk factors for development of Crohn disease of the pouch [66]. Therefore, while we do not routinely obtain serologic markers in most straightforward cases of IBD, we do consider them in children with severe colitis that may be facing surgery.

Recent progress in IBD has focused on identifying genetic and microbial markers that may differentiate CD from UC; genetics are discussed in more detail in Chap. 1. Over 100 genes have been identified, and polymorphisms may increase or decrease the risk of developing IBD. Some of these genes are clearly associated with one of the two disease phenotypes. For example, NOD2 mutations are seen in approximately 25% of patients with Crohn disease, but UC patients do not have an increased prevalence of NOD2 mutations [67]. Other genetic polymorphisms, such as mutations in the tumor necrosis factor and the IL23 receptors, may increase the risk of developing either CD or UC. In particular, colonic Crohn disease and UC share many common genes [68]. At this time, genetic testing cannot reliably differentiate UC from CD of the colon, and is not routinely recommended for use in clinical practice.

Video Capsule Endoscopy

Video capsule endoscopy is increasingly being utilized in the detection of obscure small bowel lesions, and now has a proven role in the identification of Crohn disease of the small intestine. The sensitivity of this technique at identifying small bowel ulceration or stricture appears to be superior to conventional barium radiography and enteroclysis [69, 70]. In studies of adults, capsule endoscopy has an established role in identifying CD when other methods fail [70, 71]. A single pediatric study suggested diagnostic sensitivity and specificity comparable to MRI [72]. The biggest concern with capsule endoscopy is that the capsule may become impacted in a patient with a small bowel stricture. For this reason, our approach is to initially perform a barium small bowel series or MRI as the initial study. If Crohn disease is strongly suspected, colonoscopy fails to identify disease, and a barium study shows no inflammation or stricture, we then perform a capsule study to evaluate for mid-small bowel Crohn disease. In addition, if an abdominal MRI demonstrates a finding that is suggestive but not diagnostic of Crohn disease, we will perform a small bowel capsule study to determine if there is true evidence of mucosal inflammation. Depending on the degree of suspicion of small bowel narrowing, a patency capsule may be performed prior to the actual capsule study.

"Indeterminate Colitis" or "Colonic IBD Type Unclassified"

In some cases, a clinician is uncomfortable making a firm diagnosis of Crohn or ulcerative colitis based on the clinical presentation. These patients have traditionally received the diagnosis of "indeterminate colitis" (IC). The prevalence of "indeterminate colitis" appears to be higher in pediatric than in adult case series. In most adult epidemiologic studies, the prevalence of IC ranges from 5 to 10%, while pediatric series report a prevalence of IC as high as 30% [73–75]. It remains highly unclear whether or not this dramatic difference in the reported prevalence of IC between children and adults represent differences in biology or differences in what internists and pediatricians classify as UC. As the number of tests (e.g., CT, MRI, ileal biopsy, gastric biopsy, genetics, serology) used in the diagnostic evaluation of IBD has grown, so has diagnostic uncertainty.

While use of the "indeterminate colitis" classification may be easy for the clinician, this author recommends against overusing it. Specifically, classifying all UC patients as "indeterminate colitis" on the basis of nonspecific findings (e.g., nonspecific gastritis, patchiness, or backwash ileitis) may render a patient ineligible for clinical studies (which usually exclude patients with indeterminate colitis). In addition, overusing the IC classification will make epidemiologic studies of pediatric UC and CD more difficult in the future. The NASPGHAN working group has developed an algorithm to allow clinicians to differentiate CD from UC (Fig. 15.2).

The ongoing development of molecular, genetic, and serologic markers further complicates the differentiation of UC from CD from IC. For example, what if a patient with classical UC pancolitis is ASCA positive? This area remains controversial, and is the topic of ongoing active research. A recent consensus conference from Montreal concluded that the term "indeterminate colitis" be reserved for patients who have undergone colectomy, and that the term "colonic IBD type unclassified" be utilized in patients who have undergone endoscopy but still have an uncertain diagnosis [2].

In conclusion, further research studies are needed to develop reliable molecular and serum markers that will differentiate UC from CD. In the meantime, a patient may be given a putative diagnosis of indeterminate colitis if they have inflammatory bowel disease limited to the colon, and clinical features that are inconsistent with the diagnosis of UC (for example, ileal aphthae in left sided colitis, small perianal tags in a patient with pancolitis, severe growth failure in UC, or unusually severe focal gastritis). If the clinician decides to classify a patient as indeterminate colitis, it is suggested the physician clearly record the precise piece of clinical data that prompted the use of the IC diagnosis (e.g., absolute rectal sparing, small ileal ulcers without strictures or cobblestoning, backwash ileitis in a patient with left sided disease, growth failure). In the future, such a patient may benefit from additional evaluation to see if the finding prompting the IC diagnosis has changed or resolved. This may allow the clinician to establish a definitive diagnosis of CD or UC in the future, which may prove helpful to the patient.

Subclassification of Ulcerative Colitis and Crohn Disease: From Montreal to Paris

Classification systems to characterize pediatric inflammatory bowel disease have been in use since 1998, when the Vienna phenotyping system was implemented by a group of adult IBD experts [76]. This schema was revised by the Montreal working group in 2005 [2]. The Montreal working group recommends subclassifying patients with UC into one of three categories: Ulcerative proctitis (E1), left sided UC (E2), and extensive UC (E3). This classification is based on ENDOSCOPIC appearance, rather than histology. The inflammation in proctitis is limited to the rectum (typically the last 15 cm of colon). Left sided disease (E2) has endoscopic inflammation distal to the splenic flexure, while extensive disease (E3) extends proximally to the splenic flexure [2]. The term "pancolitis" is commonly used to define a patient whose entire colon is inflamed, and there is evidence

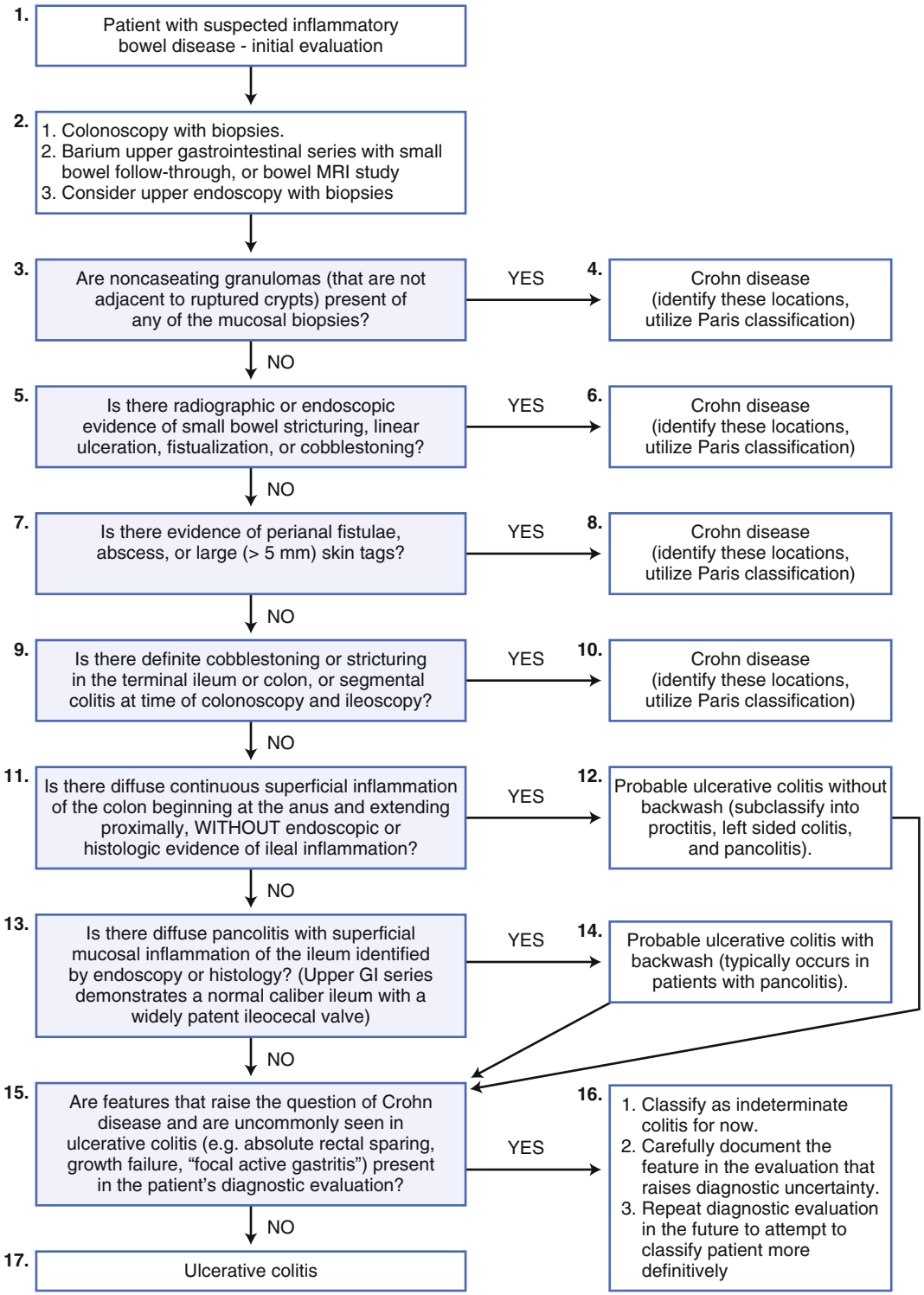

Fig. 15.2 Algorithm for differentiating UC from CD—from ref. [4]

that pancolitis is more common in children than in adults [48, 77].

Crohn disease is commonly subtyped on the basis of disease location (jejunal, ileal, ileocecal, ileocolonic, colonic only, or perianal), and disease behavior (inflammatory, penetrating, or stricturing). The Montreal classification assigns a classification code based on three variables: age (<16 years, 17–40, >40), location (ileum, colon, ileocolon, or upper GI), and behavior (inflammatory, stricturing, penetrating). One major difference from the Vienna classification

Table 15.5 Subclassification of Crohn disease—the "Montreal" and "Paris" classification. Comparison of the "Montreal" and "Paris" classifications for Crohn disease

	Montreal classification	Paris classification
Age at diagnosis	A1: Below 17 year	A1a: Below 10 year
	A2: 17–40 years	A1b: 10 to <17 year
	A3: Above 40 year	A2: 17–40 year
		A3: Above 40 years
Location	L1: Terminal ileal ± limited cecal disease	L1: Distal 1/3 ileum ± limited cecal disease
	L2: Colonic	L2: Colonic
	L3: Ileocolonic	L3: Ileocolonic
	L4:Isolated upper disease	L4a: Upper disease proximal to ligament of Treitz
		L4b: Upper disease distal to ligament of Treitz and proximal to distal 1/3 ileum
Behavior	B1: Nonstricturing nonpenetrating	B1: Nonstricturing nonpenetrating
	B2: Stricturing	B2: Stricturing
	B3: Penetrating	B3: Penetrating
	p: Perianal disease modifier	B2B3: Both penetrating and structuring disease, either at the same time or different times
		p: Perianal disease modifier
Growth		G0: No evidence of growth delay
		G1: Growth delay

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is that perianal complications by themselves no longer automatically place a patient into the "penetrating" disease behavior group. Rather, the penetrating phenotype is reserved for patients who develop internal fistulae or abdominal abscesses, and perianal disease is treated as a modifier.

Most recently, a group of pediatric investigators have proposed a modification of the Montreal Classification termed the "Paris Classification." This revised schema incorporates several new features relevant to pediatric IBD [3]. Specifically:

1. The Paris classification creates a new age classification (A1a) for children under age 10 years, which will facilitate translational studies of early onset IBD.
2. The Paris classification differentiates between upper GI tract inflammation proximal to the ligament of Treitz (Paris L4a), and mid-small bowel Crohn disease (i.e. small bowel disease distal to the ligament of Treitz, Paris L4b).
3. The Paris classification allows patient to be classified as having both structuring and perforating disease (aka B2B3 behavior).
4. The Paris classification includes a modifier for growth failure.

The current Paris system still has some drawbacks; for example, it does not differentiate a patient with classic ileocecal Crohn disease from a patient with "UC-like" pancolitis and ileitis in whom granulomas are identified on biopsy. We expect as our knowledge of genetics, microbiology, and serology improves, that additional modifications and improvements to the current phenotyping system will be included over time. At this time, it is recommended that the "Paris classification" be used for clinical and epidemiologic studies in pediatric IBD. A summary of the Montreal and Paris classifications is given in Table 15.5.

Conclusion

The correct classification of a patient with inflammatory bowel disease requires careful attention to detail. Patients presenting with signs and symptoms that suggest IBD need to be evaluated in full with a physical examination, supportive laboratory testing, stool cultures, radiographic studies, and endoscopy. If feasible, we recommend either small bowel MRI or upper GI series with small bowel follow through, upper endoscopy, and colonoscopy at the time of disease onset. Two or three biopsies should be taken from each region of the bowel, and given to the pathologist, with a careful endoscopic description that will allow correlation of endoscopy and histology. Patients with colitis and nonspecific findings such as gastritis and backwash ileitis can still have ulcerative colitis. Criteria from the Porto and Montreal groups will help reduce inter-observer variability. Additional research involving imaging, capsule endoscopy, serology, and genetics may prove helpful in the future. However, the cornerstone of IBD classification is careful endoscopic evaluation and microscopic examination of biopsied tissue.

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