Natural History of Pediatric Indeterminate Colitis

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Abbreviations

CD	Crohn's disease
IBD	Inflammatory bowel disease
IBD-U	Inflammatory bowel disease unclassified
IC	Indeterminate colitis
UC	Ulcerative colitis

Introduction

Indeterminate colitis (IC), as a classification of inflammatory bowel disease, was introduced by Kent in 1970 [1] and was intended to classify colectomy specimens that had histology findings suggestive of Crohn disease (CD), despite a patient's clinical history of ulcerative colitis (UC). Contemporarily, IC is used broadly for patients whose clinical, radiological, endoscopic, and histological findings provide a muddled picture. The 2014 Porto Criteria established a new terminology, inflammatory bowel disease unclassified (IBD-U), to reduce confusion among providers, researchers, and patients [2]. Additionally, the Paris Classification of Pediatric Inflammatory Bowel Disease strengthened the definitions of UC and CD in children to reduce misclassification [3]. However, random use of terms continues, with individuals using IC, IBD-U, uncertain colitis, and idiopathic chronic colitis interchangeably. Regardless, in adult patients, 10–15% of patients at diagnosis receive the classification of IBD-U [4], while in pediatrics this percentage is even greater, especially among those children who present with very early onset IBD [5]. In order to be consistent throughout this chapter, the diagnosis will be exclusively referred to as IBD-U, whether or not the original research classified patients as IC or IBD-U.

In this chapter, we review the clinical and histological criteria needed to establish the diagnosis of IBD-U, describe the factors that lead to the diagnosis of IBD-U, investigate occurrence of reclassification, and review the available literature about the natural history of this classification.

Definition and Diagnosis

In pediatrics, a subset of patients will be diagnosed with inflammatory bowel disease (IBD); however, they do not follow the classic definitions of CD or UC. These "in-between" patients challenge providers, as less is known about the natural history, prognosis, or efficacy of treatment of the disease. Both the 2014 Porto Criteria and European Crohn's and Colitis Organisation (ECCO) Guidelines established criteria for the diagnosis of IBD-U [2]. By providing specific criteria, a more homogenous group of patients will receive this diagnosis and potentially improve providers' ability to understand and manage the disease process.

To address the questions, inconsistencies, and controversies in the diagnosis and classification of pediatric inflammatory bowel disease, 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 pediatric gastroenterologists and GI pathologists

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in 2003 and 2007. The goals of this working group were to establish an agreed-upon set of definitions and phenotypes and to develop an algorithm that would improve interobserver agreement in the diagnosis and classification of CD, UC, and IBD-U.

Although the working group was unable to find enough data in the literature to state a definition of IBD-U, they posited several general recommendations: (1) Clinicians should try to avoid overuse of the diagnosis of IBD-U. The recommendations specifically state that the following criteria do not preclude a diagnosis of UC in children with colitis: backwash ileitis, rectal sparing, histological patchiness, periappendiceal inflammation, and gastritis. (2) For patients diagnosed with IBD-U based on findings highly atypical for UC, such as ileal aphthae, backwash ileitis in a patient with left-sided colitis, profound growth failure, large oral aphthae, or absolute rectal sparing, clinicians should precisely specify the reason(s) for the diagnosis of IBD-U rather than UC or CD. (3) Patients given a provisional diagnosis of IBD-U should undergo additional endoscopic and radiographic evaluations after 1 year or during the next disease exacerbation to try to establish a definitive diagnosis, while acknowledging that partially treated disease may have a patchy distribution [6].

The 2014 Porto Guidelines and the Paris Classification provided pediatric specific definitions of CD and UC, decreasing confusion about proper classification. According to the Porto Criteria, IBD-U is a term that applies to patients who have definite IBD with inflammatory changes limited to the colon, but certain features render the differentiation between UC and CD difficult despite complete evaluation [2]. IBD remains a clinical diagnosis dependent on comprehensive evaluation – physical examination, radiological images, and macroscopic and microscopic endoscopic findings of both the upper and lower gastrointestinal tract. While accepted criteria can establish the diagnosis of UC and CD, several macroscopic and microscopic histological findings can make it difficult to distinguish between UC and CD in the pediatric population. We will first discuss atypical presentations of UC, obscured findings in fulminant colitis, and lack of specific findings in CD, each of which can lead to the IBD-U classification.

Pediatric UC patients provide a unique challenge, because they often deviate from classic definitions. Patients may have discontinuous disease at diagnosis, challenging accepted definitions of UC that may delay a patient's diagnosis and leading them to have a temporary diagnosis of IBD-U. In a study of the EUROKIDS registry, 5% of pediatric UC patients had rectal sparing defined as macroscopic normal disease with abnormal microscopic findings [7]. These children tended to be younger and have more extensive disease. In the same study, "backwash ileitis," or abnormal macroscopic findings in the ileum in the setting of pancolitis involving the cecum, was found in 10% of children with UC [7]. The existence of inflammation in the cecum and ascending colon in a patient with left-sided UC has been well described, often termed the "cecal patch" [8]. Newer pediatric IBD guidelines, such as the Paris Classification, encourage practitioners to label a patient with UC rather than a temporary IBD-U diagnosis in these specific instances.

Resected colectomy specimens from patients with fulminant colitis can have nonspecific histological findings [9]. Macroscopic features of IBD-U include extensive ulceration, more severe involvement of the transverse and right colon, >50% of mucosal surface involvement, diffuse disease with possible rectal sparing, and toxic dilation [10]. Microscopic findings consist of extensive v-shaped ulcerations with sharp transitions to normal adjacent mucosa, transmural lymphoid inflammation with an absence of lymphoid aggregates, absence of well-defined epithelioid granulomas distant from crypts (or histiocytic collections adjacent to injured crypts), and knife-like deep penetrating fissures [10].

Finally, patients with a clinical presentation strongly suggestive of CD might receive a diagnosis of IBD-U if no pathognomonic findings such as granulomas are seen on histology. Ideally, initial histological evaluation is completed prior to initiation of treatment; however, even in this instance, sampling error is a problem with CD, given the patchy nature of the disease [11]. Endoscopic biopsies are confined to superficial and interspersed findings, thus not providing sufficient tissue sample to evaluate for transmural inflammatory changes and sometimes identification of granulomas [12]. In one study, only 20.5% of initial colonic biopsies of untreated pediatric patients later found to have CD had granulomas. The inclusion of upper gastrointestinal tract and terminal ileal biopsies increased identification of granulomas to 61% [13]. Comprehensive evaluation should include endoscopic and radiological examination of the upper gastrointestinal tract and intubation of the ileum.

Epidemiology

Disagreement concerning the definition of IBD-U has led to varying estimates of the incidence and prevalence of this disorder. In 2009, all children and adults newly diagnosed with UC, IBD-U, or CD in specific regions of southeastern Norway were enrolled into a prospective study in order to evaluate change in IBD diagnosis. At enrollment, 843 cases of IBD were identified: 518 patients with UC, 221 patients with CD, 40 patients with IBD-U, and 64 patients with possible IBD. At 5-year follow-up, 36 (35%) patients from the IBD-U and possible IBD group (n = 104) were diagnosed with UC and 8 (8%) with CD. It should be noted that the average age of onset was 42.6 years, indicating that the study population was predominantly adult [14]. A study by Bardhan et al. created a database of IBD patients across the United Kingdom. The study collected information on 11,432

patients with IBD, with 474 (4%) of participants classified as having IBD-U, with an average age of onset of 41 years [15].

Incidence data for IBD-U is even more varied in pediatric studies. In a Wisconsin-based pediatric study, 10 out of 199 incident IBD cases (5%) were classified as IBD-U, with an overall incidence of 0.35 per 100,000. A similar pediatric study in Poland enrolled 491 IBD patients, with 144 classified as IBD-U, with an overall incidence of all types of IBD of 2.7 cases per 100,000 and incidence of IC of 0.8 per 100,000 (29.3% of all IBD cases) [16]. Additional reports from the pediatric literature estimate the proportion of newly diagnosed IBD cases categorized as IBD-U to be anywhere between 3.3 and 30%, depending in part on the age of the population [17–22].

A meta-analysis published in 2008 by Prenzel and Uhlig, including 6262 pediatric patients and 15,776 adults with IBD, found a statistically different frequency of IBD-U (12.7% in children and 6.0% in adults, $p < 0.0001$). Also, that same study suggested a correlation between the age of a patient and the frequency of IBD-U, with younger patients more likely to be diagnosed with IBD-U. In children 0–2 years old, 34% of the 133 identified patients were diagnosed with IBD-U, compared with 21% of patients 0–5 years old [5].

It is postulated that differences in the proportion of incident IBD cases categorized as IBD-U, despite relatively similar overall IBD incidence rates, represent extremes in diagnosis and categorization rather than actual "biological" differences. This variation underscores not only the heterogeneity of conditions labeled as IBD-U, but also the inadequacy of the current classification system, especially with regard to the pediatric population. Newby in 2008 suggested that for pediatric patients in particular, the training of the medical provider may also play a role in the initial diagnosis, with a "specialist pediatric unit" being less likely to diagnose IBD-U, compared with nonpediatric providers [23].

The prevalence of IBD-U is affected not only by the number of new cases, but also by the number of cases exiting the prevalent pool. Because of the chronic nature of this illness, patients leave the pediatric prevalence pool only under a limited number of circumstances: (1) becoming adults, (2) death (uncommon), and (3) having their diagnosis changed to CD or UC. Therefore, estimates of prevalence are limited not only by the diagnostic concerns addressed above, but also by the natural history and disease evolution.

Noninvasive Diagnostic Tools

Serology

While IBD remains a clinical diagnosis, a number of serum antibodies have been identified that can help differentiate CD from UC. For example, particular patterns of anti-*Saccharomyces cerevisiae* antibodies (ASCA), perinuclear antineutrophil cytoplasmic antibody (pANCA), and anti-outer membrane porin C antibody (anti-OmpC) have been noted in CD and UC. Recent studies have also attempted to determine if a unifying pattern exists for patients diagnosed with IBD-U or if antibody serology can provide an appropriate classification. Sura et al. found that the presence of pANCA was associated with an ultimate diagnosis of UC in patients diagnosed with IBD-U, who had a high clinical suspicion of UC [4, 24]. To date, no genetic or immunological markers have been shown to reliably differentiate between CD, UC, and IBD-U.

Capsule Endoscopy

Capsule endoscopy is another noninvasive modality that has been suggested to evaluate patients with IBD-U. In 2003, the FDA approved capsule endoscopy in pediatrics. In recent studies, capsule endoscopy has provided additional information, either confirming a diagnosis of CD or leading to reclassification of CD from UC or IBD-U [25–27]. Larger studies of the pediatric IBD-U population are needed to validate these findings.

Microbiome

Ongoing investigation and understanding about the fecal microbiome, virome, and fungal communities might also yield information on differentiating subtypes of pediatric IBD. Current research has suggested a bacterial dysbiosis exists in patients with IBD, and recent studies report unique phage patterns in patients with UC and CD [28, 29]. However, at this time, no unique fecal pattern has been identified that can distinguish IBD-U from CD or UC. Ongoing developments in this expanding area of research may allow identification of disease classification from a fecal sample.

Electron Microscopy

Application of electron microscopy has been proposed to gain more information from endoscopically obtained mucosal biopsies. Evaluation of endoscopic biopsy results using electron microscopy may facilitate detection of unique proteomic patterns that could help define a patient's IBD classification [30].

Medical Management

With uncertainty around the diagnosis of IBD-U, patients are often excluded from randomized clinical trials or grouped with UC patients. Results of large studies, retrospective

reviews, and observational studies may also be limited by inadvertent inclusion of IBD-U patients. From published studies and anecdotal experience, patients with IBD-U are exposed to and respond to the same classes of medications as children with UC or CD, that is, corticosteroids, aminosalicylates, immunosuppressants, and biological agents. However, no algorithms or guidelines exist for medical management of IBD-U.

Papadakis et al. [31] investigated the use of infliximab in steroid-refractory IBD-U. Of the 20 patients treated with infliximab, 14 had a complete response, 2 had a partial response, and 4 had no response. Interestingly, 10 of the 20 patients (50%) ultimately received a diagnosis of CD [31]. A retrospective study by Willot et al. [32] investigated tolerance and safety of methotrexate in children with IBD. In the study, 11 of the 79 patients had IBD-U [32]. As in many studies, the IBD-U patients were grouped together with the UC patients; however, IBD-U patients (n = 11) outnumbered the UC patients (n = 5). IBD-U patients had similar outcomes to Crohn's patients at final follow-up in terms of efficacy, tolerance, and safety of methotrexate [33]. Ultimately, few studies focus on investigating the medical management of children with IBD-U.

Surgical Outcomes

Surgeons are typically reluctant to offer surgical options to IBD-U patients, given the uncertainty of the diagnosis. However, numerous studies have investigated outcomes for ileal pouch anal anastomosis (IPAA) and have shown equivalent functional outcomes as patients with UC [34–36], although increased complications such as anal fistula formation and development of CD have been reported. Most striking though, Delany et al. reported that 93% of all subjects themselves would opt to undergo the surgery again, regardless of the outcome [34].

Summary

Children classified as having IBD-U are a heterogeneous group of patients. Variability in the application of this term among clinicians has resulted in general misconceptions, including widespread differences in the reported prevalence and confusion regarding the natural history of IBD-U. Patients with IBD-U are often excluded from clinical trials, thus interfering with our ability to gain knowledge regarding the clinical course and the efficacy of treatment regimens in these patients. While efforts have been made to standardize diagnostic criteria of IBD-U, disagreement and confusion persist. Additionally, the often-transient nature of this diagnosis makes prospectively observational and randomized studies a challenge. Pediatric patients with IBD-U are typically reclassified as UC or CD, with children under 6 years of age having a greater predisposition for eventual diagnosis of CD. Emerging understanding of noninvasive diagnostic tools such as serological and fecal markers should improve initial diagnostic classification of pediatric IBD and thus decrease the number of patients classified as IBD-U. We suspect that patients who, despite new technologies, maintain a diagnosis of IBD-U will be a more homogenous group of patients, potentially with a distinct disease entity.

Given current knowledge of IBD-U, we suggest utilization of medical management with agents that are effective in both CD and UC (i.e. steroids, salicylates, immunomodulators, and infliximab); specific therapies should be chosen based on disease location, severity, estimation of risk for recurrence, and potentially yet to be defined biomarkers. Although IBD-U patients who undergo surgical therapy such as colectomy and IPAA may be at higher risk of postoperative complications, these patients appear to have similar functional outcomes. Therefore, surgical therapy should not be withheld from IBD-U patients with refractory disease, once an attempt has been made to reclassify their disease status.

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