An Overview of Inflammatory Bowel Disease Unclassified in Children

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Keywords

Crohn's disease · Ulcerative colitis · Inflammatory bowel disease · Inflammatory bowel disease unclassified · Disease classification

Abstract

Background: The inflammatory bowel diseases cover a diverse range of conditions generally grouped into Crohn's disease (CD) or ulcerative colitis (UC) based on clinical, laboratory, radiological, endoscopic, and histological criteria. However, inflammatory bowel disease unclassified (IBDU) is used when there are clinical and endoscopic signs of chronic colitis without specific features of UC or CD but features of both. Conjecture exists regarding IBDU, especially in children, as to whether it represents a unique childhood phenotype or whether it reflects the difficulties in assigning an IBD subtype at an early age. **Summary:** This review examines the current understanding of pediatric IBDU and assesses the evidence supporting IBDU as a distinctive disease entity on the spectrum of inflammatory bowel disease. **Key Messages:** Pediatric-onset IBDU is more common than adult-onset IBDU. Therefore, an understanding of IBDU in this age group assumes more importance. However, there remains a pau-

city of information and a lack of exclusive longitudinal studies on pediatric IBDU. Subsequently there is significant disparity in the reported prevalence, clinical course, reclassification trends, and treatment responses around pediatric IBDU. Therefore, it remains challenging to chart the natural history of pediatric IBDU and consequently form an accurate understanding of where pediatric IBDU sits on the spectrum of disease.

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Introduction

Inflammatory bowel disease unclassified (IBDU) is a chronic disorder of the gastrointestinal tract and the rarest of the IBD subgroups, which includes ulcerative colitis (UC) and Crohn's disease (CD). IBDU is characterized by clinical and endoscopic signs of chronic colitis without specific features for UC or CD but rather subtle features of both [1–3]. Pediatric-onset IBDU is twice as common as adult-onset disease, with the highest prevalence among younger ages [4]. In some cohorts, clinical follow-up of pediatric IBDU shows that up to 80% of patients are reclassified as having CD or UC [4, 5]. This suggests that a

proportion of cases may be early manifestations of CD or UC [4, 6]. However, other studies have reported that up to 69% of patients maintain their pediatric-onset diagnosis of IBDU into adulthood [4].

There is an obvious conjecture in the literature regarding IBDU as to whether it represents a unique IBD phenotype associated with childhood disease or whether it reflects the difficulties in diagnosing an IBD subtype when the disease manifests at an early age [6]. This review aims to examine the existing understanding of IBDU in the literature and assess the evidence supporting IBDU as a distinctive disease entity on the spectrum of IBD.

History of the IBDU Classification

The term IBDU is allocated to cases of colitis where endoscopic and histological findings are not adequate to differentiate between UC and CD [7]. Indeed, UC and CD represent 2 major phenotypic forms of IBD, both of which comprise a spectrum of chronic intestinal inflammation [7]. UC classically presents with continuous inflammation of the superficial colonic mucosa moving proximal from the rectum, without small bowel involvement or granulomas on biopsy [8]. Among children with UC, pancolitis is seen more commonly, with isolated proctitis being rare, which contrasts directly with the patterns seen in adults with UC [9].

Conversely, CD is characterized by transmural inflammation of a noncontinuous, fibro-stricturing pathology extending anywhere from the mouth to the anus [9]. The ileo-colonic region is the most common location of CD in children, with gut involvement proximal to the terminal ileum, such as the stomach and the duodenum, occurring in over half of this cohort [9].

The term indeterminate colitis (IC) was introduced by Ashley Price [10] in 1978 as a diagnosis following colectomy among IBD patients whose pathology showed overlapping features of CD and UC [11]. Subsequently the 2006 Montreal classification replaced the IC term when it proposed the term “inflammatory bowel disease type unclassified” [12] to define the presurgical patient with evidence of clinical and endoscopic chronic IBD of the colon with no small-bowel involvement and no definitive indications of CD or UC [12]. From its origin as a postcolectomy pathological diagnosis, this IBD subtype remains a poorly understood disease entity with no definitive histological or clinical features in either children or adults [13, 14].

Succeeding the Montreal classification was the Paris classification in 2010 which aimed to capture the dynam-

ic phenotypic characteristics of paediatric UC and CD. It presented an improvement in standardization of pediatric IBD (PIBD) classifications, clarifying to a degree the endoscopic and microscopic features of UC and CD; however, the classification of IBDU was not addressed [8].

Diagnostic Criteria for IBDU

Currently the revised Porto criteria published in 2014 [8] integrates the most recent evidence from the Paris classification to guide clinicians in evidence-based diagnosis of subtypes of PIBD [13]. The Porto criteria addresses advancements in diagnostic tools and the increased sensitivity of lesion detection; however, this has amplified the uncertainty of IBD subtype classifications as many features overlap. It also reiterates the significance of mandatory upper gastrointestinal endoscopy, ileocolonoscopy, and small-bowel imaging such as magnetic resonance enterography for all instances of suspected IBD [13, 14].

The Porto classification of PIBD is based on the identification of typical features consistent with CD or UC, as well as knowledge of the atypical features still consistent with a diagnosis of one or the other [8]. An IBDU diagnosis is considered one of exclusion [4]. Indeed, features in a child with the untreated colitis phenotype were tabulated in relation to their likelihood of occurring in UC using a hypothesis-driven analysis for pediatric differentials [13]. If a patient shows any features that are significant deviations from typical UC (class 1 features) this amounts to a CD diagnosis, while an increase in uncommon UC features increases the prospect of IBDU or colonic CD (class 2 and 3) [13].

The Porto criteria's general scheme states that a patient with 2 or 3 of the following “class 3” features is suggestive of a diagnosis of IBDU [8]. These features include: severe scalloping of the stomach or duodenum (not explained by other causes such as coeliac disease or *Helicobacter pylori* infection), focal chronic duodenitis on multiple biopsies or marked scalloping of the duodenum (not explained by other causes), focal active colitis on histology in more than one biopsy from an endoscopically inflamed site, and nonbloody diarrhea and/or aphthous ulcerations in the colon or upper gastrointestinal tract [8].

Additionally, one class 2 feature (those features rare with UC [$<5\%$]) also infers a diagnosis of IBDU; however, the likelihood of a CD diagnosis over an IBDU diagnosis increases with an increasing number of class 2 features

[8]. These features involve a colitis phenotype with ambiguous features such as: combined endoscopic and microscopic rectal sparing, significant growth delay, transmural inflammation without acute severe UC, nonspecific upper gastrointestinal ulcers, a reverse gradient of mucosal inflammation (more proximal than distal), and ambivalent serological markers [8, 15].

Clinical Features of IBDU

Currently there are no distinct clinical or histological features that are diagnostic of IBDU [14]. Studies have attempted to quantify the clinical features more suggestive of IBDU compared to those indicative of UC and CD [16]. Children diagnosed with IBDU tend to have clinical features similar to those of UC patients, with the most dominant trait being bloody diarrhea and rectal bleeding [7]. A 2015 study obtained a registry of 3,991 children with IBD to assess the initial diagnostic symptoms and characteristics of PIBD and compared these findings across IBD subtypes [17]. That study reported that abdominal pain was a universally significant symptom (59.2% of UC patients ($n = 71$), 77.3% of Crohn's patients ($n = 132$), and 57.9% of IBDU in patients aged <10 years), while diarrhea was slightly less common in CD patients [17]. Overall, the largest difference was "blood in stool," which was reportedly more common in UC and IBDU than in CD [17].

Prevalence of IBDU

Pediatric-onset IBDU is twice as common as adult onset IBDU, occurring in approximately 13% of PIBD cases and 6% of adults [4, 18, 19]. Within the pediatric population IBDU rates decline with age, with one fifth of IBD pediatric cases younger than 6 years and one third of cases aged under 3 years receiving an initial IBDU diagnosis [20, 21].

This was demonstrated in a large study involving 1,370 children, where the incidence of pediatric IBDU was skewed by the age of the patients [22]. In that study the overall IBDU incidence was 13% ($n = 179$), which accounted for 33% of all IBD patients aged <2 years, compared to only 9% in those older than 13 years [22]. This higher IBDU rate among the very-early-onset IBD patients has been speculated to reflect the difficulties in initial classification of PIBD and potentially higher occurrences of incomplete diagnostic workups among this age group [6, 23].

However, there are discrepancies over the prevalence of IBDU, differing between populations and between variabilities in diagnostic methods, and most significantly with follow-up reassessments [15]. Additionally, a higher IBDU rate has been reported in prospective compared to retrospective studies [4, 21]. This may be attributed to retrospective studies capturing the disease evolution and thus including the high rates of IBDU reclassification over the long term, which prospective studies cannot predict.

Birimberg-Schwartz et al. [13] advocates IBDU as a distinct IBD phenotype based on the justification that the frequency of IBDU in adults has remained relatively constant at approximately 10% over the past 30 years despite the introduction of newer diagnostic methods [11, 13]. Although several studies have also noted that there is an increasing prevalence of pediatric IBDU, ranging from 4 to 29% [13, 24]. Everhov et al. [24], who investigate IBDU subtype classification in the Swedish population, reported that pediatric IBDU increased from 9 to 14% from 2006 to 2014. Additionally, a recent study in Singapore evaluating the incidence trend of PIBD over 22 years (1994–2015) reported no pediatric IBDU cases prior to 2010 [25]. However, the final 6 years of the study reported an IBDU incidence of 0.30 per 100,000 (95% CI 0–0.45) during 2010–2012 and 0.47 per 100,000 (95% CI 0.12–0.69) in 2013–15 [25]. This notable rise in IBDU classifications follows an almost 10-fold increase in PIBD over the period of the study. This upward trend in IBD incidence mirrors Western trends; however, the incidence and prevalence of IBD in Asian countries remain overall lower in comparison to values in Western countries [25].

There are relatively few studies that specifically investigate PIBD in Asian countries [26]. The Singaporean study published in 2018 claims to be the first population-based study reporting the incidence trends of PIBD in a South-East Asian country [25]. In regions where overall PIBD rates are low, this may impact IBDU classification where it may not be routinely considered, and this may therefore foster a possible underrepresentation of pediatric IBDU [26]. A recent Japanese study on PIBD required a clear diagnosis of UC or CD for inclusion in the study [26]. Ultimately if PIBD rates continue to increase in Asian countries then IBDU should be a consideration and be closely monitored [25].

One clear limitation of reported incidence and prevalence values of pediatric IBDU is the inconsistent application of the IBDU classification. Studies have theorized that the growing proportion of PIBD patients who are classified as IBDU can be attributed to the clearer defini-

tions and stricter subtype classifications of IBD recommended by the Porto criteria, as well as access to better diagnostic tools [27]. Contrastingly, other recent studies have documented a lower frequency of IBDU among paediatric patients, such as a 2017 study reporting 7.5% (26/344) IBDU, which decreased to 4.3% after a median follow-up period of 5.7 years [14]. This was consistent with the EUROKIDS registry that asserted that IBDU incidence is lower than reported by previous studies, on the premise that follow-up reinvestigations reduced IBDU rates of 7.7–5.6% [6]. Many other studies are consistent with these results [3, 4, 28] and some speculate that clearer diagnostic criteria will reduce the rate of pediatric IBDU further [6].

Subsequent Reclassification of IBDU

Assessment of IBDU reclassification is a vital element of uncovering the natural course of this IBD entity, aiding future diagnosis, care, and management of all IBD subtypes. Controversy surrounds IBDU reclassification, with discordant interpretation of reclassification rates and trends across the literature. Studies which report low reclassification rates advocate for IBDU as a true intermediate phenotype between obvious CD and typical UC [13, 16]. However, other studies that report follow-up reclassification rates as high as 80% argue that IBDU is only a provisional diagnosis [6].

A pediatric study by Paul and Sandhu [14] reported that 40% ($n = 10$) of the 26 IBDU cases were reclassified, 70% of which were reclassified as CD and 30% of which were reclassified as UC. This high rate of reclassification as CD contrasts with previous pediatric studies where reclassification to UC was more common [6, 14, 20]. Another recent pediatric study reported that 45% ($n = 24$) of 53 IBDU patients were later reclassified as CD and only 9% ($n = 5/53$) were reclassified as UC. However, only 89% of these patients initially underwent a full diagnostic workup that involved comprehensive endoscopy and imaging [4]. These studies suggest that pediatric CD commonly presents as isolated colitis, especially in the earlier age groups, explaining the high frequency of IBDU among children, which is subsequently reclassified to CD as the disease progresses [1].

In contrast, lower CD reclassification rates have been reported in other studies, indicating that UC reclassification is more common among pediatric IBDU patients [9, 20]. In a large study involving 210 pediatric patients from 6 tertiary pediatric gastroenterology centers, 40% ($n = 8$)

of the IBDU cohort ($n = 20$) were reclassified (75% to UC and 25% to CD) after being followed for a mean period of 2.9 years from the date of diagnosis [29]. In another more recent pediatric study, Winter et al. [6] reported that one third of individuals labeled as IBDU were reclassified following reevaluation (12% to CD and 20% to UC), while 69% retained the IBDU classification [6]. Notably, that study also noted that only half (48%) of patients initially classified as IBDU had undergone a complete diagnostic workup. This suggests that a substantial proportion of those reclassified from IBDU to CD/UC was consequent to misdiagnosis at the primary clinical assessment due to an insufficient diagnostic workup and may misrepresent the true patterns of IBDU [6].

Misdiagnosis resulting in IBDU classification at the primary assessment due to an incomplete diagnostic workup argues that reclassification at follow-up cannot be considered valid grounds for decreeing IBDU as an early stage of CD or UC. Thus, improved diagnostic criteria to better distinguish between IBD subtypes and strict adherence to proficient diagnostic investigations are vital to understanding the true natural history of IBDU. This is somewhat evident, with Birimberg-Schwartz et al. [13] reporting a reclassification rate of 21% of pediatric IBDU; this is lower than the previous reported rates of around 23–34% of a pre-Porto criteria publication [18].

Disease Location

Studies have shown that IBDU and UC share similar disease locations [7]. Disease location via complete esophagogastroduodenoscopy, colonoscopy to the cecum, and terminal ileum visualization of 158 IBDU patients was assessed in accordance with the Paris classification [8]. The majority (58%) of patients presented with pancolitis, followed by ulcerative proctitis (17%), left-sided colitis (7.6%), and extensive colitis (7.0%) [6]. These findings are supported in a more recent study which reported pancolitis as a feature in 61% (147/241) of the pediatric IBDU cohort [13].

Diagnostic histological and endoscopic findings in a different study also demonstrated the extensive nature of IBDU across the GI tract, including significant endoscopic colitis as well as gastric and esophageal involvement and histological ileal disease [30]. This study also remarked on the reduction in disease extent for IBDU patients from diagnosis to the initial follow up (average period of 1.9 years) in both endoscopic and histological extents at all sites except the duodenum [30].

The predominance of the pancolitic phenotype is reiterated by Winter et al. [6], where a striking 23% of pediatric IBDU patients also showed abnormal esophagogastroduodenoscopy results, with redness, aphthous lesions, erosions, and ulcers in the stomach, duodenum, or both [6]. Thus, it is known that IBDU presents an atypical array of inflammatory features at various locations [4].

Rinawi et al. [4] reported their IBDU cohort to have a significantly higher proportion of extensive colonic involvement at diagnosis than pediatric-onset UC (70 vs. 45%, $p = 0.02$), suggesting that at diagnosis pediatric IBDU may be more extensive than UC. This finding is comparable to the results of other pediatric studies where pancolonic involvement at diagnosis with follow-up progression to pancolitis is high among IBDU patients [1, 5, 16].

Role of Serology

Various serological tests have been examined as a way of differentiating IBD subtypes and predicting long-term disease outcomes [11, 19]. Most notably perinuclear anti-neutrophil cytoplasmic antibody (pANCA) and anti-*Saccharomyces cerevisiae* antibody (ASCA) have been considered [2]. It is the combination of both markers used to differentiate the more homogenous colonic phenotype that is important, with the diagnostic value dropping significantly among patients with overt CD and typical UC [2, 19].

In a recent multicenter study of 406 cases of PIBD, the diagnostic utility of serological studies in distinguishing IBDU from other colonic subtypes was examined [2]. This study found that ASCA+/pANCA– can differentiate Crohn's colitis and IBDU with a high positive predictive value of 96% and a specificity of 83%, albeit with a very low negative predictive value of 13% [2]. UC was differentiated from IBDU by the presence of pANCA+/ASCA– with a positive predictive value of 94% but also with a reported low negative predictive value (38%), sensitivity (65%), and specificity (66%), suggesting that the diagnostic utility of serological profiles in differentiating IBD subtypes is limited [2]. That study also reported that the most prevalent serologic profile in IBDU was pANCA–/ASCA– (41%), which aligns with findings previous reported in the literature [5, 11, 16].

Additionally, marker positivity was numerically suggestive of IBDU reclassification [2, 11] with 4/5 (80%) pANCA–/ASCA+ patients changing their initial IBDU classification to CD and 5/8 (63%) pANCA+/ASCA– IBDU patients reclassified to UC [2]. These findings, along with ASCA/pANCA positivity rates for IBDU in

the middle range between UC and CD, supports IBDU as an intermediate phenotype on the spectrum of IBD. Interestingly a recent study by Chandradevan et al. [31] further supported this serological profile of pediatric IBDU insofar that IBDU has a serology similar to that of UC, though it differs by ANCA. Furthermore they also investigated the genetic profile of IBDU, which again suggests the IBDU is on the spectrum between CD and UC, although it more closely aligns with UC [31].

Treatment and Remission of IBDU Patients

IBDU in adults has been associated with a poorer prognosis than UC in terms of a higher relapse frequency, a higher colon cancer risk, and worse outcomes following ileal pouch-anal anastomosis [19]. Contrastingly, pediatric patients labeled with IBDU have been reported to have a milder disease course than other subtypes [14]. Aloï et al. [1] reported that 69% (135) of 196 children with IBDU presented with remission/mild disease activity at the final follow-up of their study, compared to 46% (100/217; $p < 0.001$) of subjects with CD and 64% (174/271; $p = 0.3$) of those with UC. Another recent study that analyzed the pattern of mucosal healing of pediatric IBD subtypes over 3 years found that IBDU showed a reduced endoscopic and histological extent of disease at all sites excluding the duodenum [30].

The treatment burden has been reported to be significantly less for children with IBDU than for those with CD, reporting a lower use of treatment modalities including early steroid use, exclusive enteral nutrition, and immunomodulatory and biological agents [1]. The initial treatment strategies for IBDU are similar to UC, excluding surgery rates, which are higher among UC patients [1]. Remission rates and maintenance of remission with aminosalicylates alone is much higher in IBDU than in CD and UC, with studies counseling the use of aminosalicylates as the first-line treatment for active IBDU [21].

Discussion

Despite refinements in definitions of IBDU in recent years, there remain unresolved conjectures concerning the clinical features and disease course of children with IBDU. From the literature, some cases of IBDU are clearly due to a primary misdiagnosis in the face of early disease stages, especially among very young children, or incomplete investigations. Indeed, studies have reported that strict adherence to the Porto criteria including a complete

diagnostic workup has led to a reduction in IBDU rates [6] and further predict that implementation of this diagnostic criteria will reveal reduced IBDU rates among pediatric populations. However, many other studies have revealed opposing cohorts where IBDU rates remain relatively constant in the face of stricter diagnostic methods [13].

Irrespective of these differing clinical outcomes there remains a proportion of children who maintain their primary diagnosis of IBDU and as such exist in a void, presenting as neither CD nor UC but rather as a poorly classified intermediate phenotype. This warrants the need for a deeper clinical understanding of this entity, which can be achieved through wider recognition and consistent application of the current classification. More studies are warranted, with larger patient populations and longer study periods to better delineate this abstruse IBD phenotype. Reducing the ambiguity around this subtype will produce greater precision in distinguishing all PIBD subclasses, improve management and aid prognostic prediction of the clinical course.

Future understanding of IBDU aims to establish either that IBDU is an early incarnation of CD or UC and therefore evolve CD/UC definitions to accommodate for these premature stages and allow an earlier diagnosis, or rather to establish that IBDU is a separate disease entity which warrants clear diagnostic criteria and treatment/management separate to CD and UC.

Conclusion

To better demarcate cases of IBD where clinical and endoscopic features of chronic colitis do not adhere to the specific features of CD or UC, the term IBDU was proposed [11]. Under this novel term remains significant disparity around prevalence, clinical course, reclassification trends, and treatment responses for IBDU. Pediatric onset of this disease entity is more common than adult disease and thus understanding IBDU assumes more importance in this age group [15]. Despite this, the paucity of information and the lack of exclusive longitudinal studies confirm the challenge of understanding IBDU and the importance of characterizing the natural history of pediatric IBDU. Nevertheless, based on our current understanding we would advocate for acceptance of pediatric IBDU as a distinct diagnosis that can remain with the patient. We believe that with such acceptance, treatment regimes for IBDU will become more standardized and allow for better health outcomes for those who retain an IBDU diagnosis.

Disclosure Statement

The authors declare no conflict of interests.

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