

Clinical Report

Differentiating Ulcerative Colitis from Crohn Disease in Children and Young Adults: Report of a Working Group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America

ABSTRACT

Background: Studies of pediatric inflammatory bowel disease (IBD) have varied in the criteria used to classify patients as having Crohn disease (CD), ulcerative colitis (UC), or indeterminate colitis (IC). Patients undergoing an initial evaluation for IBD will often undergo a series of diagnostic tests, including barium upper gastrointestinal series with small bowel follow-through, abdominal CT, upper endoscopy, and colonoscopy with biopsies. Other tests performed less frequently include magnetic resonance imaging scans, serological testing, and capsule endoscopy. The large amount of clinical information obtained may make a physician uncertain as to whether to label a patient as having CD or UC. Nevertheless, to facilitate the conduct of epidemiological studies in children, to allow the entry of children into clinical trials, and to allow physicians to more clearly discuss diagnosis with their patients, it is important that clinicians be able to differentiate between CD and UC. **Methods:** A consensus conference regarding the diagnosis and classification of pediatric IBD was organized by the Crohn's and Colitis Foundation of America. The meeting included 10 pediatric gastroenterologists and 4 pediatric pathologists. The primary aim was to determine the utility of endoscopy and histology in establishing the diagnosis of CD and UC. Each member of the group was assigned a topic for review. Topics evaluated included differentiating inflammatory bowel disease from acute self-limited colitis, endoscopic and histological features that allow differentiation between CD and UC, upper endoscopic features seen in both CD and UC, ileal

inflammation and “backwash ileitis” in UC, patchiness and rectal sparing in pediatric IBD, periappendiceal inflammation in CD and UC, and definitions of IC.

Results: Patients with UC may have histological features such as microscopic inflammation of the ileum, histological gastritis, periappendiceal inflammation, patchiness, and relative rectal sparing at the time of diagnosis. These findings should not prompt the clinician to change the diagnosis from UC to CD. Other endoscopic findings, such as macroscopic cobblestoning, segmental colitis, ileal stenosis and ulceration, perianal disease, and multiple granulomas in the small bowel or colon more strongly suggest a diagnosis of CD. An algorithm is provided to enable the clinician to differentiate more reliably between these 2 entities.

Conclusions: The recommendations and algorithm presented here aim to assist the clinician in differentiating childhood UC from CD. We hope the recommendations in this report will reduce variability among practitioners in how they use the terms “ulcerative colitis,” “Crohn disease,” and “indeterminate colitis.” The authors hope that progress being made in genetic, serological, and imaging studies leads to more reliable phenotyping. *JPGN* 44:653–674, 2007. **Key Words:** Biopsy—Child—Classification—Colonoscopy—Crohn disease—Histology—Indeterminate colitis—Inflammatory bowel disease—Pathology—Phenotyping—Ulcerative colitis. © 2007 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

INTRODUCTION

In the last 30 years the evaluation of children with suspected inflammatory bowel disease (IBD) has changed significantly. In part because of the increased availability of skilled pediatric endoscopists and improved sedation techniques, the diagnosis of colitis is established by colonoscopy, rather than by barium enema or sigmoidoscopy. In many pediatric centers children undergo a combined upper endoscopy, colonoscopy, and terminal ileoscopy as

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the initial diagnostic procedure. During this initial procedure, different regions in the gastrointestinal (GI) tract may routinely be biopsied to look for histological evidence suggestive of IBD. In addition, new laboratory assays such as antibodies to *Saccharomyces cerevisiae* (ASCA), and new imaging modalities (bowel magnetic resonance imaging [MRI], bowel ultrasound, ^{99m}T scanning, and video capsule endoscopy) have been developed to assist the clinician in determining the type of disease, extent of involvement, and severity of activity. Although not routine practice in IBD at this time, genetic testing is commonly used in other chronic illnesses (eg, cystic fibrosis, familial polyposis). Testing for the *NOD2* and other IBD genes may become part of the diagnostic evaluation of patients in the near future. A standard diagnostic evaluation including contrast imaging of the small bowel, esophagogastroduodenoscopy, colonoscopy, ileoscopy, and multiple biopsies from the GI tract was recently recommended by a European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) expert panel (1).

The large amount of diagnostic data available to the clinician has resulted in questions about how to properly classify patients with IBD in epidemiological studies and clinical trials. Investigators collaborating in such multicenter studies or trials may themselves disagree about patient classification. For example, a physician performing colonoscopy on a child with rectal bleeding may find pancolitis and mild histological inflammation of the terminal ileum. One investigator may call such a patient "ulcerative colitis with backwash ileitis," another investigator may call that patient "indeterminate colitis," and a third investigator may call the same patient "Crohn's ileocolitis." In a similar way the finding of endoscopic or histological gastritis may result in a subset of physicians changing the diagnosis from ulcerative colitis (UC) to Crohn disease (CD). The majority of the epidemiological literature evaluating CD and UC does not address these controversies; in fact, there is lack of uniformity in the definitions of IBD used in different epidemiological studies (Table 1).

The lack of a standardized diagnostic schema for pediatric IBD has led to the overuse of the term "indeterminate colitis" (IC), defined as "patients with colonic disease who cannot be classified into one of the two major forms of IBD" (2,3). In pediatric series, the prevalence of IC ranges from 5% to 30%, suggesting that there is variation in classification criteria, and uncertainty about when to classify a patient as CD or UC (4–6). Although it is tempting to use the term IC whenever there is even a small amount of clinical uncertainty, overuse of the IC classification is counterproductive for 2 reasons. First, an unclear diagnosis leads to uncertainty when the clinician and patient are choosing therapeutic options (eg, medication vs surgery), or when discussing long-term prognosis (permanent ostomy vs ileoanal pouch anastomosis).

Second, if a patient is classified as IC, then he or she may be ineligible for clinical trials of investigational agents that are targeted toward a specific disease (CD or UC). For example, if a patient with pancolitis and a normal ileum is classified as having IC on the basis of a non-specific gastritis identified on upper endoscopy, then that patient may be less willing to undergo surgery or be considered ineligible for a UC clinical trial.

To address some of the current controversies in the diagnosis of pediatric IBD, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America jointly organized a working group of 10 pediatric gastroenterologists and 4 expert GI pathologists. Each member of the working group was previously given an assigned topic and had performed a comprehensive literature search and summary in advance of the meeting. The principal aims of the working group were as follows:

1. To establish a set of definitions and phenotypes, and develop an algorithm that will improve interobserver agreement in the diagnosis and classification of CD, UC, and IC
2. To aid clinicians in understanding specific terms that are currently used in the IBD literature, but may be misinterpreted because they are not well defined (eg, "backwash ileitis," "indeterminate colitis," "focal active gastritis," "cecal patch")

This clinical report focuses primarily on the utility of clinical, endoscopic, and histological findings in differentiating between CD and UC. The utility of radiography, serology, and capsule endoscopy is discussed in brief. This report also does not review the classification of CD and UC subtypes; for this, the reader is referred to the excellent paper by Silverberg and colleagues containing the Montreal classification (7). Although the questions the present working group addressed do not have definitive answers, we hope this report will signify progress in standardizing the diagnosis and classification of IBD in children.

METHODS

Members of the working group were selected because of prior expertise in clinical studies or the epidemiology of IBD. Controversial areas in the diagnosis and classification of IBD were identified through a series of conference calls. Members of the group conducted literature searches relevant to their area of expertise through the search engine MEDLINE and/or EMBASE. Because many of the diagnostic controversies were related to histological findings, a team of pathologists (D.A., J.G., G.J., P.R.) with expertise in interpreting pediatric IBD biopsies was also organized. After initial preparation through conference calls and literature searches, the group met in December 2003. Available evidence regarding the classification of IBD cases was discussed, and the quality of the evidence was graded (see Appendix). In controversial areas

TABLE 1. Definitions of CD and UC used in some epidemiological studies of children and adults: variability among study definitions

Ref	Population	UC	CD	Other/comments
(10)	Children and adults	<p>Definite case:</p> <p>1a. Diarrhea and rectal bleeding for >6 wk</p> <p>1b. Either: Sigmoidoscopy or colonoscopy with friability, contact bleeding, or petechiae</p> <p>OR</p> <p>barium enema with ulceration or shortening of the colon</p> <p>OR</p> <p>characteristic changes at colectomy</p> <p>1. Macroscopic appearance by endoscopy; diffuse continuous disease with rectal involvement, superficial ulcers, granularity, no fissuring</p> <p>2. Compatible histology; hyperemia, crypt abscesses, mucosal atrophy, and rectal involvement</p> <p>3. Normal small bowel documented either by radiography or ileoscopy</p>	<p>1. Definite case: Characteristic positive histological report from an operative or autopsy specimen</p> <p>2. Probable case:</p> <p>2a. Laparotomy without histology</p> <p>2b. Equivocal histology</p> <p>2c. Colonoscopic report</p> <p>2d. Radiological examination suggestive of intestinal or colonic CD with obstructive or fistulous features</p> <p>Either:</p> <p>1. Radiological findings (segmental distribution, deep ulcers, cobblestoning, fistulae)</p> <p>OR (2 of these criteria):</p> <p>2. Macroscopic appearance at endoscopy compatible with CD (patchy penetrating lesions, discrete ulcerations, fissuring, strictures)</p> <p>3. Microscopic features (edema, cytoplasmic mucin, granulomas, lymphoid aggregates)</p> <p>4. Fistulae in ileum, colon, or rectum</p> <p>2 of 5 criteria below:</p> <p>1. Clinical history: abdominal pain, weight loss, fatigue, rectal bleeding</p> <p>2. Endoscopic findings: cobblestoning, linear ulceration, skip areas, perianal disease</p> <p>3. Radiological findings of stricture, fistula, mucosal cobblestoning, or ulceration</p> <p>4. Macroscopic appearance of bowel wall induration, creeping fat, or mesenteric lymphadenopathy or ulceration</p> <p>5. Histological finding of transmural inflammation or granulomas</p> <p>Histologically confirmed discontinuous chronic inflammation, confirmed and supported by clinical, biochemical, and radiological evidence of CD</p>	<p>1. Probable and possible cases also defined for UC</p> <p>2. Ulcerative proctitis defined as disease limited to rectum</p> <p>3. IC not defined</p> <p>4. No definitions of endoscopic or histological morphology of CD</p> <p>1. Carefully describes endoscopic and histological abnormalities</p> <p>2. Aside from granulomas, many histological abnormalities are nonspecific for CD</p> <p>1. "Backwash ileitis" allowable in patients with UC</p> <p>2. Other causes for colitis (infection, ischemia) excluded</p> <p>IC defined as continuous endoscopic disease in setting of discontinuous microscopic disease, or inflammation extending beyond muscularis mucosa</p>
(16)	Children (age <15 y)	<p>1. Continuous histological inflammation limited to colon, extending proximally from involved rectum</p> <p>2. Histological inflammation not extending past muscularis mucosa</p>		
(13)	Children and adults	<p>1. Definite UC: At least 2 studies separated by 6 mo</p> <p>1a. Diffusely friable or granular mucosa on endoscopy</p> <p>1b. Continuous involvement as observed by endoscopy or barium x-ray</p> <p>2. Potential cases: Only 1 diagnostic study, or 2 diagnostic studies separated by <6 mo</p>		
(6)	Children (<18 y)	<p>1. Continuous histological inflammation limited to colon, extending proximally from involved rectum</p> <p>2. Histological inflammation not extending past muscularis mucosa</p>		

where a paucity of literature was available, consensus among the experts was achieved by nominal group technique.

It was also agreed by consensus that infants and children under age 2 years with IBD may represent a different population of patients. Thus, the definitions and classification scheme below may not necessarily apply to these young children.

OVERVIEW OF PUBLISHED EPIDEMIOLOGICAL STUDIES OF UC, CD, AND IC

There are more than 40 published epidemiological series on the incidence and prevalence of UC and CD in children and adults. In Table 1, a small subset of these studies is summarized. In general, the definition of UC is more consistent among epidemiological studies than the definition of CD (6,8–21). The epidemiological diagnosis of UC relies on the presence of the following:

1. Bloody diarrhea with negative stool cultures
2. Endoscopic evidence of diffuse continuous mucosal inflammation involving the rectum and extending to a point more proximal in the colon

The presence of “backwash ileitis” does not exclude a diagnosis of UC; however, the term “backwash ileitis” is often not well defined in these studies.

In contrast, epidemiological definitions of CD are more variable and reflect the heterogeneity and variable distribution of the disease. The diagnosis of CD is straightforward if there is clear radiographic and/or endoscopic evidence of small bowel involvement, multiple noncaseating granulomas on endoscopic mucosal biopsy, or evidence of severe perianal disease (fissures, fistulae). However, when CD is limited to the colon and granulomas are not present on biopsies, the diagnosis is more difficult. The differentiation of Crohn colitis from UC is then established by the endoscopist, based on observation (at the time of initial colonoscopy) of focal discontinuous inflammation, deep fissuring ulcers, and aphthous lesions superimposed on a background of normal colonic mucosa (21). Figures 1A and B demonstrate the differences in the endoscopic appearance between UC and CD of the colon.

In epidemiological studies before 1990, the diagnosis of UC or CD was established by a combination of clinical features, radiography, and pathological features at the time of bowel resection. In contrast, recent studies have placed less emphasis on radiographic studies such as barium enema, but instead emphasize the importance of histology to confirm endoscopic findings. For example, in the study of Kugathasan et al, the prevalence of focal disease or inflammation extending below the muscularis mucosa on a colonic biopsy in a patient with colitis changed a patient’s diagnosis from UC to IC (6). In

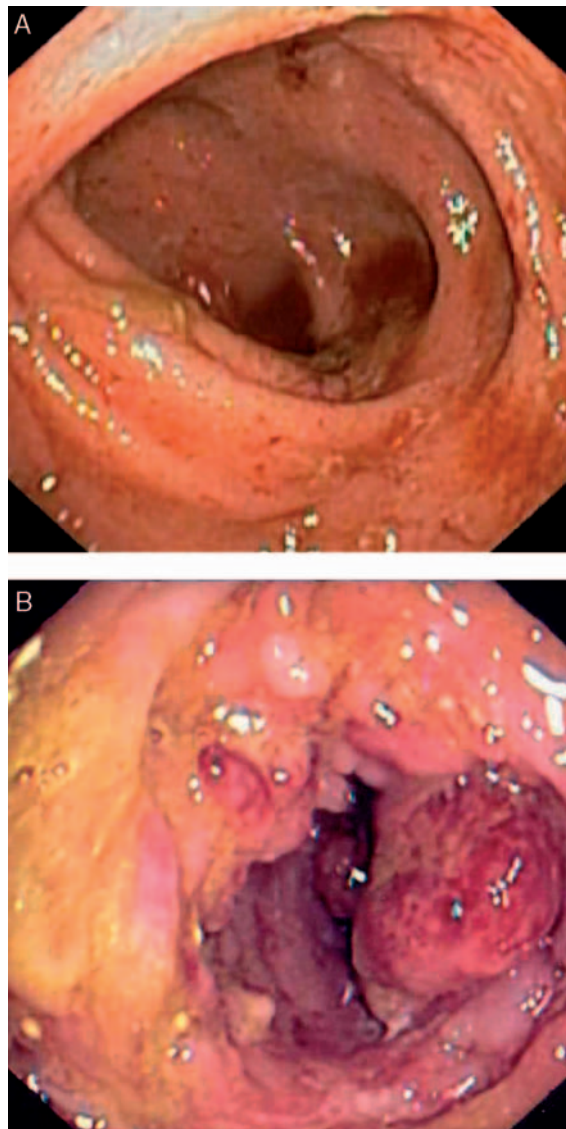


FIG. 1. Endoscopic features of IBD. A, UC: diffuse erythema, friability, granularity, and loss of vascular pattern in the colon. B, Colonic CD: deep fissuring ulcers and “cobblestoned” mucosa are present.

another study by Joosens et al, a patient was not classified as having UC if there was any microscopic inflammation of the ileum. In these studies the exact criteria for the histological interpretations of the biopsies were not well established or standardized, and biopsies were read by different pathologists (22). The result of relying too much on histological interpretation, without appropriately integrating clinical and gross endoscopic findings, is that patients with UC may be inappropriately classified as CD on the basis of nonspecific mucosal inflammatory changes. Conversely, if an endoscopist relies solely on the visual morphology of the colon without appropriate

tissue sampling, there is a risk of failing to identify granulomatous inflammation that would change the diagnosis from UC to CD.

DISTINGUISHING ACUTE SELF-LIMITED COLITIS FROM IBD IN PATIENTS WITH ACUTE HEMORRHAGIC DIARRHEA

Patients with infectious colitis, UC, and Crohn colitis may present with abdominal pain and bloody diarrhea. The primary findings used to differentiate infection from IBD are stool cultures and duration of diarrhea. Patients with no identified pathogen and/or an illness duration of >2 weeks are likely to have IBD. Pathogens typically tested for include *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Escherichia coli*, and *Clostridium difficile*. If indicated, analysis may also be performed for *Amoeba* and *Mycobacterium tuberculosis*. Unfortunately, the sensitivity of stool cultures in acute diarrhea only ranges from 40% to 80%. In addition, an infectious agent such as *Campylobacter* or *Clostridium difficile* may trigger an exacerbation of UC. To add further confusion, a small number of documented cases of infectious colitis last longer than 30 days (23,24).

Because both criteria (culture results and duration of illness) may be misleading, investigators have examined the utility of early colonoscopy with biopsy in the differentiation of acute self-limited colitis (ASLC) from IBD. Mantzaris et al performed colonoscopy in 114 adults with acute colitis of <5 days' duration to determine whether colonoscopy could successfully distinguish between infectious colitis and IBD. All of the patients were studied clinically and had serial flexible sigmoidoscopies at 1, 3, 6, and 18 to 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; of these, only 35 patients (52%) had positive cultures for infectious pathogens (25). The other 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 ASLC had a significantly higher prevalence of patchy erythema and microapthoid ulcerations.

Although ASLC and IBD may look similar to the endoscopist, histology is useful in distinguishing IBD from ASLC. Multiple biopsy studies in adult patients with new-onset UC have consistently shown that involvement by IBD can be differentiated from causes of ASLC such as infection, even early in the course of the disease. The histological features present in UC but rarely, if ever, seen in ASLC are crypt architectural distortion (including irregular crypt shape or placement, branching, atrophy, or surface villiform change), basal lymphoplasmacytosis,

and crypt Paneth cell metaplasia in left colonic biopsies (Fig. 2a and 2b) (24,26–28). In the study by Mantzaris et al, for example, histological features that identified UC and not ASLC included basal plasmacytosis, basal lymphoid aggregates, and crypt branching (25). Nostrant et al prospectively studied 168 consecutive patients with bloody diarrhea (48 with ASLC, 36 with first episode of UC, 84 with recurrent UC) (24). Biopsies were blindly scored as diagnostic of ASLC, active UC, quiescent UC, focal cryptitis, or suspicious of ASLC. Although endoscopic visual appearance did not reliably distinguish between ASLC and UC, all cases of ASLC were scored as diagnostic of or suspicious of ASLC or focal cryptitis, and all biopsies of UC were correctly diagnosed as active or quiescent UC. Crypt distortion and basal plasmacytosis

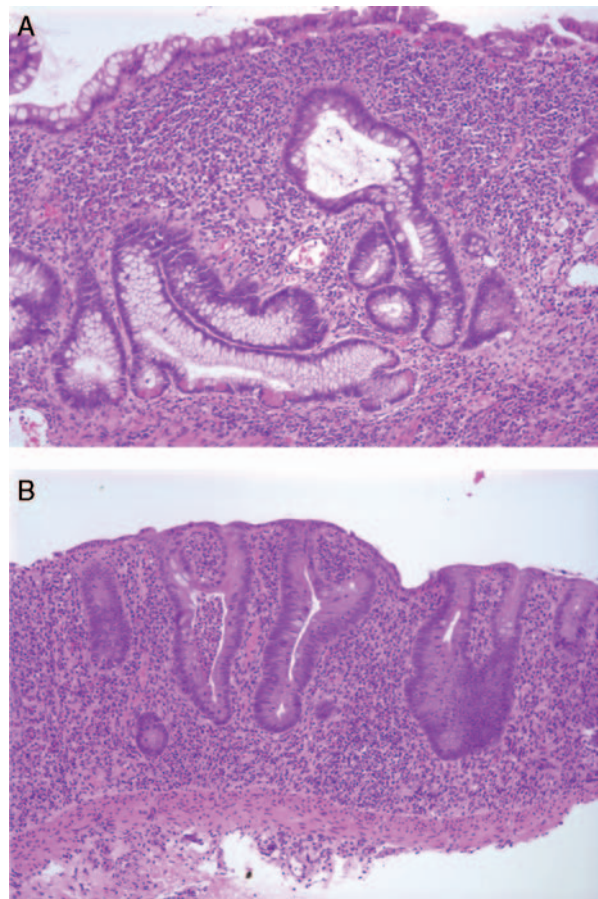


FIG. 2. Histological features useful in differentiating chronic IBD from ASLC. A, Colectomy specimen from 15-year-old boy with history of colitis for several years. There is extensive crypt distortion with branching, and Paneth cell metaplasia (hematoxylin & eosin, original magnification $\times 100$). B, Colonic biopsy from 10-year-old boy with several months' history of bloody stools. Dense lymphoplasmacytic infiltrate pervades the lamina propria, especially in the deep mucosa, lifting the base of the crypts from the muscularis mucosae. Note the presence of a crypt abscess (hematoxylin & eosin, original magnification $\times 100$).

were consistently absent from cases of ASLC. Surawicz et al performed a blinded retrospective study in adults by examining rectal biopsies in 52 patients with ASLC, 51 patients with new-onset (<3 months) UC, and 30 patients with chronic IBD. The authors showed that chronic changes were reliably present in most patients with IBD as early as 7 days after the onset of symptoms; in contrast, branched glands were present in only 3 of 37 patients with ASLC, and no patient with ASLC had evidence of basal lymphoid aggregates (29). Another study investigated 209 consecutive biopsies from 38 patients with confirmed UC, 12 with CD, and 105 with other colitides for a variety of histological parameters. A combination of 3 parameters (increased lamina propria plasma cells, crypt distortion, and crypt atrophy) had 94% sensitivity and 96% specificity in distinguishing IBD from other colitides (30). Because these studies were performed in the era before routine testing for enterohemorrhagic *E coli* and *C difficile* toxins A and B, they may have underestimated the prevalence of infectious colitis infection. Despite this limitation, the above data suggest that in patients with acute colitis and negative cultures, colonoscopy with biopsy within 5 to 7 days of symptom onset can successfully differentiate between ASLC and IBD in adults.

Biopsy studies of pediatric patients with new-onset UC have reached similar conclusions, but have also disclosed important distinctions. Most notably, the initial colonic or rectal biopsies from a significant minority (10%–34%) of pediatric patients ultimately shown to have UC lacked architectural distortion or other histological features of chronic colitis (30–35). In retrospect, many of these patients were initially suspected of having ASLC on the basis of subtle or absent features of chronicity. The reasons for these differences are unclear. It has been proposed that pediatric patients may have a shorter duration of symptoms before their initial diagnostic procedure than do adults, resulting in less established histological features of chronicity. Alternatively, the time of progression to classical histological “chronic colitis” may simply be longer in children than in adults.

Although colonic and ileal biopsies of patients with CD share many of the same features of chronic colitis described above, mucosal lesions in Crohn colitis (particularly early in the disease course) can be patchy and show subtle or absent features of chronicity. The earliest discernable lesion in CD may consist of a focus of active colitis associated with a lymphoid aggregate, corresponding to the endoscopic aphthous erosion.

Focal active colitis (FAC) is described as a hallmark of some types of ASLC as well as an aspect of idiopathic inflammatory bowel disease. However, FAC must be precisely defined and distinguished from iatrogenic changes to be diagnosed reproducibly and, therefore, be useful in histological and clinicopathological studies. Agents and preparations used to cleanse the colon before

endoscopy may produce mucosal lesions. Sodium phosphate preparations (and, to a lesser extent, magnesium citrate) may produce aphthous ulcers, detected predominantly in the rectosigmoid against a background of otherwise unremarkable mucosa (Fig. 3A). Such discrete small ulcers are not rare, with a reported prevalence of 6% to 24% in recent series (36–39). At histological examination the correlate of the aphthous ulcer is either an erosion overlying a lymphoid aggregate or a focal, typically superficial, ischemic-type

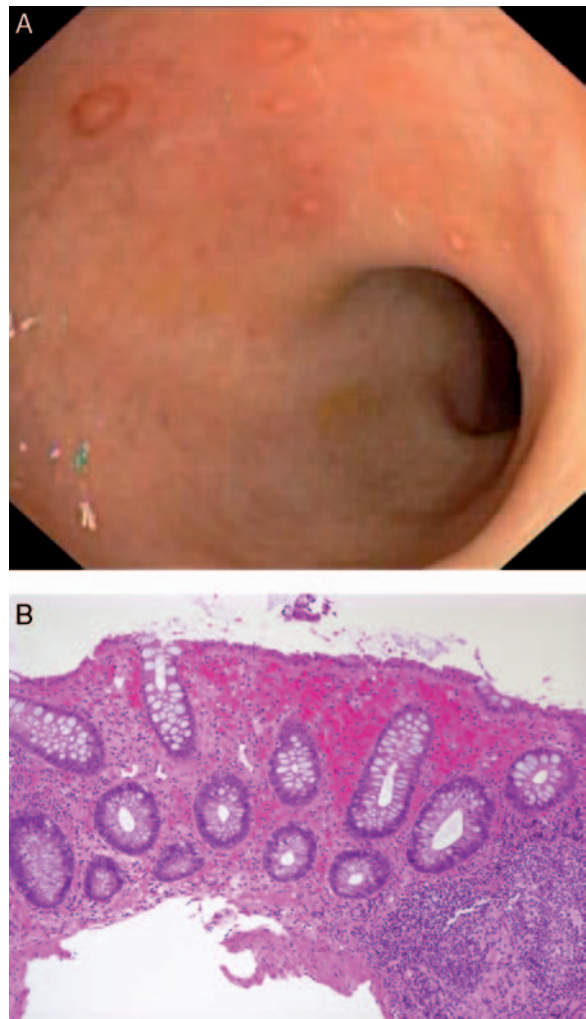


FIG. 3. Colonic inflammation as a result of phosphosoda preparations. A, Endoscopic appearance of colonic inflammation occurring due to use of phosphosoda preparations. There are small focal aphthae in the rectosigmoid colon, with an otherwise normal background. B, Histological features of phosphate enema effect. There is focal mucin depletion of the surface epithelium, with a mild inflammatory infiltrate and hemorrhage, essentially limited to the superficial portion of the mucosa. No significant inflammation of the crypts is present (hematoxylin & eosin, original magnification $\times 100$).

lesion characterized by mucin-depleted crypts, modest active inflammation, and fibrinous exudates (36). In a pediatric patient presenting with diarrhea, hematochezia, and/or abdominal pain, these findings invoke the differential diagnosis of infectious colitis, drug-related (eg, nonsteroidal anti-inflammatory drug) injury, and IBD, especially CD. Integration of all of the clinical data plus recognition of the possible iatrogenic origin of aphthous lesions should result in correct categorization of the findings.

Oral sodium phosphate preparations may also induce increased epithelial cell proliferation and mild abnormalities at the base of crypts (Fig. 3B) (37,38,40). The crypt injury consists of apoptosis and a modest infiltrate of neutrophils and/or eosinophils (mild basal cryptitis) that is not accompanied by crypt destruction (ie, crypt abscess formation), increased mononuclear inflammation in the adjacent lamina propria, or crypt architectural distortion. Therefore, such minimal deviations from normal should be interpreted with circumspection and categorized as nonspecific in nature (particularly if the type of bowel preparation is unknown) rather than as an unequivocally disease-related FAC with all of the implications inherent in the latter diagnosis.

Compared to the findings just described, FAC that is more likely to be caused by disease is characterized by minimal apoptosis and more florid cryptitis (with or without crypt abscesses) that is surrounded by an increased concentration of lymphocytes and macrophages (possibly with mucin granulomas) in the adjacent lamina propria. The predictive value of true FAC for the development or recognition of CD has recently been examined. In a cohort of 29 pediatric patients with FAC, 8 (28%) developed CD. Most of the other patients had either infectious colitis or remained idiopathic (41).

It is recognized that the biopsy diagnosis of chronic colitis and ileitis is subject to interobserver variability and subjective error. Because some of the critical histological features are relatively subtle, this variability is related in part to the level of the pathologist's experience with GI biopsy diagnosis (42). Accuracy of diagnosis may be improved by examination of multiple biopsies, particularly for the diagnosis of CD (43).

Conclusions

1. During the endoscopic evaluation of a child with suspected IBD, it is suggested that random biopsies be obtained from the terminal ileum and each segment of the colon (cecum, ascending, transverse, descending, sigmoid, rectum). Biopsies from each location should be placed in separate specimen containers, with the location of the biopsy clearly labeled. Descriptions of the endoscopic appearance of the bowel in the regions where the biopsies are

taken should be provided to the pathologist. (Evidence level D)

2. Histological features that are seen in IBD but not ASLC include crypt architectural distortion, basal lymphoplasmacytosis, and Paneth cell metaplasia in the left colon. These features may not necessarily be seen early in the course of IBD in children. (Evidence level B)
3. Children with IBD may initially present with nonspecific histological features of FAC. In a patient with FAC the clinician must determine whether the cause of the inflammation is ASLC, bowel preparation artifact, or early IBD. (Evidence level B)

DIAGNOSIS AND CLASSIFICATION OF UC

The diagnosis of classic UC is established by colonoscopy in a patient with typical clinical symptoms, in whom enteric infections have been excluded (Table 2). Rectal bleeding occurs in 83% to 95% of patients with UC (as opposed to 40% of patients with CD). Abdominal pain around the time of defecation accompanies rectal bleeding in moderate to severe colitis. It is unusual for diarrhea to be present without blood in UC. Other clinical symptoms may include weight loss, fatigue, skin manifestations (pyoderma gangrenosum, erythema nodosum), but none of these distinguish UC from CD. In classic UC there is diffuse continuous inflammation extending from the rectum proximally. The endoscopic findings include granularity (sandpaper appearance to the mucosa), friability (bleeding of the mucosa when touched by the

TABLE 2. Diagnosis of classic UC in children

Clinical features—symptoms should be present for at least 2 wk
Gross or occult rectal bleeding
Diarrhea
Abdominal pain with or around time of defecation
Exclusion of appropriate enteric pathogens (including <i>Salmonella</i> , <i>Shigella</i> , <i>Yersinia</i> , <i>Campylobacter</i> , <i>E coli</i> 0157:H7, <i>C difficile</i>) by stool analysis
Endoscopic features
Diffuse and continuous inflammation beginning in rectum and extending proximally to a variable extent; features of inflammation may include the following:
Granularity (rough, “sandpaper” appearance to mucosa)
Loss of vascular pattern
Friability (contact hemorrhage—mucosa bleeds when touched by endoscope)
Small superficial ulcers in a background of diffuse inflammation
Mucopurulent exudates
Line of demarcation—an abrupt transition between abnormal and normal colon in a patient whose colitis does not involve entire colon
Histological features—features of chronicity must be present for a definitive histological diagnosis of IBD
Activity: cryptitis, crypt abscesses
Chronicity: mucin depletion, crypt distortion, crypt branching, crypt atrophy, basal lymphoplasmacytosis, villous transformation of mucosal surface

TABLE 3. *Histologic features helpful in distinguishing UC from CD*

	Typical/definite	Less common but compatible (or needs further study)	Incompatible
UC	Chronic or chronic active colitis (crypt architectural distortion, basal lymphoplasmacytosis, distal Paneth cell metaplasia) Inflammation limited to mucosa Continuous involvement, including rectum No extracolonic involvement	Deeper or transmural inflammation (in fulminant colitis) Discontinuous inflammation in cecum or appendix Absent or subtle features if chronic colitis early in disease course Backwash ileitis Duodenitis or gastritis not typical of CD	True (nonpericrypt) granulomas Ileal or small intestinal involvement not consistent with backwash ileitis Transmural lymphoid aggregates Perianal granulomatous inflammation within skin tags
CD	Chronic or chronic active ileitis or colitis, (colonic findings similar to UC but commonly patchy)– ileal findings include active ileitis, crypt distortion, pyloric metaplasia) Granulomas (nonpericrypt) Discontinuous inflammation with intervening zones of normal bowel Fissuring ulceration, stricture and fistula formation	Inflammation limited to mucosa	None

endoscope), and small superficial ulcers superimposed on a background of colonic inflammation. There should be no evidence of discontinuous inflammation, and the endoscopic findings should be uniform (19,20).

During endoscopy, UC is typically classified into proctitis (disease limited to the distal 15 cm of colon past the anal verge), left-sided disease (disease extending from the rectum to a point distal to the splenic flexure), subtotal colitis (disease extending from the rectum to a point proximal to the splenic flexure, but not involving the whole colon), and pancolitis (disease extending from rectum to cecum and involving the whole colon). Most epidemiological studies do not differentiate between subtotal colitis and pancolitis, and the Working Group of the World Congress of Gastroenterology recently recommended 3 subgroups: ulcerative proctitis (E1), left-sided UC (E2), and extensive UC (E3, which includes both subtotal colitis and pancolitis, or any UC proximal to the splenic flexure) (7). In left-sided disease or proctitis, the endoscopist will often identify a clear transition between normal and abnormal mucosa (line of demarcation) somewhere in the colon. Studies in children suggest that in approximately 80% of patients with UC, inflammation extends proximal to the splenic flexure or involves the whole colon (ie, >80% of children have extensive UC) (6,11,16).

If biopsies are obtained at the time of initial presentation and before treatment, then the degree of histological inflammation should be uniform throughout. In classic UC histological features of both chronic inflammation (eg, crypt atrophy, crypt distortion, basal plasmacytosis, basal lymphoid aggregates) and active inflammation (cryptitis, crypt abscess) should be present in all biopsies (32,35). Histological features useful in distinguishing UC from CD are outlined in Table 3.

A number of nonclassic clinical, endoscopic, and histological findings may be present in a child presenting with UC (Table 4). These findings include backwash ileitis, gastritis, periappendiceal inflammation, patchiness, and rectal sparing. The clinical significance of each of these findings is reviewed below (32,33,35).

“NONCLASSIC” FEATURES SEEN IN PATIENTS WITH UC

Backwash Ileitis

Backwash ileitis is a term used originally 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, but the ileitis in UC may

TABLE 4. *Nonclassic findings at presentation in patients with UC that do not exclude diagnosis of UC*

Clinical
Small anal fissures or skin tags (<5 mm)
Oral ulcers
Growth impairment
Endoscopic
Gastritis without aphthae
Backwash ileitis–ileal erythema without linear ulceration
Periappendiceal inflammation in a patient without pancolitis
Rectal inflammation less severe than in more proximal colon (relative rectal sparing)
Histological
Microscopic ileitis without granuloma
Microscopic gastritis without granuloma
Relative rectal sparing (histological inflammation less severe in rectum)
Patchiness (normal colonic mucosa between 2 areas of colonic inflammation)

TABLE 5. Studies of the prevalence of backwash ileitis in UC

Ref	Patients	Synopsis of study	Frequency of ileitis
(45)	590 consecutive patients with pathologically confirmed UC (476 pancolitis, 114 left-sided colitis) who have had colectomy and restorative surgery	Designed to assess backwash ileitis as a risk factor for colorectal cancer; backwash ileitis defined as "inflammation over minimum of 5 cm of ileum"	107 of 590 (18%) 107 of 476 with pancolitis: (22%) 0 of 114 with left-sided UC
(47)	18 children newly presenting with UC	Designed to compare MRI with ileoscopy and biopsy	7 of 18 (39%) erythema; no erosions or ulcers; associated microscopic nonspecific inflammation
(46)	151 pediatric patients (≤ 21 y; mean 18 y) undergoing IPAA	Analysis of predictors of poor outcome following IPAA; perioperative terminal ileitis 1 of variables analyses (was not a predictor)	16 of 109 patients with confirmed UC in 5-y follow-up (15%) (16 of 76 [22%] with pancolitis)
(49)	200 consecutive patients with UC undergoing ileoproctocolectomy and IPAA	Evaluation of nature and extent of inflammatory changes in resected portion of terminal ileum	Inflammatory changes in ileum in 34 of 200 (17%) patients

IPAA indicates ileoanal pouch anal anastomosis.

also represent primary ileal mucosal inflammation (44). The prevalence of backwash ileitis in both children and adults has been evaluated in several studies (Table 5). The most comprehensive study in adults was performed by Heuschen et al, who evaluated 590 adults with UC undergoing colonic resection. Although 107 of 476 patients with pancolitis (22%) had evidence of backwash at colectomy, 0 of 114 patients with left-sided UC had evidence of backwash (45). The prevalence of backwash is similar in children. In 1 study evaluating the success of ileoanal pouch surgery in children, the prevalence of backwash ileitis, defined as mild mixed inflammatory infiltrate of the lamina propria without crypt distortion, atrophy, or epithelial changes and contiguous with active inflammation in the colon, did not increase the risk of pouch failure (46).

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 (44,45,47). At endoscopy a patient with backwash ileitis has a normal ileocecal valve without signs of stricture, stenosis, or ulceration. Ileal erythema and granularity are diffuse, and usually extend for only a few centimeters (usually <10 cm) proximal to the ileocecal valve. In backwash ileitis normal lymphoid nodules may be present, but no linear ulcerations, deep fissures, or areas of cobblestoning are seen.

The histological features of backwash ileitis, and what specific features differentiate this entity from CD of the ileum, are unclear. Koukoulis et al detected gastric pyloric gland intestinal metaplasia in 10 of 45 terminal ileum biopsies from adult patients with CD and suggested that it was a useful diagnostic feature (48). In a recent study Haskell and colleagues found a 17% (34 of 200 patients) prevalence of inflammation in the terminal ileum of ileocolectomy specimens from patients

with UC. These changes were generally mild, consisting of villous atrophy, increased mononuclear cells in the lamina propria, and scattered crypt abscesses. Of these 34 patients, 32 had pancolitis, but in 2 patients colonic inflammation was subtotal or left sided (49).

Some investigators have automatically classified a patient as having CD or IC if there is histological inflammation on an ileal biopsy (3,22). Based on the data presented, the conclusion of the working group was that identification of nonspecific or microscopic ileitis in a patient with typical features of UC does not warrant a change of diagnosis, unless there are additional specific features suggesting CD (eg, linear ulcers, cobblestoning, granulomas). Rather, if nonspecific ileitis is identified, then the term "UC with backwash ileitis" is more appropriate.

Additional research is needed on the clinical significance and prognosis of macroscopic and microscopic ileitis in patients with pancolitis. In the meantime, to facilitate communication among different clinicians caring for the patient, as well as to minimize variability in ileitis descriptions, the working group suggested the descriptions of ileitis summarized in Table 6.

Conclusions

1. Ileal inflammation (backwash ileitis) is seen in approximately 25% of adults with UC involving the entire colon (pancolitis). The prevalence of backwash ileitis in children is not known. (*Evidence level C*)
2. Ileal inflammation is rare in UC limited to the left colon. (*Evidence level C*)
3. Features that differentiate Crohn ileitis from backwash ileitis include ulceration and stenosis of the ileocecal valve, cobblestoning or linear ulcerations in the ileum, and granulomatous inflammation on ileal biopsy. (*Evidence level B*)

TABLE 6. *Ileitis: suggested descriptions*

Normal ileum: an ileum that is both macroscopically and microscopically normal, without features of inflammation; lymphoid nodularity of terminal ileal Peyer's patches should be considered a normal finding
Histological backwash ileitis (microscopic inflammation of the ileum): active ileitis (focal or diffuse) with or without features of chronicity identified on histological examination, with an endoscopically normal ileum
Endoscopic and histological backwash ileitis: endoscopic erythema and granularity of terminal ileum, confirmed upon histology with findings of active or chronic ileitis
CD of ileum: linear ulceration, cobblestoning, and narrowing of ileum, often associated with ulceration of ileocecal valve; findings may be demonstrated either by endoscopy of terminal ileum or by barium upper GI with small bowel follow-through contrast study; the histology may be normal (due to focal nature of inflammation) or demonstrate acute and chronic ileitis; presence of noncaseating granulomas on ileal biopsy automatically classifies a patient as having CD of ileum (assuming exclusion of infections causing ileitis)

4. The presence of nonspecific ileal inflammation identified at endoscopy in a patient with pancolitis is not pathognomonic for CD. (*Evidence level B*)

Gastritis in Patients With UC

In addition to colonoscopy, esophagogastroduodenoscopy (EGD) is increasingly being performed as part of the initial evaluation in children with suspected IBD. Though the value of this test is still a topic of debate, ESPGHAN's Porto working group has recommended routine upper endoscopy at initial presentation to aid in the diagnosis of pediatric IBD (1). Esophagogastroduodenoscopy may identify gastric pathology that requires additional medical treatment (eg, omeprazole, sucralfate, immunomodulators) in children with IBD. However, in patients with colitis, endoscopic or histological findings may also raise uncertainty as to whether the patient has CD or UC.

It has been known for almost 20 years that upper GI inflammation is present in 30% of patients with CD and that this inflammation may cause functional abnormalities such as delayed gastric emptying (50–52). More recently, however, it has been demonstrated that adults and children with UC also have gastric inflammation at the time of diagnosis. In 1997 Kaufman reported a case series of 5 children with colitis initially diagnosed as CD on the basis of chronic active gastritis. Subsequent colectomy and clinical follow-up demonstrated that these children actually had UC (53). A number of subsequent prospective studies suggest that the prevalence of inflammation seen in the esophagus, stomach, and duodenum is comparable in both CD and UC (Table 7). However, the performance of routine biopsies of the esophagus, stomach, and duodenum in patients with IBD at initial diagnosis will identify noncaseating granulomas in 12% to 28% of patients, which will establish the formal diagnosis of CD (54–58). In a study by Kundhal et al, 39 children with UC or IC and normal barium small bowel radiographs underwent upper endoscopy. Granulomas were present on antral biopsy in 5 patients (14%), thus changing the diagnosis to CD (55). In a review of duodenal, antral, and esophageal biopsies from children with CD and UC in whom *Helicobacter pylori* infection had been excluded, Tobin noted inflammation in biopsies from these sites in significant numbers of children (58). The methodology included a semiquantitative scoring system to assess the degree of acute or chronic inflammation, crypt destruction, and ulceration. Differentiating features included granulomas and duodenal cryptitis in CD in 40% and 26% of patients, respectively. The published studies suggest that although granulomatous inflammation may be present in any area of the upper GI tract in patients with CD, it is probably more common in the stomach.

Granulomatous inflammation of the stomach may be seen in a number of other conditions besides IBD, including *H pylori* infection, adenocarcinoma of the stomach, and sarcoidosis (59). Assuming other causes

TABLE 7. *Upper endoscopic findings in children with UC and CD*

Ref	Population	Findings in UC	Findings in CD
(57)	CD: N = 40 UC: N = 40	Esophagitis: 13 (32%) Esophageal ulcer: 1 (3%) Nonspecific gastritis: 25 (62.5%) Duodenitis: 6 (15%) Duodenal ulcer: 3 (8%) Upper GI granulomas: 0	Esophagitis: 16 (40%) Esophageal ulcer: 2 (5%) Nonspecific gastritis: 22 (55%) Duodenitis: 9 (23%) Duodenal ulcer: 2 (5%) Upper GI granulomas: 10 (25%)
(54)	CD: N = 81 UC: N = 34	Esophagitis: 4 (12%) Gastritis: 14 (41%) Duodenitis: 5 (15%) Upper GI granulomas: 0	Esophagitis: 20 (25%) Gastritis: 48 (59%) Duodenitis: 22 (27%) Upper GI granulomas: 23 (28%)
(58)	CD: N = 28 UC: N = 14	Esophagitis: 5/10 (50%) Gastritis: 9/13 (69%) Duodenitis: (3/13) Upper GI Granulomas: 0	Esophagitis: 18/25 (72%) Gastritis: 24/26 (92%) Duodenitis: 9/27 (33%) Upper GI granulomas: 10/25 (40%)

of granulomatous inflammation are excluded, children with colitis on colonoscopy and gastric granulomas on upper endoscopy can be classified as having CD.

Both nonspecific gastritis and focally enhanced gastritis may be identified in the gastric biopsies of patients with IBD. Focally enhanced gastritis is defined as a perifoveolar or periglandular mononuclear or neutrophilic infiltrate around gastric crypts (Fig. 4). A prospective study of consecutive adult patients with known CD and UC, with pathologists blinded to clinical information, determined that focally enhanced gastritis was significantly more common in CD than in UC (sensitivity 43%, specificity 90%, positive predictive value 89%, negative predictive value 47%, likelihood ratio 4.43 in patients without *H pylori*) (56). In a retrospective study of 238 children with upper GI biopsies, focal gastritis was present in 5 of 24 (20.8%) patients with UC, but it was more common in CD patients (28 of 43, or 65.1%) compared to 2.3% of controls without IBD and 1 of 39 with *H pylori* (60). Similar results were obtained in an historical cohort study in which patients were classified as having either CD, UC, or IC based on independent examination of colonoscopy photographs and colonoscopy and histopathology reports (κ 0.77–0.81) (55). Focal gastritis was significantly more common in CD than in UC (sensitivity 52%, specificity 79%, positive predictive value 81%, negative predictive value 48%, likelihood ratio 2.43 for CD vs UC or IC, or 6.24 for CD vs UC). Pascasio reviewed 438 consecutive biopsies in children with gastritis looking for specific histopathological parameters, including markers for CD such as focal neutrophilic glandulitis (61). Of these cases, 58 were diagnosed as having CD by colonic biopsy and

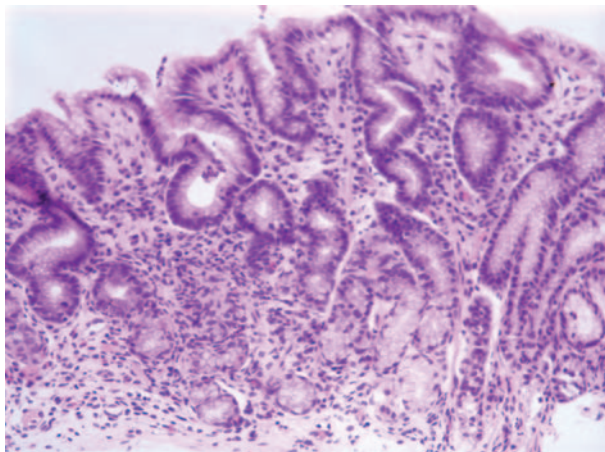


FIG. 4. Histology of focally enhanced gastritis. Eight-year-old with severe active chronic colitis found on colonic biopsies. Upper endoscopy performed at the same time was visually normal. A single focus of mild active gastritis was found in this biopsy from the gastric antrum (hematoxylin & eosin, original magnification $\times 200$).

other standard criteria, 77% of whom were predicted to have CD by gastric biopsy alone. Eosinophils were a significant component in many of the inflammatory foci. In their experience none of the focal glandulitis biopsies had a history of UC (Fig. 5).

Conclusions

1. Endoscopic and histological gastritis are frequently seen in children with both UC and CD. (*Evidence level B*)
2. Granulomatous inflammation identified on endoscopic biopsies from the esophagus, stomach, or duodenum is consistent with a diagnosis of CD

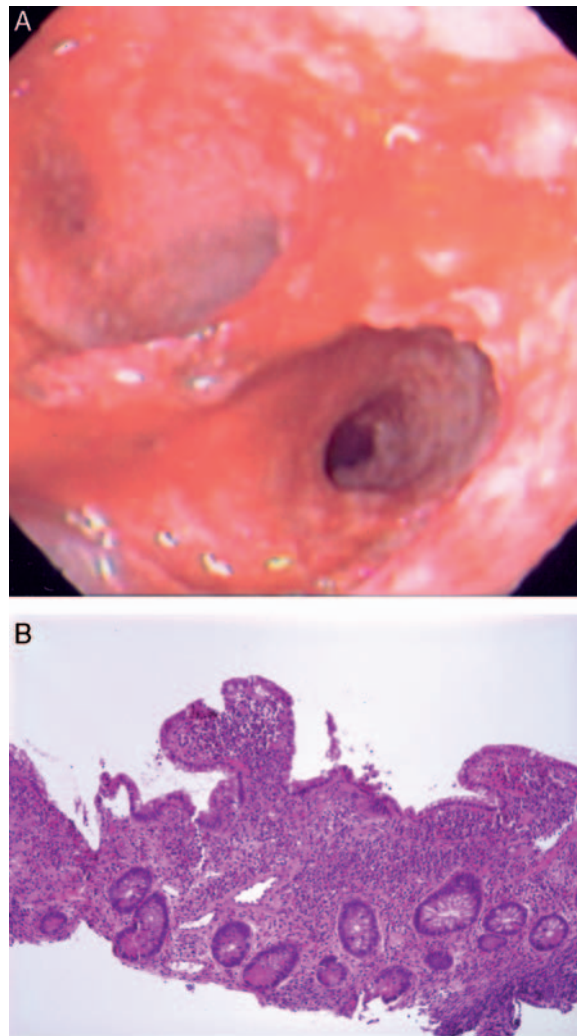


FIG. 5. Endoscopic and histological features of pouchitis. Sixteen-year-old girl with chronic rectal pain following total colectomy for UC. The biopsy from the pouch consists of ileal mucosa characterized by villous blunting, crypt loss, and distortion, and a marked mixed inflammatory infiltrate (hematoxylin & eosin, original magnification $\times 100$).

assuming other causes of granulomatous inflammation (eg, *H pylori* gastritis) have been excluded. (Evidence level B)

3. Focal active gastritis on biopsy is more frequently seen in patients with CD, but does not reliably distinguish between CD and UC. (Evidence level B)

Periappendiceal Inflammation in UC

Ulcerative colitis is classically regarded as a disease with diffuse lesions beginning in the rectum and extending proximally without skip areas. However, patients with UC that does not extend to the cecum may have an inflamed distal colon, a normal proximal colon, and evidence of periappendiceal and cecal inflammation (ie, a “cecal patch”). Several retrospective histopathological studies using colectomy specimens appear to show that appendiceal involvement as a skip lesion of UC can be seen in 15% to 86% of patients undergoing surgery (62–66). More recently, with the use of colonoscopy, D’Haens et al found that 75% of patients had periappendiceal involvement at the time of diagnosis of distal UC, where inflammation was limited to the left side of the colon (67). Several prospective and retrospective studies of colonoscopy and histology have confirmed that periappendiceal inflammation is common in UC (66,68–72). Yang et al reported that involvement at the appendiceal orifice is not a consequence of therapy for extensive UC, but rather a distinctive skip lesion in patients with distal UC (72). Only 1 pediatric study examined appendices from resected intestinal specimens of patients with IBD who failed medical therapy and found that all of the patients in the study (17 UC, 24 CD) had appendiceal involvement (73).

Thus, appendiceal inflammation may occur in both CD and UC. The clinical significance of such inflammation remains unclear. The periappendiceal inflammation in UC is a patch of erythema in the cecum, which can be visualized by colonoscopy around the appendiceal orifice. Histology will demonstrate focal cryptitis, or

more extensive mucosal inflammatory changes. Periappendiceal inflammation is more commonly seen in proctosigmoiditis rather than in more extensive UC involvement. The description of periappendiceal inflammation in UC is largely limited to studies of adults, and prospective studies in children are needed to determine the prevalence and clinical significance of periappendiceal inflammation in UC.

Conclusions

1. Periappendiceal inflammation alone, without more extensive and significant cecal inflammation, is frequently seen in UC. Such inflammation should not be regarded as supportive evidence for the diagnosis of CD. (Evidence level B)

Rectal Sparing and Patchiness

According to traditional dogma, UC is a diffuse continuous disease that begins in the rectum and extends proximally, to some point higher up in the colon, without skip areas. The term “absolute rectal sparing” refers to a rectum with a normal appearance during endoscopy, and with normal rectal histology. Another term sometimes used is “relative rectal sparing,” in which the rectum has inflammation that is less severe than the more proximal colon. The term “patchiness” has been defined as areas of normal mucosa (either endoscopically or histologically) between 2 areas of colonic inflammation. A number of studies challenge the classical notion that rectal sparing and patchiness of inflammation indicate a diagnosis of CD. These studies suggest that rectal sparing and patchiness can be seen in ASLC, new-onset untreated UC in children, and medically treated UC in adults (32,34,35,74).

Recent studies emphasize that colonic inflammation may be less severe in children than in adults with new-onset UC, leading to the appearance of patchiness and relative or absolute rectal sparing (32,35). These studies are summarized in Table 8. Three of these studies

TABLE 8. Studies of patchiness and rectal sparing in children with UC

Ref	Population	Tissue examined	Findings
(33)	12 children with untreated UC, age 5–15 y at time of diagnosis	Rectosigmoid biopsies only	5/12 children had either mild patchy inflammation or normal histology
(35)	53 children (ages 15 mo–17 y) with new-onset disease	Rectosigmoid biopsies, follow-up biopsies, or colonic resections	Decreased rectal inflammation, increased “relative rectal sparing compared to adults”
(32)	73 children (ages 2.5–18 y), 38 adults with new-onset untreated UC	Colonic biopsies	Patchy disease in 21% of children Rectal sparing (absolute 4%, relative 26%) in 30% of children vs. 3% of adults.
(34)	25 children ages 1–17 y, 15 adults	Colonic biopsies	Abnormal rectal histology in all patients; children under age 10 had less crypt branching, cryptitis, and crypt abscesses

compared new-onset UC in children to that in adults, and all 3 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. The precise reason why pediatric histology of new-onset UC differs from that in adults is unclear. Investigators have proposed younger age (<10 years in particular) and shorter duration between symptoms and endoscopy as potential explanations (34). Faubion et al identified a 27% prevalence of rectal sparing in children with IBD and sclerosing cholangitis, suggesting the possibility that rectal sparing may be more common in this subset of patients (75).

The available evidence strongly suggests that UC in children is typically a pancolitis with variable degrees of inflammation on histology. Relative or absolute rectal sparing may occur in a subset of patients with UC however, and does not preclude a UC diagnosis. It is important to note that this conclusion is based on patients who have untreated UC at the time of disease onset. The institution of therapy is known to cause patchy inflammation in adults, and presumably has a similar effect in children (74,76,77).

Conclusions

1. "Patchy colitis" and "relative rectal sparing" are frequently seen in children with new-onset UC, and are also seen in treated colitis. (*Evidence level B*)
2. "Absolute" rectal sparing, with a normal rectum both endoscopically and histologically, is more consistent with CD, but has also been reported in UC. (*Evidence level C*)

TOWARD A MORE PRECISE DEFINITION OF IC

"Indeterminate colitis" has been used for more than 25 years to delineate a group of patients with IBD limited to the colon, but who have features that make the clinician uncertain as to whether the diagnosis is CD

or UC. Unfortunately, most published studies of IC do not specify the precise clinical features that made the investigator uncertain of the diagnosis (Table 9). As more laboratory, radiographic, endoscopic, and histological data are obtained on patients at the time of initial diagnosis, the definitions of IC in research studies have become more complex. For example, when Joosens et al studied the role of serology in IC, they excluded patients with colitis and microscopic ileitis (22). The study of Kugathasan et al used submucosal histological inflammation as a diagnostic criterion for IC, although this criterion has not been validated (6). Thus, each published study of IC is probably describing a different patient population. Silverberg et al, in a report of the Working Party of the 2005 World Congress of Gastroenterology, suggested that the diagnosis of IC be made only after colectomy, and that the term "colonic IBD type unclassified" be used instead in patients who have not undergone colectomy (7). However, the present literature uses the term IC in patients both with and without colectomy, and it is unclear whether the "unclassified" terminology will be adapted.

Epidemiological studies in adults typically cite a prevalence of IC of 5% to 10%, whereas pediatric studies report a prevalence of IC up to 30% (4,11,18,78). From reading the literature, however, it is difficult to ascertain whether there are true biological differences between the 2 populations or whether pediatricians are more likely than adult gastroenterologists to use the term "indeterminate colitis." In addition, studies reporting patients with IC typically do not study patients longitudinally to document what percentage of patients have their diagnosis changed from IC to either UC or CD. In the study by Mamula et al of children diagnosed with IBD before age 6 years, changes in diagnoses occurred more frequently in patients whose diagnoses were made before 1990 (78). These authors' findings could be explained either by the longer duration of follow-up (which allowed the establishment of the correct diagnosis) or by improvements in technical aspects of pediatric colonoscopy during the last

TABLE 9. Definitions of IC in the literature: a partial list

Ref	Definition
(14)	Endoscopy and histopathology divergent with regard to diagnosis of CD or UC
(19)	IBD in which neither criteria for a diagnosis of CD nor a diagnosis of UC were met
(102)	Clinical, radiographic, endoscopic and histological criteria are not sufficient to differentiate between CD and UC
(103)	Patients with colonic disease who cannot be classified into 1 of the 2 major forms of IBD despite an early and accurate clinical workup
(22)	Chronic IBD, without small bowel involvement, in which endoscopy was inconclusive and microscopy indicated patchy and transmucosal architectural distortion and an absence of diagnostic features for either CD or UC; small bowel involvement was excluded by macroscopic and macroscopic inflammation of terminal ileum at ileocolonoscopy and by small bowel barium follow-through studies or enteroclysis
(6)	Inflammatory colitis in setting of histopathological changes indicative of chronic IBD colitis, containing both endoscopic and microscopic features that were consistent with both CD and UC; presence of continuous endoscopic disease in setting of either discontinuous microscopic disease or inflammation extending across muscularis mucosa was included in indeterminate category

decade (which allow better visualization and tissue sampling of the terminal ileum).

The present literature is hampered by the lack of a precise definition of IC, the wide variability in the use of this term, and the paucity of studies reporting long-term follow-up of these patients. It is unclear whether IC patients have a different long-term outcome than UC patients, whether they are at increased risk of pouchitis after surgery, and what percentage of IC patients develops classic features of CD. The primary determinant of whether a patient receives an IC diagnosis may not be the available clinical information, but rather the diagnosing physician's clinical practice style.

Our group did not find enough data in the literature to formally state what specific features should make a patient be classified as having IC. We suggest that clinicians try to avoid overuse of the IC diagnosis. Specifically, physicians should be aware that backwash ileitis, rectal sparing, histological patchiness, periappendiceal inflammation, and gastritis all can be seen in children with UC at the time of diagnosis. Medical therapy of UC before biopsy or resection can also result in attenuation of inflammation, resulting in less severe histological inflammation, focal disease, or even normal biopsies.

A patient may be given a putative diagnosis of IC if he or she has IBD limited to the colon, and clinical features that are inconsistent with the diagnosis of UC (Table 10). If the clinician decides to classify a patient as having IC, then it is suggested the physician clearly state in the medical record the precise piece of clinical data that prompted the use of the IC diagnosis (eg, absolute rectal sparing, small ileal ulcers without strictures or cobblestoning, backwash ileitis in a patient with left-sided disease, growth failure). At some point after diagnosis, patients may benefit from additional endoscopic and radiographic evaluation to determine whether the finding prompting the IC diagnosis has changed or resolved and to attempt to establish a definitive diagnosis of CD or UC.

POUCHITIS: MORPHOLOGICAL FEATURES AND DISTINCTION FROM "CD OF THE POUCH"

In patients with IBD who undergo ileal pouch anal anastomosis, the ileal pouch mucosa is subjected to an

TABLE 10. *Features that suggest IC in patients with colitis*

Colitis with an endoscopically and histologically normal rectum (absolute rectal sparing)
Mild ileitis with features atypical for backwash (eg, ileal aphthae)
Microscopic ileitis seen in a patient with colitis limited to left colon
Severe focal gastritis
Pancolitis with anal fissures or anal tags
Colitis with growth failure

abnormal luminal environment. In addition to stasis of luminal contents, there are changes in the types and numbers of luminal bacteria. Additionally, imbalances or deficiencies of bile salts and short-chain fatty acids may alter mucosal integrity. As an adaptation to this novel environment, the ileal mucosa commonly undergoes a modification consisting of mild villous blunting and slight crypt hyperplasia accompanied by either no increase or a minimal increase in inflammation in the lamina propria (79–82).

In the context of these morphological changes, portions of the ileal mucosa may assume a colon-like appearance with complete loss of villi and crypt hyperplasia. The notion that the inflamed mucosa now resembles that of UC is reinforced by the detection of a mucin histochemical profile similar to that of colonic epithelium and by an inflammatory immunoprofile like that seen in UC (83–86). These findings support the hypothesis that the majority of cases of relapsing or chronic pouchitis develop in transformed, UC-like, mucosa. In addition, the unique environment of the pouch may induce morphological changes that mimic those of CD (83,85–87).

On endoscopic examination, the features of pouchitis vary from mild (mucosal hyperemia and edema, diminished vascular pattern, contact friability) to severe (mucosal hemorrhage, aphthous or larger ulcers, pseudo-membrane formation). The abnormalities may be focal or diffuse, are often more severe in the distal compared to the proximal pouch, and may affect the ileal mucosa proximal to the pouch (83,85,88,89). On microscopic examination, parts or all of the mucosal biopsy specimens obtained from these pouches typically demonstrate partial to complete villous blunting with crypt hyperplasia and increased mononuclear inflammatory cells and eosinophils in the lamina propria. Areas of pyloric gland metaplasia of crypt epithelium may be present. Superimposed activity is characterized by neutrophils in the lamina propria, cryptitis, crypt abscesses, and, in severe cases, erosions or ulcers. The active inflammatory component is more often focal than diffuse. Granulomas of the mucin or foreign body type may also be identified (83,85,89).

A minority of patients develop pathological changes in the pouch that mimic those seen in CD. These abnormalities include perianal abscesses, anal fissures, inflammation of the ileal limb proximal to the pouch, strictures (typically in the proximal pouch), and fistulas. In pouches removed to treat these complications, histological evaluation may document deep or transmural inflammation (83,85,89). Other pouch abnormalities that are related to the surgical procedure itself include ulcers and/or strictures at anastomotic lines, chronic ischemic changes secondary to vascular compromise, and pouch mucosal prolapse changes (crypt hyperplasia, extension of smooth-muscle fibers from the muscularis mucosae into the lamina propria, and superficial erosions with fibrinoinflammatory exudate) (85).

In view of the previous discussion, a diagnosis of CD should be considered only in the following circumstances:

1. Review of the prior colectomy specimen reveals unequivocal features of CD, particularly nonmucin granulomas and deep mural or transmural lymphoid aggregates beneath nonulcerated mucosa. (*Evidence level C*)
2. CD develops in parts of the GI tract distant from the pouch; however, with the recent recognition that upper GI lesions are equally prevalent in pediatric patients with either UC or CD, it is becoming clear that only certain findings (granulomas and, to a lesser degree, focal gastritis/duodenitis) are supportive of a diagnosis of CD. (*Evidence level C*)
3. The presence of nonmucin and nonforeign body-type granulomas within the pouch (83,85,89). One concern about this finding arises if such granulomas are found only in the pouch and not on review of the colectomy specimen and pre- and postcolectomy biopsy specimens from portions of the gut other than the pouch. This scenario raises the possibility that the granulomas have developed as a result of the abnormal luminal environment of the pouch rather than from unrecognized CD. (*Evidence level C*)

ROLE OF IMAGING, SEROLOGY, GENETICS, AND VIDEO CAPSULE ENDOSCOPY IN THE DIFFERENTIATION OF UC FROM CD

It is beyond the scope of this report to fully review the role of radiography, serology, genetics, and capsule endoscopy in the diagnosis of CD and UC. However, the role of barium radiography in differentiating between CD and UC is well established. In CD of the ileum, the terminal ileum, ileocecal valve, and cecum demonstrate various degrees of narrowing, ulceration, and stenosis (90). In contrast, in backwash ileitis the terminal ileum has a granular appearance, the ileocecal valve is wide open, and the cecum is a normal caliber. Thus, the barium radiograph has a well-established role in the diagnosis and localization of small bowel involvement in IBD, and in the differentiation of UC from CD. Some authors have questioned the utility of barium radiography in otherwise healthy patients with a normal ileoscopy (90). In addition, it is unclear how often the barium radiograph changes the diagnosis from UC to CD in a patient with pancolitis and a normal ileum. Nevertheless, it is the opinion of the experts in this working group that a barium radiographic examination of the stomach and small intestine is an important part of the evaluation in a child with new-onset IBD.

The role of other imaging modalities (ultrasound, nuclear medicine, CT, and MRI studies) in the differen-

tiation of CD from UC is less clear. All of these modalities have been used in the diagnosis of patients with IBD, with sensitivity and specificity ranging from good to excellent (47,91–93). Of the above studies, MRI appears to have the greatest potential for distinguishing CD from UC. In 1 study the performance of MRI with polyethylene glycol oral contrast successfully demonstrated wall thickening of the ileum in CD, compared to “mild contrast enhancement” in patients with backwash ileitis. In this same study, using endoscopy as the gold standard, the sensitivity (84%) and specificity (100%) for the detection of Crohn ileitis were also excellent (47). Another study also demonstrated sensitivity and specificity >90% for the detection of CD of the small bowel (47). Although it is unclear whether MRI offers any advantage over conventional barium radiography, the decreased radiation exposure warrants further studies of this modality in the evaluation of the patient with new-onset IBD.

Multiple studies have also been published on the role of serology in CD and UC, in both adults and children. The anti-neutrophil cytoplasmic antibody (pANCA) is identified in approximately 75% of patients with ulcerative colitis, and up to 20% of patients with CD (94–96). ASCA is present in 40% to 80% of patients with CD, seems to preferentially identify CD of the ileum and cecum, and may predict risk of ileocecal resection. Thus, the presence of a positive ASCA antibody in a patient with IBD strongly suggests the diagnosis of CD. However, patients with CD limited to the colon often have an ANCA-positive serotype similar to patients with UC; therefore, a positive ANCA does not differentiate between UC and Crohn colitis.

The value of serology in the patient with IC remains a topic of study. In the largest prospective study of serological markers of IC, 97 patients with IC underwent serological testing and were observed prospectively; of these 97, 31 patients were reclassified as either UC or CD. According to the authors, a positive ASCA and a negative ANCA were associated with the development of CD in 8 of 10 patients. However, the majority of patients with IC remained seronegative for both ASCA and ANCA (22).

Genetic testing cannot as yet reliably differentiate UC from CD of the colon. The *NOD2* genotyping test reliably identifies 25% of patients with CD, but these patients typically have fibrostenosing CD of the terminal ileum and can be readily differentiated from UC by conventional radiographic and endoscopic means (6,97,98). Multiple studies have demonstrated that *NOD2* mutations are generally not seen in individuals with UC.

Video capsule endoscopy is increasingly being used in the detection of obscure small bowel lesions and now has a proven role in the identification of CD of the small intestine. The sensitivity of this technique at identifying small bowel ulceration or stricture appears to be superior

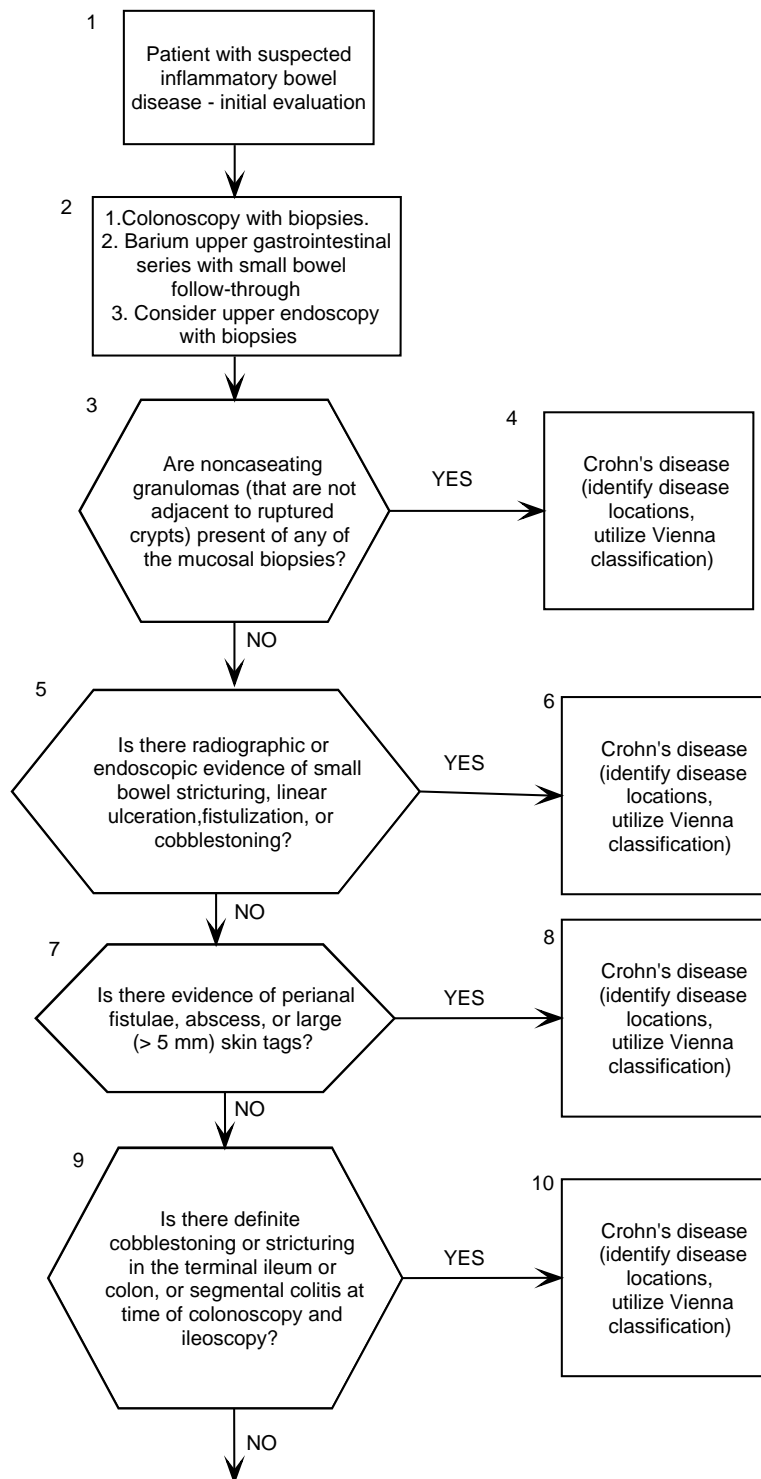


FIG. 6. Algorithm to assist clinicians in differentiating UC from CD. In patients with suspected CD, additional phenotyping may be performed utilizing the Vienna or Montreal classification systems (7,101). The modification of the Vienna classification termed the Montreal Classification system is increasingly being used in the literature (7).

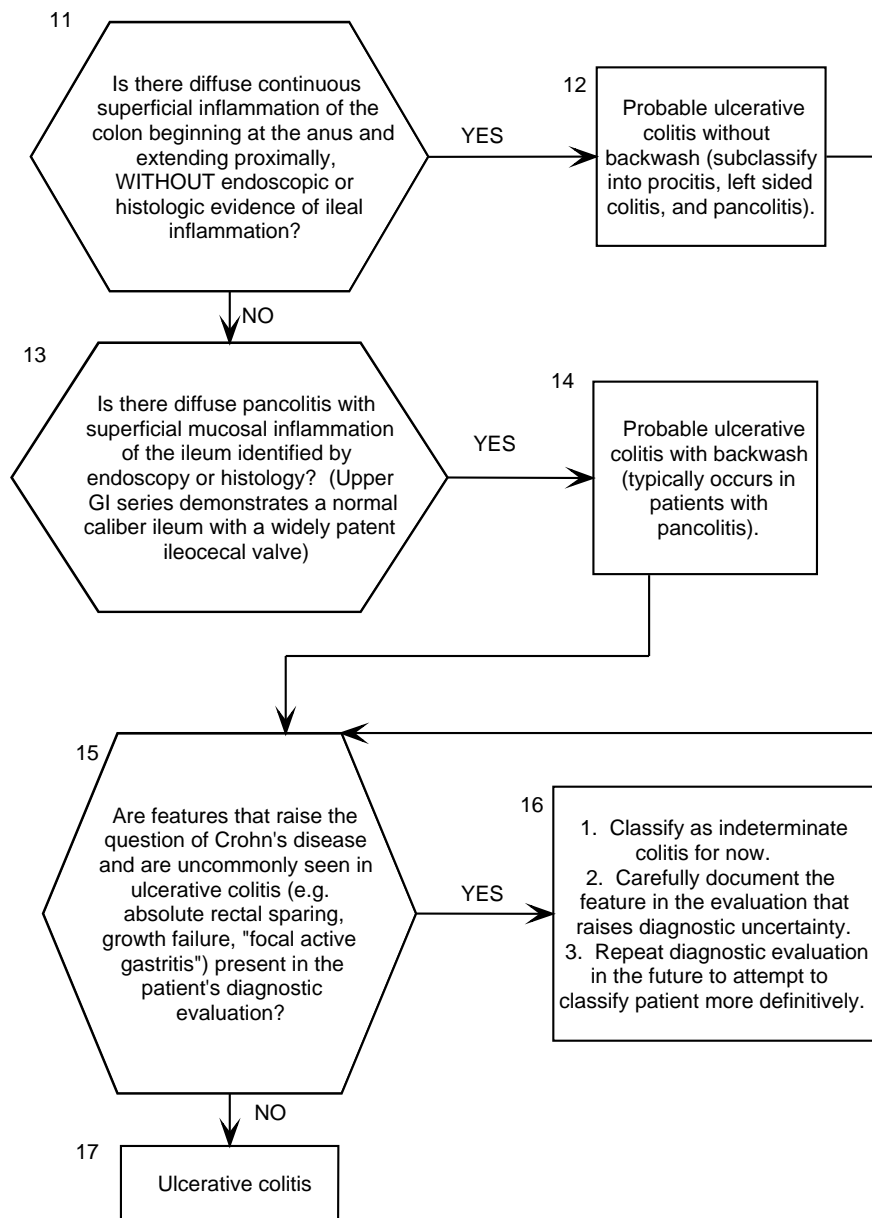


Fig. 6 (continued).

to conventional barium radiography and enteroclysis (99,100). Drawbacks of capsule endoscopy include the cost of the test, as well as the potential risk of capsule impaction in strictured areas of the small bowel. Future studies may determine whether capsule endoscopy should be performed as a routine examination on new-onset patients with colitis and normal contrast studies. At this time, we recommend that this

test be used primarily when CD of the small bowel is strongly suspected but cannot be documented by other modalities.

SUMMARY AND RECOMMENDATIONS

The correct classification of IBD as either CD or UC is essential to conducting proper clinical and epidemiological

Endoscopist's Global assessment		
<input type="checkbox"/> Ulcerative colitis <input type="checkbox"/> Pancolitis <input type="checkbox"/> Subtotal (proximal to splenic flexure) <input type="checkbox"/> Left sided (distal to splenic flexure) <input type="checkbox"/> Proctitis (limited to rectum or distal 15 cm)	<input type="checkbox"/> Crohn's disease <input type="checkbox"/> Small bowel only <input type="checkbox"/> Small bowel and cecum <input type="checkbox"/> Small bowel and colon (past cecum) <input type="checkbox"/> Colon only <input type="checkbox"/> Isolated perianal	<input type="checkbox"/> Indeterminate colitis (State or check reason for this classification) <input type="checkbox"/> Atypical upper tract findings <input type="checkbox"/> Atypical ileal findings <input type="checkbox"/> Discontinuous colitis <input type="checkbox"/> Endoscopic and histologic rectal sparing
Specific Findings	Ulcerative colitis	Crohn's disease
Terminal ileum Intubated <input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Normal <input type="checkbox"/> Erythema <input type="checkbox"/> Granularity <input type="checkbox"/> Surface ulceration	<input type="checkbox"/> Normal <input type="checkbox"/> Linear ulcers <input type="checkbox"/> Cobblestoning <input type="checkbox"/> Stenosis
Ileocecal valve	<input type="checkbox"/> Normal	<input type="checkbox"/> Normal <input type="checkbox"/> Ulcerated <input type="checkbox"/> Stenotic
Cecum / periappendiceal area	<input type="checkbox"/> Normal <input type="checkbox"/> Erythema <input type="checkbox"/> Friability <input type="checkbox"/> Exudate (mucopus) <input type="checkbox"/> Granularity <input type="checkbox"/> Loss of vascular pattern	<input type="checkbox"/> Normal <input type="checkbox"/> Linear / serpiginous ulcers <input type="checkbox"/> Aphthae <input type="checkbox"/> Exudate (mucopus) <input type="checkbox"/> Cobblestoning <input type="checkbox"/> Stenosis/stricture
Ascending colon	<input type="checkbox"/> Normal <input type="checkbox"/> Erythema <input type="checkbox"/> Friability <input type="checkbox"/> Exudate (mucopus) <input type="checkbox"/> Granularity <input type="checkbox"/> Loss of vascular pattern	<input type="checkbox"/> Normal <input type="checkbox"/> Linear / serpiginous ulcers <input type="checkbox"/> Aphthae <input type="checkbox"/> Exudate (mucopus) <input type="checkbox"/> Cobblestoning <input type="checkbox"/> Stenosis/stricture
Transverse colon	<input type="checkbox"/> Normal <input type="checkbox"/> Erythema <input type="checkbox"/> Friability <input type="checkbox"/> Exudate (mucopus) <input type="checkbox"/> Granularity <input type="checkbox"/> Loss of vascular pattern	<input type="checkbox"/> Normal <input type="checkbox"/> Linear / serpiginous ulcers <input type="checkbox"/> Aphthae <input type="checkbox"/> Exudate (mucopus) <input type="checkbox"/> Cobblestoning <input type="checkbox"/> Stenosis/stricture
Descending colon	<input type="checkbox"/> Normal <input type="checkbox"/> Erythema <input type="checkbox"/> Friability <input type="checkbox"/> Exudate (mucopus) <input type="checkbox"/> Granularity <input type="checkbox"/> Loss of vascular pattern	<input type="checkbox"/> Normal <input type="checkbox"/> Linear / serpiginous ulcers <input type="checkbox"/> Aphthae <input type="checkbox"/> Exudate (mucopus) <input type="checkbox"/> Cobblestoning <input type="checkbox"/> Stenosis/stricture
Sigmoid colon	<input type="checkbox"/> Normal <input type="checkbox"/> Erythema <input type="checkbox"/> Friability <input type="checkbox"/> Exudate (mucopus) <input type="checkbox"/> Granularity <input type="checkbox"/> Loss of vascular pattern	<input type="checkbox"/> Normal <input type="checkbox"/> Linear / serpiginous ulcers <input type="checkbox"/> Aphthae <input type="checkbox"/> Exudate (mucopus) <input type="checkbox"/> Cobblestoning <input type="checkbox"/> Stenosis/stricture
Rectum	<input type="checkbox"/> Normal <input type="checkbox"/> Erythema <input type="checkbox"/> Friability <input type="checkbox"/> Exudate (mucopus) <input type="checkbox"/> Granularity <input type="checkbox"/> Loss of vascular pattern	<input type="checkbox"/> Normal <input type="checkbox"/> Linear / serpiginous ulcers <input type="checkbox"/> Aphthae <input type="checkbox"/> Exudate (mucopus) <input type="checkbox"/> Cobblestoning <input type="checkbox"/> Stenosis/stricture
Perianal area	<input type="checkbox"/> Normal <input type="checkbox"/> Small (<5 mm) skin tags	<input type="checkbox"/> Normal <input type="checkbox"/> Small skin tags <input type="checkbox"/> Large (> 5 mm) skin tags <input type="checkbox"/> Perianal fistulae <input type="checkbox"/> Perianal fissures

FIG. 7. Sample report form for colonoscopy in suspected IBD.

studies. Unfortunately, there is a lack of agreement and consensus among experts as to the criteria for diagnosing UC, CD, and IC. Based on the available literature, we propose the algorithm in Fig. 6 as a method to standardize the approach to patients who may be difficult to diagnose. In addition, we propose more accurate documentation of the endoscopic findings in patients undergoing evaluation (Fig. 7). We propose first looking for features that definitely suggest CD, such as granulomas not adjacent to crypts, small bowel involvement, colonic stricturing, cobblestoning, or pronounced perianal disease. If these features are not present in patients with IBD limited to the colon and histological features of chronicity, then the diagnosis is most likely UC.

A patient with UC may also have backwash ileitis (superficial ileal inflammation), gastritis, periappendiceal erythema (cecal patch), histological patchiness, and relative rectal sparing. If superficial ileal inflammation is present in the patient with pancolitis, but barium radiography of the ileum is normal, then that patient should be classified as having UC with backwash ileitis. A patient with features that are highly atypical for UC (eg, ileal apthae or backwash ileitis in a patient with left-sided colitis, growth failure, large oral apthae, or absolute rectal sparing) can be given a provisional diagnosis of IC, and evaluated subsequently (eg, after 1 year, during the next disease exacerbation, before surgery) to determine whether a diagnosis of CD or UC can be made. In re-evaluating a patient, the clinician needs to keep in mind that medical therapy can cause variable healing, and thus result in endoscopic and histological patchiness of disease.

We hope this report will serve as a useful primer on the diagnosis and classification of the patient with new-onset IBD, and will allow the physician who sees IBD less frequently to more easily classify his or her patients as having CD or UC and to use the IC classification less frequently. The reader is also referred to the recent excellent report by the ESPGHAN IBD working group, which outlines a recommended diagnostic evaluation in the patient with suspected IBD (1). Further research should examine, among other areas, the degree of interobserver variation in the diagnosis of UC, CD, and IC; the interobserver agreement between pathologists and endoscopists in their descriptive findings; the ability of upper endoscopic findings to allow physicians to differentiate between CD and UC in IBD involving the colon; radiographic, endoscopic, and histological features that help physicians differentiate between "backwash ileitis" and "Crohn ileitis"; and the role of surrogate laboratory markers (genetics, serology, microbiology) in distinguishing these entities. We realize that this is a rapidly changing field and hope that the ongoing progress in IBD genetics will

allow us to more precisely and definitively subtype our patients.

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APPENDIX

Coding Scheme for Quality of Evidence

Level A: Conclusion based on ≥ 2 controlled studies that compare the prevalence of the pertinent study finding (eg, rectal sparing) in children with the prevalence in adults.

Level B: Conclusion based on a single study that compares the prevalence of the pertinent study finding (eg, rectal sparing) in children with the prevalence in adults.

Level C: Conclusion based on 1 or several observational or cross-sectional studies of the pertinent study finding, either in children or in adults.

Level D: No studies available; recommendation based on expert opinion and consensus of the committee.

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