

Pediatric Inflammatory Bowel Disease: New Insights and Controversies

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Introduction

The category of “inflammatory bowel disease” (IBD) has been traditionally defined as encompassing two entities, ulcerative colitis (UC) and Crohn’s disease (CD). The etiology of these two conditions is as yet unknown; therefore, there is no gold standard for their diagnosis. The pathogenesis of both UC and CD is not yet well defined but involves an interplay of generic susceptibility, abnormalities in the gut lining epithelium, imbalances between beneficial and pathogenic gut bacteria, and host immune response dysregulation (1). Diagnosis is achieved by (1) eliminating known causes of acute, self-limited enteritis and colitis (e.g., infections, allergies, medication-related injury) and (2) recognizing clinical, imaging, endoscopic, and histologic features characteristic of these two conditions. Although the classic forms of pediatric UC and CD are extensively described in the pathology literature, recent advances in imaging techniques, the increasing use of upper gastrointestinal endoscopy and colonoscopy to evaluate these conditions, the use of video capsule endoscopy to directly visualize the entire small intestine, and the implementation of diagnostic procedures early in the course of disease have resulted in the recognition of new findings and deviations from “classic” teachings that may confound the diagnosis of UC and CD and even raise the possibility of other types of IBD. In this presentation, the findings of classic UC and CD in the colon will be reviewed, but the emphasis is on atypical and newly described aspects detected in mucosal biopsies that may cause diagnostic difficulties in pediatric patients.

Histologic Features of Mucosal Colitis

Distinguishing an acute self-limited colitis (ASLC) from IBD is important because of the long-term psychological and medical management aspects of IBD. This distinction may be problematic in some cases for the following reason. The usual cases of ASLC are diagnosed by a combination of clinical, epidemiologic, and/or microbiological findings. Only the unusual cases with a prolonged clinical course, atypical laboratory findings, and/or negative infectious workups eventuate in colonoscopy. Colonic mucosal biopsy specimens from such patients may contain indeterminate findings that are difficult to categorize with certainty. The histologic features of active and chronic colitis in mucosal specimens are summarized below, followed by a discussion of the distinction between ASLC and IBD.

Active colitis

Activity is characteristic of both ASLC and IBD. The features of activity are well known:

- 1) Neutrophils in the lamina propria;
- 2) Cryptitis and crypt abscesses;
- 3) Erosions and ulcers.

Marginated neutrophils (i.e., neutrophils confined to the endothelial layer of small vessels) may be the result of the bowel cleansing process or the colonoscopic procedure itself; it is, therefore, not included as a manifestation of active colitis. These findings may be focal or diffuse; in my opinion, their pattern of distribution cannot reliably be used to distinguish infectious colitis from IBD. Inflammatory pseudomembranes, increased eosinophilia of the lamina propria, and mucin-depleted (“withered”) crypts associated with a relative paucity of neutrophils are findings most suggestive of an ischemic injury or infection with toxin-producing bacteria such as *C. difficile* and enterohemorrhagic *E. coli* (2-6).

Chronic colitis

The histologic features of chronic colitis are summarized below:

- 1) Increased mononuclear cell inflammation in the lamina propria;
- 2) Crypt distortion and atrophy;
- 3) Surface villiform change;
- 4) Basal plasmacytosis in colonic mucosa distal to the cecum;
- 5) Basal lymphoid aggregates;
- 6) Paneth cells identified distal to the transverse colon.

Determination of increased mononuclear cell inflammation in the lamina propria is the most subjective and probably the least reliable criterion of chronic injury. This analysis is hampered by the fact that mononuclear cells are normally more numerous in the right than in the left colon, by variations in section thickness that may give the false impression of increased cellularity, and by the fact that increased mononuclear cell inflammation is typical of the resolving phase of infectious colitides (5,7). Precision in diagnosis is important because the pathologist’s diagnosis of “increased mononuclear inflammation” in colonic mucosa may be translated by clinicians to mean IBD (7). In most cases of established IBD, other features to support chronicity are present, particularly if multiple specimens are submitted. Basal plasmacytosis distal to the cecum is an excellent marker of chronicity but may be absent in the early phase of IBD and may diminish over time in inactive disease (8).

These changes of chronicity, however, are not synonymous with IBD. They may develop with the healing of any severe mucosal injury such as necrotizing enterocolitis of newborn infants or the colitis associated with Hirschsprung’s disease. The diagnosis of IBD, therefore, must be supported by appropriate clinical, imaging, endoscopic, and, in some cases, serologic data. If the pathologist has no information about the patient, it is best to diagnose such specimens descriptively as “findings compatible with healed injury” rather than “chronic inactive colitis” because the latter phrase will typically be interpreted as IBD by clinicians.

Changes of chronicity may be focal or diffuse within a mucosal specimen or among specimens. In addition, finding even a single abnormality among those summarized earlier is sufficient to support a diagnosis of chronic injury. Multiple abnormalities secondary to chronicity may be infrequent in pediatric IBD, particularly in the earlier phases of disease (see later discussion) and/or with limited mucosal sampling (9).

In both ASLC and IBD, inflammatory changes may be focal or diffuse within a mucosal specimen. In IBD, active inflammation is distributed throughout the lamina propria, whereas it tends to be confined to the upper half of the lamina propria in ASLC (7); however, this feature may not be evident if only one specimen is available for diagnosis. As expected, the major discriminator between ASLC and IBD is the presence of unequivocal features of chronicity in initial or follow-up biopsy specimens (3-5,7,10). Once chronicity is established, the clinician can correlate this finding with the remainder of the patient's profile to exclude known causes of chronic injury (such as *Yersinia* infections and certain parasitic diseases) before establishing a diagnosis of IBD.

Artifacts That May Confound the Interpretation of Colonic Mucosal Inflammation

The colonoscope itself may be associated with minor mucosal damage. Since biopsies are obtained as the last procedure of the endoscopy, the colonoscope may have had time to irritate the mucosa, resulting in vascular congestion as well as edema and fresh hemorrhage in the lamina propria. When unaccompanied by epithelial damage or an inflammatory infiltrate, these findings, which are most prevalent in the distal colon, are best interpreted as iatrogenic in origin (2,11,12).

The colonic cleansing procedure may also induce iatrogenic lesions. Oral non-absorbable lavage agents and isotonic saline enemas are gentle and do not injure colonic mucosa; therefore, they are favored for use in infants and young children (13). The cleansing process, however, may be prolonged, resulting in poor compliance and inadequate cleaning. Therefore, a more vigorous but shorter cleansing protocol using sodium phosphate (taken orally and/or as enemas), oral magnesium citrate, and/or bisacodyl enemas and suppositories is often employed, particularly in older children and adolescents. These agents may produce mucosal lesions.

Sodium phosphate preparations (and, to a lesser extent, magnesium citrate) may produce aphthous ulcers with these characteristics:

- 1) Endoscopy: Discrete, small (1-3 mm), sharply defined erosions, surrounded by an erythematous halo. Most frequent in the rectosigmoid. Adjacent mucosa typically unremarkable;
- 2) Histology: Either an erosion overlying a lymphoid follicle or a focal, superficial, ischemic-type lesion with mucin-depleted crypts, modest active inflammation, and fibrinous exudate (14).

The prevalence of this change varies from 6% to 24% in recent clinical series (13-16). In a pediatric patient being evaluated for the cause of diarrhea, the differential diagnosis of these findings includes infectious colitis, drug-related injury (e.g., NSAID's), and low-grade IBD, particularly Crohn's disease. Recognition of the possible iatrogenic origin of the finding plus integration with all clinical data should permit correct categorization.

Another very common effect of oral/enema sodium phosphate preparations is the development, in otherwise unremarkable mucosa, of discrete foci of basally localized neutrophil cryptitis associated with apoptosis and, in some cases, an infiltrate of eosinophils. This constellation of findings is unaccompanied by crypt destruction (crypt abscesses), crypt architectural distortion, or increased mononuclear cell inflammation and macrophages in the surrounding lamina propria (13,15-17).

In the strictest sense, this constellation of findings does represent a "focal active colitis". Given the fact that it is typically iatrogenic in origin, however, I recommend using a more descriptive term such as "non-specific basal cryptitis", with a comment that such changes may be the result of bowel cleansing agents. The reason for this usage is that, based on my experience, the unqualified term "focal active colitis" will be interpreted by clinicians as representing either an infectious colitis or IBD, especially Crohn's disease (7). As discussed by Xin and colleagues (18), focal active colitis that is likely caused by disease is characterized by involvement of a longer length of the crypts by inflammation than in iatrogenic injury, by the development of crypt abscesses, and by an increased concentration of lymphocytes and macrophages (or even mucin granulomas) in the adjacent lamina propria. Some biopsies may contain changes intermediate between typical iatrogenic effect and the classic features of true focal active colitis just described. In this situation, a descriptive diagnosis is again justified to alert the clinician that the differential diagnosis for the histologic findings includes infections, IBD, and bowel prep effect.

Inflammatory Bowel Disease

Accurate categorization of IBD cases as UC and CD has become increasingly important for several reasons:

- 1) Surgery is considered curative for UC but not for CD;
- 2) Patients with UC but not CD are candidates for creation of ileoanal pouches;
- 3) More specific treatments to treat the two conditions are emerging. For example, infliximab (Remicade), a chimeric monoclonal antibody to tumor necrosis factor-alpha has been successful in inducing remission in many patients with therapy-resistant CD. Proper patient selection is crucial because use of infliximab has been associated with a significant risk of serious infections, including reactivation of latent tuberculosis (19).

Clinical features

IBD is common in young patients: about 10% of cases develop before age 15 years and 30% of cases before the age of 25 years (20). It develops more commonly in Caucasians than in other races, and recent data from this country suggest that CD is becoming more common than UC (21). The clinical features of pediatric UC and CD are, in general, similar to those in adults. Features unique to pediatric IBD, however, are delayed puberty and growth failure. The latter is twice as prevalent in CD as in UC, is related more to disease activity than to corticosteroid therapy, and is especially associated with ileal disease (20,22). A family history of IBD is noted in 10% to 30% of patients (21).

Unlike the situation in adults, pediatric patients with certain congenital disorders may present with signs and symptoms that mimic IBD. The major conditions having this presentation include:

- 1) Glycogen storage disease, type Ib: terminal ileitis/colitis; perianal disease (mimics CD);
- 2) Chronic granulomatous disease: chronic active colitis with non-necrotic granulomas (mimics CD);
- 3) Wiskott-Aldrich syndrome: a UC-like colitis (21).

These entities are characterized by immunodeficiencies and impaired processing of infectious agents. In infants and young children with chronic colitis, these conditions should be ruled out; true idiopathic IBD is rare before the age of 2-3 years (21).

The findings of several recent studies also support the notion of an increased risk of IBD in celiac disease, with rates of IBD 3 to 8 times greater than in controls (23). This association suggests that patients not responding to adequate treatment for celiac disease should be evaluated for ileocolitis; conversely, treated IBD patients with persistent diarrhea should raise the possibility of concurrent but unrecognized celiac disease. The various possibilities can be sorted out by clinical, endoscopic, histologic and serologic findings. For example, increased villous intraepithelial lymphocytes are not characteristic of the duodenitis associated with IBD; their presence should at least raise the possibility of undiagnosed celiac disease (23,24).

Natural history

Pediatric IBD is characterized by exacerbations and remissions, but the natural histories of UC and CD are somewhat different (22). At first presentation, UC is characterized by more extensive endoscopic and histologic disease in children than adults. In recent series, pancolitis has been documented 50% or more of children compared to 8% to 20% of adults; conversely, proctitis or localized left-sided disease is present in approximately 25% of children but in up to half of adults at initial evaluation (20-22,25-27). Over time, progression to more extensive disease, including pancolitis, occurs in 50% to 70% of children with initially limited disease (compared to 10% to 30% of adults), especially those with an early age of onset and/or severe disease (20,28-31). At least one relapse will have

been documented in about 90% of pediatric UC patients after 10 years of follow-up, and approximately one-third will have had a colectomy, chiefly because of unresponsiveness to medical therapy, prepubertal growth failure or fulminant colitis (“toxic megacolon”) (20). Since by current definition UC is a disease confined to the colon, proctocolectomy is curative, and the patients are excellent candidates for creation of an ileoanal pouch.

Pediatric CD first presents as small bowel disease in 40% of patients, as ileocolitis in 30%, and colitis in 30%. Of interest, CD tends to present in the colon in very young patients, with ileal disease rarely documented before the age of 8 to 10 years. Ileal disease then increases in prevalence throughout adolescence. The reason for this finding is unclear, but may be related to immunologic changes associated with lymphoid follicle development and enlargement (Peyer’s patches) in the second decade of life (32).

Early surgery is much more common than in UC: up to 50% of pediatric patients with CD will have surgery for complications of the disease within 5 years of diagnosis and up to 90% will have an operation within 15 years (22). Surgery is performed for reasons like those for UC and for additional CD-related indications including treatment of intestinal fistulas and abscesses, gut obstruction, and intractable perianal disease (20,33). Since CD is a condition that may involve the entire gastrointestinal tract, surgery is limited to removal of clinically significant lesions and is usually not curative. Asymptomatic recurrences have been documented in up to 70% of patients within one year of surgery, and symptomatic recurrent disease is common within five years. Recurrences typically occur proximal to sites of previous anastomoses or ostomies. Patients with CD are usually not considered good candidates for ileoanal pouches because of the risk of recurrent disease in the pouch (20,22).

Pathologic findings

The pathologic features of UC and CD are identical in children and adults and have been codified in many recent reviews (6,7,34). The distinguishing features of classic UC and colonic CD are summarized in Table 1.

Classic UC begins in the rectum and, if it progresses, does so in a continuous retrograde fashion. Although by definition UC is confined to the colon, it may be accompanied by superficial mild non-specific mucosal inflammation in the terminal ileum (“backwash ileitis”) (see later discussion). At microscopy, the inflammatory process in UC is superficial (confined to the mucosa and submucosa) and is diffuse within the mucosa of the involved segment (34).

In contrast, colonic CD typically begins as localized right-sided or multifocal disease and progresses in a patchy fashion, with “skip areas” of uninvolved mucosa. Characteristic histologic findings include granulomas, deep or transmural inflammation (often characterized by the presence of lymphoid aggregates in the muscularis propria and/or at the muscularis/serosal interface), deep mural fissures or fistulas, and, in a minority of patients, a necrotizing or giant cell vasculitis. In the mucosa, the inflammatory lesions are often focal rather than diffuse (34,35).

Although diagnostically important, granulomas are not invariably present in otherwise typical cases of Crohn's colitis. Even with serial sectioning, granulomas are detected in only approximately one-third of mucosal biopsy specimens from patients with Crohn's colitis. In children with Crohn's colitis, granulomas tend to be more common in the rectosigmoid than elsewhere in the colon. Also, prospective data suggest that the prevalence of granulomas decreases with increasing duration of disease, perhaps due to the effects of medical therapy; thus, granulomas may be more often detected in children than in adults (36).

The sarcoid-like granulomas characteristic of CD must be distinguished from foreign body-type granulomas and from the non-specific mucin granulomas that may be present in both UC and CD. Mucin granulomas are typically adjacent to or in direct contact with inflamed or ruptured crypts, tend to be poorly formed, and often contain giant cells (2,34). Their true nature can be determined by detection of intracytoplasmic mucin using stains such as the alcian blue-PAS with diastase pretreatment.

In mucosal biopsy specimens from untreated patients, the presence of non-mucin granulomas and focality of colitis are the best discriminators for CD (6,7). Focality of colitis in the rectosigmoid in children, however, should be interpreted with caution since it may be present at the onset of UC in this population (see later discussion). In adults, villiform surface change, crypt architectural distortion and crypt epithelial mucin depletion are said to be more common in UC than CD (6,7), but I have not found these to be particularly helpful distinguishing characteristics in pediatric IBD. The pathologist can offer the largest amount of useful information if, at the onset of pediatric IBD, colonoscopy (rather than flexible sigmoidoscopy) with protocol sampling of even endoscopically unremarkable mucosa is performed. Of 42 pediatric patients ultimately proven to have IBD in one recent study, 10 had normal rectosigmoid biopsy specimens. Additional, more proximal, sampling confirmed a diagnosis of CD in 60%; the remaining four patients were later classified as either UC or indeterminate colitis (26). Finally, as noted earlier, ileal disease is rare in CD before the age of 8 to 10 years. Therefore, untreated idiopathic colitis without distinguishing features (granulomas, focality) in very young patients can only be tentatively classified as UC; some of these cases may declare themselves to be CD later in their clinical course by the development of unequivocal ileal involvement (27,32).

Table 1
Classic Distinguishing Features of Ulcerative Colitis (UC) and Crohn's Colitis (CC)

	UC	CC
Gross features		
Isolated right-sided colitis	No	Yes
Rectal involvement	Yes	Variable
Distribution	Diffuse	Diffuse or focal
Method of extension	Continuous ^(a)	Often discontinuous ("skip areas" of normal colon)
Involvement of gut proximal to colon	No ^(b)	Common
Fistulas	No	Occasional
"Creeping" serosal fat	No	Common
Thickened bowel wall	No	Yes
Strictures	Rare	Occasional
Microscopic features		
Inflammation confined to mucosa and submucosa	Yes	Uncommon
Transmural inflammation	No ^(c)	Common
Fissuring ulcers	No ^(c)	Yes
Fistulas	No	Yes
Sarcoid-like granulomas	No	Yes
Distribution of inflammatory changes in mucosal specimens	Diffuse	Focal or diffuse
Vasculitis	No	Yes

^(a)Recent studies document appendiceal or cecal involvement in some cases of localized left-sided UC

^(b)Possible upper gastrointestinal involvement by otherwise classic UC is a subject of current debate (see text for details)

^(c)May be present in fulminant colitis/toxic megacolon

Atypical Features and Controversial Aspects of Pediatric IBD

Unusual features in rectosigmoid mucosal biopsies at the onset of pediatric UC

At first presentation and before therapy, the majority of adult patients with UC (>90%) will have diffuse active colitis, usually with features of chronicity, in rectosigmoid mucosal specimens (25,37). Initial rectosigmoid specimens in children ultimately shown to have UC, however, demonstrate focal colitis and/or the absence of chronic changes in approximately one-third of patients and are completely normal in 4% to 8% (25,37,38).

These atypical findings are not specifically related to the patients' ages at the onset of colitis (although they are predominantly found in patients younger than 10 years), the duration of symptoms before endoscopy, the symptoms themselves, or the ultimate evolution of UC (i.e., development of diffuse distal disease, proximal progression over time) (9,25,38). The reasons for these findings are unknown. One suggestion is that children may be evaluated earlier in the course of UC than adults (25-37); however, it is also clear that changes of chronicity may develop within a few weeks or months of symptom onset (5,9).

This presentation of distal UC with focal disease and a paucity or lack of features of chronicity in pediatric patients raises several diagnostic possibilities and stresses the need for a complete evaluation of the patient. First, it should be recognized that ulcerative colitis is not excluded by these findings (18,25,37,38). Second, they may represent a non-relapsing, infectious-type colitis, which often is patchy and may have rectal sparing (39). Crohn's disease also enters the differential diagnosis; detection of focal proximal colitis, granulomas, ileal disease or perianal disease would support that diagnosis.

The predictive value of focal active colitis for development or recognition of CD once the confounding conditions discussed in the preceding paragraph have been eliminated has recently been examined. In a cohort of 29 pediatric patients with focal active colitis, 8 (28%) developed CD; most of the remainder had either infectious colitis or remained idiopathic (18). In contrast, focal active colitis in adults evolved into a diagnosis of CD over time in fewer than 15% of patients (40,41). One possible reason for the difference in outcome between the two populations is that unlike the case in adults, colonoscopy in children is typically performed for evaluation of abdominal pain, diarrhea or hematochezia rather than cancer surveillance, thus creating a bias towards detection of inflammatory diseases. As in children, many cases of "focal active colitis" (particularly those with minor abnormalities) in adults are likely secondary to effects of bowel cleansing agents such as sodium phosphate (18,40,41).

Effects of medical therapy on the histology of UC in colonic mucosal biopsy specimens

The classic teaching has been that quiescent UC heals with fixed morphologic changes that permit continued recognition of the colonic mucosa as injured. In 1993, however, Odze and colleagues demonstrated that medical therapy of left-sided UC with topical 5-aminosalicylic acid caused reversion of colonic mucosa to a normal appearance in 64% of patients (42). Since that time, several authors have confirmed and extended this observation. The results of these studies document that in patients with established extensive or pancolitis receiving contemporary medical therapy, histologic diffuse disease has become focal within the colon in up to 54% of patients and the rectum has become unremarkable in up to 34% on one or more occasions during follow-up (8,43-47). These results were not related to the duration of disease or the type of therapy employed (systemic or topical) (47).

Rectal sparing and focal colitis are typical of CD. Thus, to avoid diagnostic confusion, it is important to know the medication history of patients with presumed UC in whom such findings are documented. In both children and adults with chronic IBD, unfortunately, such information is often not available at the time of biopsy specimen interpretation. In this situation and in the absence of granulomas, focality and rectal sparing should be described but not interpreted, with the comment that prior medical therapy may have affected the histologic findings.

Appendiceal involvement as a “skip lesion” in UC

In several retrospective studies of colectomy specimens, the authors have attempted to determine the prevalence of appendiceal inflammation in patients with UC of various extents. Appendiceal involvement by UC must be distinguished from incidental acute appendicitis and has been defined as a lesion confined to the mucosa with architectural and cellular features of chronicity that may or may not be accompanied by activity (48). Not unexpectedly, the prevalence of chronic appendicitis in patients with pancolitis (whether due to UC or CD) is high, occurring in approximately 60% of cases (48,49).

Of greater interest is the prevalence of this finding in UC patients with less than pancolitis (i.e., with at least cecal/right-sided sparing in the colectomy specimen). In this group, appendicitis has been reported in 15% to almost 100% of pediatric and adult patients, giving rise to the notion of appendicitis as a “skip lesion” in otherwise classic UC (48,50-53). In a follow-up study of ileoanal anastomoses performed on patients with appendicitis as a presumed “skip lesion” of UC, there were no cases with outcomes suggesting that a diagnosis of CD had been missed (54).

A criticism of these studies relates to their retrospective nature (49,55). The extent of sampling of the cecum and right colon has not been performed in a standardized fashion, so that the extent of sampling has been either limited or unknown. Also, information about prior medical therapy and its possible effects on damaged mucosa has not been provided. Thus, whether or not this portion of the colon has been truly “normal”

at all times is debatable. However, appendiceal involvement has been documented in some cases that clearly represent otherwise localized left-sided UC (52). At present, an apparent appendiceal “skip lesion” should not be construed as evidence of CD without additional supportive clinical, imaging and/or histologic data.

Cecal periappendiceal orifice inflammation as a “skip lesion” in UC

Another proposed “skip lesion” of UC is endoscopic and histologic colitis confined to the periappendiceal cecal mucosa in patients with left-sided UC. Strict criteria to exclude CD are needed to support this interpretation: no granulomas, perianal disease, ileal disease or other documented colonic skip lesions should be present (55). The gross periappendiceal mucosal endoscopic findings vary from erythema and tissue granularity and friability to erosions and ulcers (55).

In several recent prospective endoscopic and biopsy surveys of patients with left-sided UC, the prevalence of periappendiceal localized colitis has varied from 54% to 75% (55-58). Biopsies examined from the colon between the left side and the periappendiceal area were normal in most instances (55-57) but on occasion demonstrated microscopic foci of colitis in endoscopically normal mucosa (58). In the study by Yang and colleagues, the prevalence of focal periappendiceal disease was the same in patients with and without prior medical therapy (55), and in an 8-year follow-up of their patients, d’Haens et al detected no features of CD (56). Although there are some issues with the interpretation of the histology in some of these series, the weight of evidence from these prospective studies supports the idea that the endoscopic periappendiceal cecal patch in children and adults does represent a skip lesion of UC and in isolation, therefore, should not be interpreted as evidence of CD.

The conundrum of backwash ileitis in UC

A perennial problem in both pediatric and adult IBD at the imaging, endoscopic and pathologic levels is the separation of ileitis due to CD from non-specific terminal ileal inflammation in patients with UC (“backwash ileitis”). Part of the problem relates to the lack of a modern consensus-derived gross and microscopic definition of backwash ileitis (34, 59). A contemporary provisional diagnosis of backwash ileitis in UC has been provided by Heuschen et al: a 5.0 cm or longer segment of terminal ileal mucosal inflammation with no granulomas. In resection specimens, no mural inflammation should be identified (60).

In a recent pediatric series, backwash ileitis (not precisely defined) was identified in 22% of colectomy specimens with pancolitis. Its presence did not predict any excess of problems with ileoanal pouches (such as refractory pouchitis and pouch failure) (61). A combined imaging, endoscopic and histologic study of backwash ileitis (not precisely defined) published in 2003 gave a prevalence of 39% in 18 pediatric patients with UC (62). In the absence of a standardized definition, such studies do not contribute to our understanding of this condition and its precise relation to IBD in children. A recent study by Haskell and colleagues, primarily in adults, has, however, extended our knowledge of

terminal ileal inflammation in patients with UC in a study of 200 resection specimens in which CD had been rigorously excluded. In this cohort receiving contemporary medical treatment, ileitis was found in a minority of patients (17%), was typically mild and confined to the mucosa, was commonly (but not invariably) associated with pancolitis, and was not associated with an increased risk of ileoanal pouch complications compared to control patients lacking ileal inflammation in their resection specimens (59).

Based on the available data and in the absence of granulomas, ileal mucosal specimens with inflammatory changes should be diagnosed descriptively. In addition to being related to UC itself, such changes could be due to concurrent infection in patients on immunosuppressive therapy for their disease or to drug effects (e.g., NSAID's). In addition, since some cases are associated with sparing of or minimal activity in the right colon, the term "backwash" is best avoided in the diagnosis, given the absence of definitive information on the pathogenesis of the ileal findings (59,60).

Upper gastrointestinal tract involvement in inflammatory bowel disease

Upper gastrointestinal inflammatory lesions of the esophagus, stomach, and/or duodenum in patients with CD have been well described in the literature. Among the possible findings, granulomas, focal duodenitis and focal gastritis in mucosal biopsy specimens are most closely associated with or are the best predictors of colonic CD (63-65). Focal (or "focally enhanced") gastritis is defined as a localized and sharply defined area of gastritis, with active and chronic inflammation and gland injury, that is surrounded by normal mucosa and is easily identified at low-power inspection (64-67).

In contemporary medical practice, upper gastrointestinal endoscopy with biopsy is often performed before the institution of therapy in pediatric patients with newly diagnosed colonic IBD (both UC and CD). This procedure has led to some interesting findings that are summarized in Table 2. The protocols and the extent of histologic sampling have not been uniform in these studies, but most are prospective in nature.

Although the gross and microscopic abnormalities are not always described in detail, an intriguing finding in these studies is that the overall prevalence of endoscopic and histologic inflammatory lesions in the esophagus, stomach and duodenum is roughly equal in patients with newly diagnosed and typical colonic UC and CD. When known causes of such inflammation (such as reflux esophagitis and *Helicobacter pylori*-associated gastritis) are excluded, there still remains a high prevalence of non-specific lesions, particularly *H. pylori*-negative diffuse gastritis, in both conditions (67-71). Whether this gastritis is incidental or related to IBD is unknown, but the important point is that the mere presence of upper gastrointestinal inflammatory lesions can no longer be used to automatically categorize a patient as having CD.

The presence of granulomas in upper intestinal mucosal biopsies is highly specific for a diagnosis of CD (see Table 2). Their prevalence has varied from 14% to 60% in recent pediatric series, and they are most often found in gastric mucosa (67-71). In contrast, they are much less common in the stomach of adults with CD (a prevalence of

only 5% in the study of Parente and colleagues) (66). In children, they are often detected in gastric and duodenal specimens even when synchronous colonic mucosal biopsies are negative for this finding (67,69,70).

Although focal gastritis can be seen in a minority of UC patients (8% to 21%) and non-IBD controls (2%-19%), it is more common in patients with CD (43% to 65%) with a calculated positive predictive value for colonic CD of 70% to 80% (66,67,71). All examples of gastritis, whether focal or diffuse, should be carefully evaluated to exclude *Helicobacter* infections as well as allergic and chemical-type injuries. As in the colon, “IBD-associated gastritis” is a diagnosis of exclusion.

In summary, upper endoscopy can be helpful in classifying colonic IBD. Biopsy specimens should be obtained from grossly normal as well as abnormal mucosa to detect treatable localized conditions, such as *H. pylori*-associated gastritis, and to detect granulomas and focal gastritis (66-68,70,71). In recent pediatric studies of the stomach in IBD, 70%-87% of patients had various inflammatory changes in antral biopsies despite the fact that only a minority (<40%) had endoscopically detectable mucosal changes (chiefly erythema and small ulcers) (67,71). The recent recognition that diffuse, non-*Helicobacter* chronic gastritis is common in patients with classic UC raises an interesting question: Is it a manifestation of UC? Perhaps adding credence to this possibility is a small number of pediatric and adult cases of “ulcerative enteritis” developing in patients with classic UC, typically after colectomy for treatment of the colitis. In these patients, as recently reviewed by Rubenstein and colleagues, the enteritis is diffuse, confined to the mucosa, lacks granulomas, and responds to the usual medical therapies for UC (72). Clarification of the exact nature of this enteritis (as well as the non-specific gastritis) will require additional prospective studies.

Use of wireless capsule endoscopy will likely increase the detection of small-bowel lesions in patients with IBD. For example, in a recent pediatric study of 20 patients aged 10 to 18 years suspected of having small-bowel CD but negative imaging studies of the gut as well as negative upper and lower endoscopy, 10 (50%) had multiple erosions/ulcers in the jejunum and ileum compatible with CD (73). It will be interesting to determine the rate of similar lesions in pediatric patients thought to have UC.

Table 2
Upper Gastrointestinal Findings in Pediatric Patients with Crohn's Disease and
Ulcerative Colitis

Series	Findings	Crohn's Disease	Ulcerative Colitis	Controls
Kundhal et al	Non-specific gastritis	92%	75%	None
	Focal gastritis	52%	8%	
	Granulomas	60%	0%	
Tobin et al	Esophagitis	72%	50%	91% ^(a)
	Gastritis	92%	69%	27%
	Duodenitis	33%	23%	9%
	Granulomas	40%	0%	0%
Abdullah et al	Abnormal endoscopy ^(b)	64%	50%	None
	Abnormal histology ^(b)	82%	71%	
Ruuska et al	Endoscopic and/or histologic inflammatory lesions ^(b)	80%	75%	23% ^(c)
	Granulomas	25%	0%	0%
Sharif et al.	Focal gastritis	65%	21%	2.5%
	Diffuse, non-H. pylori gastritis	34%	50%	15%
	Granulomas	14%	0%	0%

^(a)Controls = patients with reflux esophagitis

^(b)Includes esophagus, stomach and duodenum

^(c)Mixture of non-IBD patients

Summary

Because of the complexity of diagnosing and accurately classifying patients with pediatric IBD, it is clear that any one examination technique, such as histologic analysis of colonic mucosal biopsies, will seldom give a precise diagnosis. Rather, integration of all clinical, imaging, laboratory and morphologic data is necessary to achieve diagnostic accuracy. Pathologists, who usually lack the full range of clinical information, should not feel pressured to render specific diagnoses based on examination of limited colonic mucosal material. Our task is first to determine whether or not colitis is present. If it is, we can state whether it is active, chronic or both and, in untreated patients, give its distribution (focal or diffuse). Finally, the presence or absence of more specific features such as granulomas should be mentioned. Our reports will then be an important contribution to the clinician who must integrate all the data to obtain the most appropriate diagnosis.

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