Pediatric IBD-unclassified Is Less Common than Previously Reported; Results of an 8-Year Audit of the EUROKIDS Registry

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Background: Inflammatory bowel disease–unclassified (IBD-U) is diagnosed in ~10% of pediatric and adolescent onset IBD patients. The EUROKIDS registry (2004) initiated by the Porto IBD working group of ESPGHAN prospectively monitors diagnostic workup of newly diagnosed pediatric and adolescent onset IBD patients. We aimed to describe diagnostic workup, phenotype, and change of diagnosis over time in pediatric IBD-U patients.

Methods: Data were collected on children from 52 centers across 20 European countries and Israel, diagnosed with IBD from May 2005 through November 2013. Full endoscopy plus small bowel radiology was considered complete diagnostic workup. Participating centers reporting IBD-U patients were queried in 2014 for follow-up data.

Results: IBD-U was the provisional first diagnosis in 265 of 3461 children (7.7%) (91/158 [58%] with pancolitis; 140 [53%] male), diagnosed more frequently under the age of 10 (median age 12.3 years, 89 [34%] under 10 years). Half (48%) had undergone complete diagnostic workup. Lack of small bowel radiology was the prevailing reason for incomplete workup. As a result of reinvestigations (endoscopy in 54%, radiology in 38%) during a median follow-up of 5.7 years (interquartile range, 2.5–7.8), a change in diagnosis from IBD-U to Crohn's disease (12%) or ulcerative colitis (20%) was reported.

Conclusions: Only half of patients reported as IBD-U in EUROKIDS had undergone complete diagnostic workup. Follow-up with reinvestigations resulted in a reduction of IBD-U rate to 5.6%. A diagnosis of IBD-U becomes less likely in case of complete diagnostic workup. Implementation of clear diagnostic criteria will further reduce the rate of IBD-U in the future.

(Inflamm Bowel Dis 2015;21:2145–2153)

Key Words: IBD-unclassified, childhood and adolescence, Porto criteria, diagnosis, EUROKIDS registry

Thorough investigation is needed to distinguish between Crohn's disease (CD) and ulcerative colitis (UC), as the diagnostic value of presenting clinical symptoms alone (including the classic triad of diarrhea, weight loss, and abdominal pain) is limited.[1,2] Over the past 40 years, patients with "UC-like" colitis and soft features that may suggest the diagnosis of CD but without certainty

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ibdjournal.org).

Received for publication February 18, 2015; Accepted April 17, 2015.

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These findings are the result of data collected in the EUROKIDS registry, supported by the Paediatric IBD Porto Group of ESPGHAN. The views expressed in this article are those of the authors, no official endorsement by the Paediatric IBD Porto Group of ESPGHAN is intended or should be inferred.

The overview of contributing investigators from the Paediatric IBD Porto Group of ESPGHAN are listed in the Table, Supplemental Digital Content 1, http://links.lww.com/IBD/B120.

The authors have no conflicts of interest to disclose.

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DOI 10.1097/MIB.0000000000000483

Published online 9 July 2015.

have been classified as either "unclassified" (inflammatory bowel disease, type unclassified, IBD-U) or "indeterminate" colitis. The latter is a term now reserved for patients showing overlapping macroscopic and microscopic features of CD and UC in surgical specimens.[3] At the 2005 Montreal World Congress of Gastroenterology, a Working Party of investigators interested in IBD subclassification suggested that the term "inflammatory bowel disease, type unclassified" (IBD-U) should be used.[4] For pediatric patients, the original Porto criteria of the IBD working group of ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition) published in 2005 state that a diagnosis of IBD-U is acceptable only when complete diagnostic workup has been performed.[2]

Since the publication of the original Porto criteria, atypical phenotypes in pediatric and adolescent onset IBD (PIBD) presenting with colitis have been described that pose a risk of misclassification of patients.[5] In addition, novel diagnostic imaging modalities, such as magnetic resonance enterography (MRE) and wireless capsule endoscopy (WCE), have emerged, further improving our ability to detect mucosal lesions in the small bowel and to characterize PIBD subtypes.

Currently, MRE is the recommended diagnostic imaging modality for small bowel visualization,[6] because it can detect typical IBD-associated features and estimate intestinal inflammation and the degree of damage. Validation-based scoring systems are available for adult IBD patients[7,8] but still under development for PIBD patients.[9]

WCE is able to visualize the entire small bowel with minimal discomfort and can detect mucosal lesions with high sensitivity but low specificity.[10] Its use depends on local availability and expertise, and there is currently a lack of validated diagnostic criteria. Altogether these modalities have presented new challenges on how to interpret their results and correctly classify a patient suspected of PIBD.

The 2014 revised Porto criteria integrated methods for diagnosing PIBD and defining the PIBD subtypes.[6] In particular, the revised Porto criteria summarize different diagnostic features that can occur in pediatric patients with an untreated colitic phenotype as seen in IBD-U and offer recommendations on their likelihood of occurring in UC and CD versus IBD-U. As such, the revised Porto criteria provide the requirements upon which to base a diagnostic approach of IBD-U in future daily clinical practice.

We aimed to describe demographic characteristics, initial diagnostic workup, and disease phenotype at the first presentation of pediatric IBD-U patients as registered in the European registry of newly diagnosed patients (EUROKIDS) during the years 2005 to 2013. Furthermore, we provide follow-up data on diagnostic workup and disease course in these patients initially diagnosed as IBD-U.

MATERIALS AND METHODS

EUROKIDS Registry

The EUROKIDS registry is a prospective, ongoing, web-based registry of newly diagnosed patients aged 0 to 18 years in Europe and Israel, initiated in May 2004 by the IBD working group of ESPGHAN.[5,11,12] The first purpose of EUROKIDS was to enable evaluation of the quality of diagnostic workup and to describe the phenotypes at the first presentation of PIBD patients in Europe and Israel. When reporting a newly diagnosed patient to EUROKIDS, each participating pediatric gastroenterologist decides individually on the type of IBD diagnosed, as based on clinical judgment and experience, as well as results from the diagnostic workup performed within the first 3 months. Currently, 52 centers in 20 countries have participated and more than 4000 patients have been included. Details on the establishment of the registry and data collection have been previously reported.[11]

Patients

Because histological data on the presence or absence of granulomas were not available in the first year of registry, only patients diagnosed from May 2005 onward (second year of the registry) were eligible for analysis, for reasons of uniformity of data collection. Eligibility criteria further dictated a maximum age at diagnosis of 18 years and available information on the type of IBD diagnosed. All PIBD patients were sorted for age at diagnosis according to cutoffs recommended in the Paris classification (<10 years, ≥ 10 years, <17 years, and ≥ 17 years).[13] Ethics committee approval was either waived or obtained in all participating centers.

Data Inclusion Errors

All patient data for the current study were retrieved from the online EUROKIDS registry on November 12, 2013. Possible inclusion errors in diagnosing IBD-U and/or misinterpretation of results from diagnostic workup were retrospectively taken into account by examining disease phenotype and reported disease features. Only patients with colitis on (ileo)colonoscopy were deemed IBD-U in final analyses on disease phenotype. Furthermore, patients with features incompatible with IBD-U (such as granulomas, [peri-]anal disease, proven disease involvement of the small bowel) were excluded from disease phenotype analysis. Patients retrospectively excluded from disease phenotype analysis were still eligible for analysis on follow-up data.

Diagnostic Workup

The Porto criteria, originally published by the Porto IBD working group of ESPGHAN in 2005[2] and revised recently,[6] propose uniformity in diagnostic workup and classification of pediatric IBD. Both the original and the revised criteria recommend a diagnostic workup consisting of esophagogastroduodenoscopy (EGD), ileocolonoscopy (including histology in biopsies taken from all visualized bowel sections), and small bowel imaging in all suspected IBD patients; however, the latter can be deferred in otherwise typical UC. In the first years of the EUROKIDS registry, the diagnostic imaging modality for the small bowel currently recommended, MRE, was relatively novel as was WCE; small bowel follow through (SBFT) was often the first choice. Abdominal ultrasound is mostly useful in initial screening, with an ability to detect lesions of the terminal ileum but not the proximal small bowel.

For the purpose of this study, completeness of diagnostic workup was evaluated without considering histological data on the gastrointestinal (GI) tract, given the large number of patients

without a complete set of biopsies (taken from all designated GI segments). EGD and colonoscopy up to the cecum, visualization of the terminal ileum through endoscopy or radiology, and small bowel imaging if the subtype diagnosed was CD or IBD-U (i.e., by SBFT, MRE or WCE) were considered a complete diagnostic workup. Each segment visualized by EGD or ileocolonoscopy could be registered as macroscopically "normal" or "abnormal" (i.e., abnormalities consistent with IBD, such as ulcerations [including aphthous and erosions], cobblestoning, and strictures). In a similar manner, results from small bowel imaging ("normal" or "abnormal") were registered per segment of the GI tract.

Disease Location

To classify disease location reliably, we selected IBD-U patients who had undergone a complete workup at diagnosis as described above. Disease location was determined by mucosal appearance at endoscopy and was categorized as in UC according to the Paris classification[13]: (E1) ulcerative proctitis; (E2) left-sided colitis (distal to splenic flexure); (E3) extensive colitis (distal to hepatic flexure); (E4) pancolitis (proximal to hepatic flexure). Data registration did not allow for differentiation between "UC-like" continuous colitis and CD-like patchy colitis involving multiple, continuous segments.

Follow-up of Disease Course in IBD-U Patients

Patients diagnosed with IBD-U were identified for each center participating in the EUROKIDS registry. Digital follow-up forms were sent to the respective participating pediatric gastroenterologists of each IBD-U patient in the period of June until August 2014, inquiring on the use of diagnostic methods for their IBD-U patients since the date of diagnosis (i.e., EGD, ileocolonoscopy, SBFT or enteroclysis, MRE, abdominal ultrasound, CT scan, WCE, and surgery findings). Participants were asked to identify one or more diagnostic methods that were instrumental in changing the diagnosis of IBD-U into CD or UC, if applicable.

Statistical Analysis

Data were analyzed with SPSS (version 21.0; SPSS Inc., Chicago, IL). Descriptive statistics were calculated as percentages for categorical data. Continuous variables are presented as mean and SD if normally distributed, otherwise as medians and interquartile ranges (IQRs). For comparison of continuous data, the Mann–Whitney U test or Kruskal–Wallis test was used, as appropriate for the data normality and the number of contrasting groups. Statistical significance was defined as a 2-tailed P-value <0.05.

RESULTS

Demographic Characteristics of the EUROKIDS Cohort

A total of 4038 patients were entered in the EUROKIDS registry as of November 12, 2013. The number of registered patients per site varied considerably (range, 2–393). Altogether,

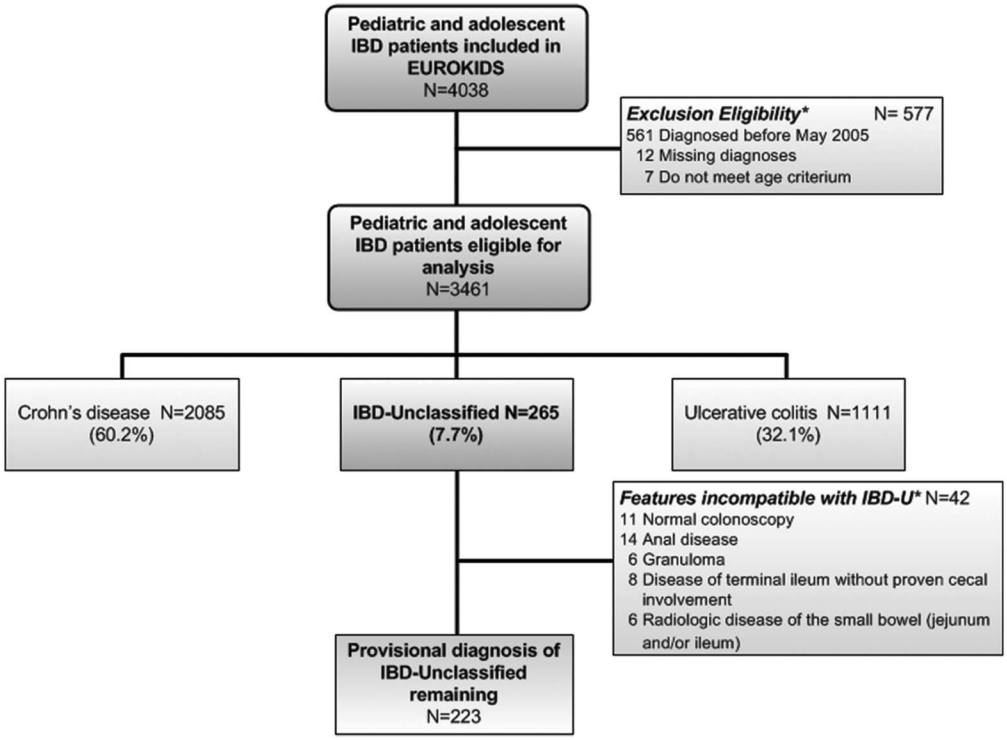

FIGURE 1. Flowchart of pediatric and adolescent inflammatory bowel disease patients from the EUROKIDS registry eligible for analysis. Features incompatible with IBD-U at diagnosis were present in 16% (42/265) of IBD-U patients. After exclusion of these patients, 223 remained with the provisional diagnosis of IBD-U. Asterisk indicates that multiple features can be present in one patient simultaneously.

TABLE 1. Basic Demographic Characteristics of PIBD Patients of the EUROKIDS Registry

	All PIBD	CD	UC	CD and UC	IBD-U
N (%)	3461	2085 (60.2)	1111 (32.1)	3196 (92.3)	265 (7.7)
Male gender (%)	1961 (56.6)	1254 (60.1)[a]	565 (50.9)	1819 (56.9)	140 (52.8)[b]
Age at diagnosis (IQR) (yr)	13.1 (10.4–15.0)	13.3 (10.9–15.1)[a]	12.9 (9.8–14.9)	13.2 (10.6–15.0)[c]	12.3 (8.5–14.8)[b]
Time symptoms to diagnosis (IQR) (mo)	4.0 (2.0–9.0)	4.9 (2.0–10.0)[a]	3.0 (1.92–6.96)	4.0 (2.0–9.0)	4.1 (2.0–9.0)[d]
Ethnicity					
White European	2998 (87.7)	1807 (87.8)	953 (86.8)	2760 (87.4)	238 (91.2)
Arab	130 (3.8)	77 (3.7)	45 (4.1)	122 (3.9)	8 (3.1)
Asian	92 (2.7)	51 (2.5)	36 (3.3)	87 (2.8)	5 (1.9)
African-Caribbean	44 (1.3)	26 (1.3)	16 (1.5)	42 (1.3)	2 (0.8)
Other	154 (4.5)	98 (4.8)	48 (4.4)	146 (4.6)	8 (3.1)
Positive family history (%)	367 (11.1)	228 (11.4)	114 (10.8)	342 (11.2)	25 (9.9)

Information on different demographic characteristics for all PIBD patients and by diagnosis of CD, UC, sum of CD and UC, and IBD-U.
[a]CD data significantly different from UC ($P < 0.05$).
[b]IBD-U data significantly different from CD ($P < 0.05$).
[c]Combined CD and UC data significantly different from IBD-U ($P < 0.05$).
[d]IBD-U data significantly different from UC ($P < 0.05$).
PIBD, pediatric inflammatory bowel disease.

577 patients were excluded from analysis because of a diagnosis before May 2005, missing information regarding diagnosis, or failure to meet the age requirement. Of the 3461 children eligible for analysis, 2085 (60%) were classified as CD, 1111 (32%) were classified as UC, and the diagnosis IBD-U was attributed to 265 (7.7%) patients (Table 1, Fig. 1).

Median age at diagnosis of IBD was 13.1 years (IQR, 10.4–15.0; 22% younger than 10 years), with 57% (n = 1961) males. Median age at diagnosis of IBD-U patients (12.3 years; IQR, 8.5–14.8) was significantly lower compared with patients diagnosed with CD (13.3 years; IQR, 10.9–15.1) or CD and UC combined (13.2 years; IQR, 10.6–15.0) (both $P = 0.001$). There was no significant difference in median age at diagnosis between IBD-U patients and UC patients (12.9 years; IQR, 9.8–14.9) alone ($P = 0.176$) or between males and females (data not shown). One-third of IBD-U patients (34%, n = 89) were younger than 10 years, significantly more than in CD (19%; $P < 0.001$) or UC (26%; $P = 0.018$). The rate of IBD-U in patients younger than 10 years was significantly higher compared with patients aged 10 years or older (89/767, 11.6% versus 176/2694, 6.5%; $P < 0.001$).

Most IBD patients were white (88%, n = 3000); 3.8% (n = 130) were of Arab origin, 2.7% (n = 92) were Asian, 1.3% (n = 44) were African-Caribbean, and 4.5% (n = 154) had another ethnicity. There was no significant difference in ethnicity between CD, UC, and IBD-U.

A positive history of IBD in first-degree relatives was found in 367 patients (11%). There was no significant difference regarding positive family history in first-degree relatives between IBD-U patients and CD patients, UC patients, or CD and UC patients combined.

IBD-U Inclusion Errors and Data Misinterpretation

One or more features incompatible with IBD-U at diagnosis were present in 42 of 265 patients (16%) reported as IBD-U; these patients were excluded from disease phenotype analysis (Fig. 1). Incompatible features included the presence of granuloma (n = 6), perianal disease (n = 14), disease of the terminal ileum without proven cecal involvement (n = 10), or radiological evidence of small bowel involvement (jejunum and/or ileum) (n = 6). In addition, 11 patients had a normal aspect of the colon during endoscopic evaluation.

Evaluation of Diagnostic Workup Within the EUROKIDS Cohort

EGD and colonoscopy had been performed in the majority of newly diagnosed PIBD patients (89% and 98%, respectively), with an overall rate of successful ileoscopies in 78%. Small bowel imaging (SBFT, MRE, and/or WCE) had been performed in 73% of CD patients compared with 62% of IBD-U patients ($P < 0.001$) and 36% of UC patients ($P < 0.001$) (Table 2). Of all patients, 60% (2083/3461) had undergone complete diagnostic workup as per our predefined criteria. Both CD patients (60%) and UC patients (64%) underwent complete diagnostic workup more frequently compared with IBD-U patients (48%, both $P < 0.001$) (Table 2).

In most cases of incomplete diagnostic workup in IBD-U patients, radiology of the small bowel had not been performed (128 cases). Other contributing causes were no evaluation of the terminal ileum either by endoscopy (75 cases) or radiology (101 cases), no or incomplete EGD (42 cases), no or incomplete

TABLE 2. Primary Diagnostic Workup in PIBD Patients of the EUROKIDS Registry

	All PIBD	CD	UC	CD and UC	IBD-U
	3461	2085	1111	3196	265
EGD (%)	3088 (89.2)	1933 (92.7)[a]	922 (83.0)	2855 (89.3)	233 (87.9)[b]
Ileoscopy (%)	2691 (77.8)	1630 (78.2)	861 (77.5)	2491 (77.9)	200 (75.5)
Colonoscopy (%)	3405 (98.4)	2037 (97.7)[a]	1104 (99.4)	3141 (98.3)	264 (99.6)[c]
SBFT (%)	944 (27.3)	639 (30.6)[a]	220 (19.8)	859 (26.9)	85 (32.1)[d]
MRE (%)	1149 (33.2)	898 (43.1)[a]	177 (15.9)	1075 (33.6)	74 (27.9)[b]
Small bowel imaging (%)	2075 (60.0)	1512 (72.5)[a]	399 (35.9)	1911 (59.8)	164 (61.9)[b]
Complete diagnostic workup (%)	2083 (60.2)	1241 (59.5)[a]	714 (64.3)	1955 (61.2)[e]	128 (48.3)[b]

Information on the use of different diagnostic (imaging) modalities for all PIBD patients and by diagnosis of CD, UC, sum of CD and UC, and IBD-U. Complete diagnostic workup was defined as EGD, colonoscopy up to the cecum, and visualization of the terminal ileum through endoscopy or radiology.
[a]CD data significantly different from UC ($P < 0.05$).
[b]IBD-U data significantly different from CD and UC ($P < 0.05$).
[c]IBD-U data significantly different from CD ($P < 0.05$).
[d]IBD-U data significantly different from UC ($P < 0.05$).
[e]Combined CD and UC data significantly different from IBD-U ($P < 0.05$).
PIBD, pediatric inflammatory bowel disease.

endoscopic evaluation of the colon (to cecum) (33 cases), or a combination of these. Technical difficulties were the predominant reason for not performing ileal intubation while EGD was often deemed unnecessary by the treating physician (Table 3). Inclusion errors as described above occurred in 16 of 128 IBD-U patients (13%) who had undergone complete diagnostic workup compared with 26 of 137 IBD-U patients (19%) with incomplete diagnostic workup ($P = 0.149$).

TABLE 3. Known Reasons for not Performing EGD or Ileal Intubation in IBD-U Patients in the EUROKIDS Registry

No EGD (N = 18)	N (%)
Not necessary as judged by endoscopist	16 (89.2)
Lack of time	2 (10.8)
No ileal intubation (N = 42)	
Technical problem	15 (35.7)
Lack of time	6 (14.3)
Insufficient preparation	6 (14.3)
Severe disease (risk of perforation)	5 (11.9)
Ileocecal stenosis	3 (7.1)
Insufficient sedation	3 (7.1)
Not necessary as judged by endoscopist	2 (4.8)
Distal stenosis	1 (2.4)
Other	1 (2.4)

Reasons for not performing either EGD or ileal intubation were analyzed. In the majority of patients, EGD was judged to be unnecessary by the treating physician (89.2%). Reasons for not performing ileocolonoscopy were more diverse and included technical difficulties, patient-related factors, and judgement by the treating physician.

The proportion of patients diagnosed with CD, UC, or IBD-U remained relatively constant during the study period (Fig. 2A). Although the quality of diagnostic workup seemed to increase during the data collection for EUROKIDS starting in 2005, the rate of complete diagnostic workup was not significantly higher when comparing the total PIBD group in 2005 to 2013 (59% versus 64%; $P = 0.360$). In UC patients, we did see a significant improvement from 2005 to 2013 (51% versus 69%; $P = 0.033$), whereas the rate of complete diagnostic workup in CD patients (65% versus 63%; $P = 0.754$) and IBD-U patients (46% versus 50%; $P = 0.768$) did not increase significantly (Fig. 2B).

IBD-Unclassified Predominantly Presents as a Pancolitic Phenotype

We determined IBD-U disease location only for those patients with complete EGD, colonoscopy up to the cecum, and visualization of the terminal ileum through endoscopy or radiology at diagnosis. A total of 158 of 223 IBD-U patients (71%) were eligible for determination of disease location according to the Paris classification.

Ulcerative proctitis (E1) was found at presentation in 17% (26/158), left-sided colitis (E2) in 7.6% (12/158), extensive colitis (E3) in 7.0% (11/158), and pancolitis (E4) in 58% (91/158). Eighteen patients (11%) displayed macroscopic patchy colitis and thus could not be classified according to the Paris classification for UC (Fig. 3). Disease extent within the IBD-U population was not dependent on age at presentation (data not shown).

In total, one-third of IBD-U patients had abnormalities on EGD and/or evaluation of the terminal ileum (n = 59; 37%), and most abnormalities were seen in patients with a pancolitic (E4) disease phenotype (Fig. 3). One in 4 had macroscopic abnormalities on EGD (n = 36; 23%) including erythema and aphthous lesions

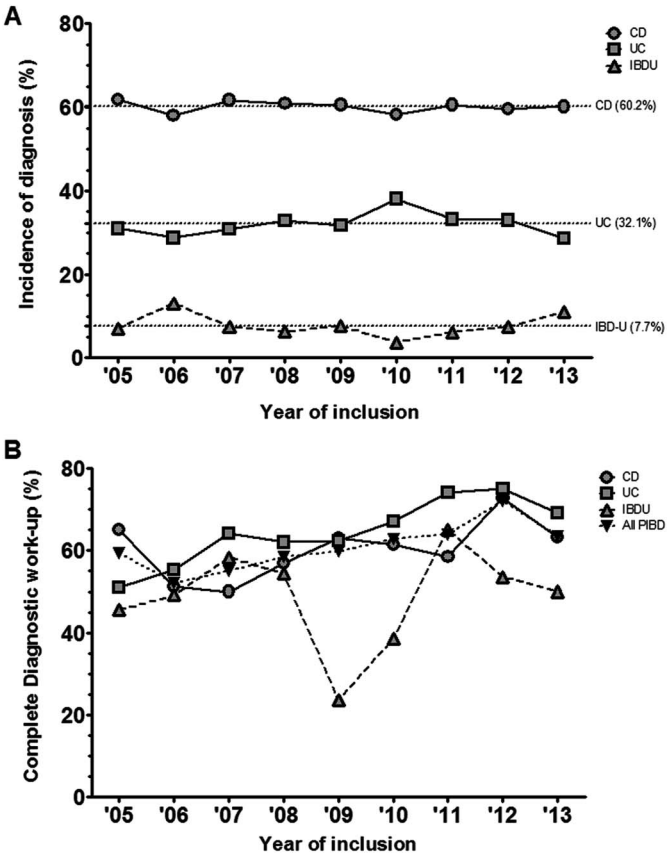

FIGURE 2. Incidence of PIBD diagnoses and rate of complete diagnostic workup within the EUROKIDS cohort from 2005 to 2013. A, The incidence of CD, UC, and IBD-U are relatively constant during the study period. Incidences within EUROKIDS for CD (60.2%), UC (32.1%), and IBD-U (7.7%) as of November 12, 2013 are indicated by their respective dotted lines. B, The rate of complete diagnostic workup within the EUROKIDS cohort for all PIBD patients and particularly UC patients steadily improved over time, whereas CD and IBD-U rates show a more variable course. Only complete diagnostic workup in UC patients has improved significantly since 2005 from 51% to 69% ($P = 0.03$). PIBD, pediatric inflammatory bowel disease.

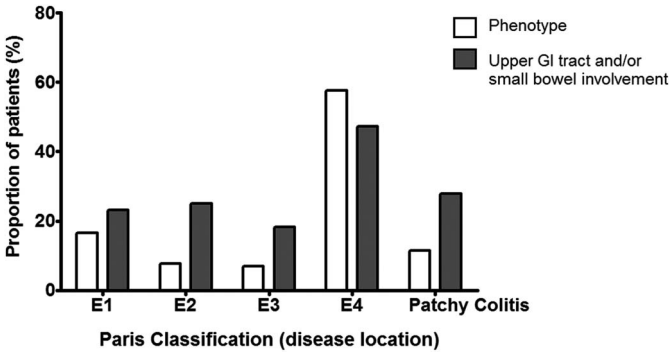

FIGURE 3. Disease location for IBD-U patients according to the Paris classification. Disease location according to Paris classification for UC was assessed for 158 pediatric IBD-U patients. More than half (58%) of IBD-U patients presented with a pancolitic phenotype (E4), followed by E1 (17%), E2 (7.6%), and E3 (7%) (white bars). One-third of patients (59/158; 37.3%) also had disease involvement of the upper GI tract and/or small bowel. Almost half of patients with E4 phenotype also had upper GI and/or small bowel involvement (43/91; 47%), followed by E2 (3/12; 25%), E1 (6/26; 23%), or E3 (2/11; 18%) (black bars). Five patients (out of 18; 28%) with a patchy colitic phenotype had disease involvement of the upper GI tract and/or small bowel. White bars represent the proportion of patients with E1, E2, E3, E4, or a patchy colitic disease phenotype. Black bars represent the proportion of patients with disease involvement of the upper GI tract and/or small bowel and the distribution per disease phenotype.

(71% in the stomach), erosions (56% in the stomach), and ulcers (in both stomach and duodenum). Disease involvement of the terminal ileum on endoscopy and/or radiology was seen in 19% (n = 30).

Taken together, a total of 112 (of the 265 originally reported) IBD-U patients remained, that had been reported correctly, had undergone complete diagnostic workup, and who had a colitis phenotype on endoscopy. Another 111 patients with a colitis phenotype were reported as IBD-U despite incomplete diagnostic workup (Fig. 4).

Repeating Diagnostic Evaluation Leads to a Further Decrease in IBD-U Incidence over Time

Follow-up forms were returned for 117 of 265 IBD-U patients (44%), including 23 patients previously excluded from disease phenotype analysis. Median time of follow-up after initial diagnosis was 5.7 years (IQR, 2.5–7.8). The provisional diagnosis of IBD-U was changed in 33% of patients (38/117); median duration until change in diagnosis was 2.7 years (IQR, 1.0–4.0). The majority was rediagnosed as UC (23/117, 20%) and the rest as CD (14/117, 12%). One patient initially diagnosed as IBD-U, in retrospect, had a non-IBD colitis. Median age at diagnosis of patients that ultimately changed diagnosis from IBD-U was 11.2 years (IQR, 7.0–14.9) and was statistically similar between patients rediagnosed as CD or UC (12.6 years; IQR, 6.8–15.4 and 10.4 years; IQR, 6.9–14.8 respectively, $P = 0.622$). Over half were males (55%), and there was no statistical difference between revised diagnosis of CD and UC concerning gender (71% versus 46% males, respectively, $P = 0.126$).

During follow-up, colonoscopy, ileoscopy, small bowel imaging, or EGD was performed at the treating physician's discretion in 50%, 45%, 38%, and 39%, respectively, of the 117 patients with follow-up data (Table 4). The rate for endoscopic reinvestigation (EGD, colonoscopy, or ileoscopy) in patients with follow-up data was 54% (63 patients), whereas the overall rate of either endoscopic or radiologic reinvestigation was 64% (75 patients). Rates of performed EGD, ileoscopy, and colonoscopy were higher in IBD-U patients who had their diagnosis changed to CD or UC (66%, 82%, and 82%, respectively) compared with patients who remained IBD-U (25%, 28%, and

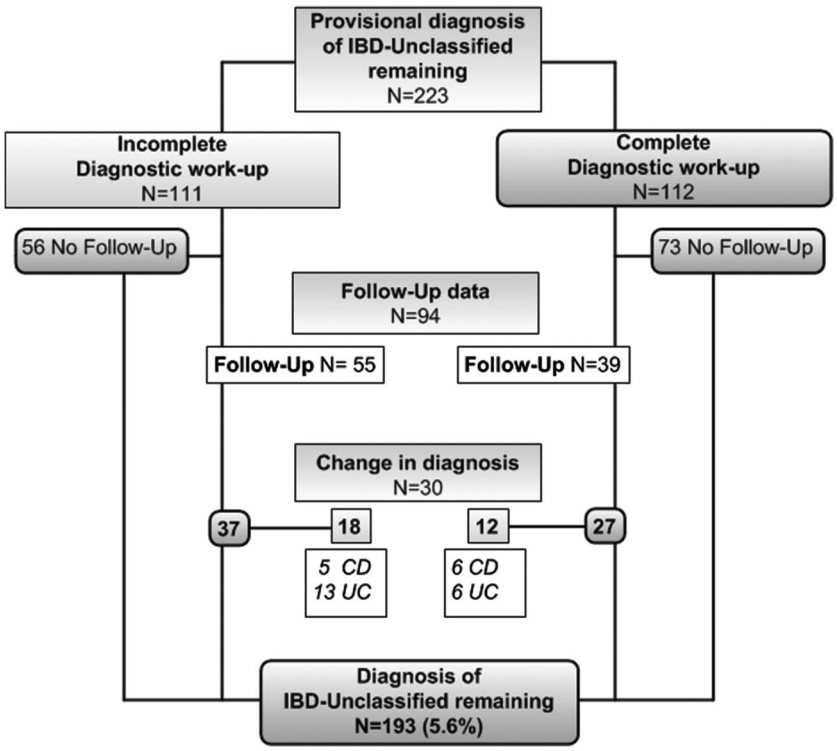

FIGURE 4. Diagnostic workup in eligible IBD-U patients at diagnosis and change of diagnosis during disease course. Half (50%) of patients with the provisional diagnosis of IBD-U had undergone complete diagnostic workup at diagnosis. Over half of patients (n = 129; 58%) did not have follow-up data and remained IBD-U. One-third of patients with (12/39; 31%) and without (18/55; 33%) complete diagnostic workup had a change of diagnosis to CD or UC over time. The diagnosis of IBD-U had not changed for all other patients with follow-up data (n = 64). Thus, incidence of IBD-U after follow-up (5.6%) is lower than initially reported at the time of diagnosis (7.7%).

34%, respectively; $P < 0.001$). Furthermore, IBD-U patients who had their diagnosis changed to CD or UC had undergone surgical procedures more often during follow-up (16% versus 3%; $P = 0.008$) (Table 4).

New insights obtained from colonoscopy (26/28 patients; 93%), ileoscopy (16/27 patients; 59%), EGD (9/20 patients; 45%), small bowel imaging (5/12 patients; 42%), or surgical intervention (2/2 patients; 100%) during follow-up were important in changing diagnosis. In 28 of 38 patients (74%), the gastroenterologist reported that histological findings altered the diagnosis of IBD-U (Table 4). There was no significant association between the use of one specific diagnostic modality and a role in changing the diagnosis of IBD-U (data not shown). Initial disease location was not significantly correlated to a change of diagnosis into either CD or UC (data not shown).

In conclusion, 12 patients (31%) with initial complete diagnostic workup had their diagnosis changed to CD or UC during follow-up. Eighteen patients (33%) with incomplete diagnostic workup at diagnosis had their diagnosis changed to CD or UC over time. Follow-up data combined with previous exclusion of patients with features incompatible with IBD-U results in a total of 193 patients (5.6%) that had maintained their diagnosis of IBD-U at follow-up (Fig. 4). The rate of IBD-U after follow-up remained higher in patients younger than the age of 10 compared with those aged 10 years or older (59/767, 7.7% versus 134/2694, 5.0%; $P = 0.004$).

DISCUSSION

After a long period of follow-up, the rate of pediatric IBD-U was reduced to 5.6% at most, much lower than the initial rate of 7.7%, which was similar to previously reported IBD-U rates of 6% to 13%, either at first presentation[1,14–17] or after reevaluation within 2 years.[18,19] Previous literature has reported a higher IBD-U rate in prospective compared with retrospective studies.[20] Our data suggest that several factors concerning both primary diagnostic evaluation and reevaluation over time account for the observed decline in IBD-U rate.

First, our analysis indicates that 16% of patients reported in EUROKIDS by their treating physician as IBD-U in retrospect had clinical, endoscopical, histological, or radiological features more compatible with CD than IBD-U. These features were more often present in patients with incomplete diagnostic workup compared with those with a complete diagnostic workup (19% versus 13%, respectively). The lack of well-defined diagnostic criteria to distinguish between (atypical) UC, Crohn's colitis, and IBD-U at diagnosis during the analyzed study period might have contributed to misdiagnosis.

TABLE 4. Follow-up Data on Repeated Diagnostic Workup in IBD-U Patients

	All Patients (N = 117)	Change of Diagnosis (N = 38)	Important Factor in Change of Diagnosis (N = 38)
EGD (%)	45 (38.5)	25 (65.8)[a]	9/20 (45.0)
Ileoscopy (%)	53 (45.3)	31 (81.6)[a]	16/27 (63.0)
Colonoscopy	58 (49.6)	31 (81.6)[a]	26/28 (92.9)
SBFT (%)	12 (10.3)	7 (18.4)[a]	1/5 (40.0)
MRE (%)	26 (22.2)	11 (28.9)	2/5 (40.0)
Small bowel imaging (%)	44 (37.6)[b]	15 (39.5)	5/12 (41.7)
Surgery (%)	8 (6.8)	6 (15.8)[b]	2/2 (100.0)
Histology (%)	—	—	28/38 (73.7)

Information on use of different diagnostic (imaging) modalities during follow-up.
[a]Significant difference between IBD-U patients who changed their diagnosis and patients who remained IBD-U.
[b]Significant difference between IBD-U patients with complete and incomplete diagnostic workup.

Second, half (52%) of PIBD patients labeled as IBD-U did not have the sufficient evaluation to warrant this diagnosis according to our predefined criteria for a complete diagnostic workup, significantly more often as compared with CD (41%) and UC (36%). Thus, lack of diagnostic criteria combined with insufficient evaluation may partially explain why a physician would prefer not to commit to type the IBD patient with colitis as either CD or UC. Interestingly, over a period of 8 years, IBD-U incidence remained relatively constant while quality of diagnostic workup for all PIBD patients improved. However, the increase in proportion of patients with complete diagnostic workup was only significant in UC and not in CD or IBD-U.

Finally, one-third of IBD-U patients with follow-up data (32%) had a change in diagnosis due to reevaluation. The proportion of patients that remained IBD-U after additional supplementary diagnostic workup during follow-up was similar for patients with complete and incomplete diagnostic workup (69% versus 67%). With improvement in primary diagnostic evaluation in children suspected of PIBD and continued reevaluation of those patients diagnosed initially as IBD-U, we expect a further decline in IBD-U incidence.

A reported positive history of IBD in first-degree relatives of 11% was similar to other reports.[17] IBD-U was more frequently diagnosed in patients younger than 10 years within our cohort, consistent with previous literature[17,18,21–23]; the high rate of IBD-U in this age group might reflect the difficulties in the initial classification of PIBD because reclassification to CD or UC often occurs.[22] In our cohort, the rate of IBD-U after follow-up declined in patients younger than 10 years (from 11.6% to 7.7%) and in patients aged 10 years or older (from 6.5% to 5.0%). Early age of disease onset (<5 years) is related to extensive disease with mostly colonic involvement.[24] The predominance of a pancolitic phenotype observed in our IBD-U patients at diagnosis might partly be due to the relatively high proportion of children younger than 10 years within our IBD-U population. Strikingly, 23% of reported IBD-U patients of all ages had an abnormal EGD with redness, aphthous lesions, erosions, or ulcers in the stomach, duodenum, or both.

To our knowledge, this is the first time demographics, diagnostic workup, and disease phenotype are described extensively for pediatric IBD-U patients. The major strengths of our study include the inclusion of many countries ensuring generalization, the prospective design, and large sample size. However, it is not without limitations. Inclusion rates have not been consistent over the years with probable underreporting in some centers. Some of the centers recorded patients retrospectively once every few months to once yearly, which may have led to some underestimation of IBD-U because with time the diagnosis often changes to UC or CD.[18,19] However, because the reported diagnosis was obtained from diagnostic workup performed within the first 3 months, we do not expect underreporting of IBD-U to have been a major factor.

Recently, the revised Porto criteria were published with specific guidelines on determining the subtypes of PIBD.[6] These guidelines are based on diagnostic features, addressing likelihood of the presence of specific features in CD, UC, or IBD-U. As such, the revised Porto criteria will result in more uniformity in subclassification of PIBD, specifically in those patients who present with an atypical phenotype.

Despite its shortcomings, the EUROKIDS web-based registry provides an excellent means of assessing disease phenotype, as well as quality and extent of diagnostic workup in daily practice currently available to pediatric gastroenterologists.

In conclusion, in-depth analysis of the data from the EUROKIDS registry show that IBD-U incidence is lower than previously reported and reinforce the importance of a complete diagnostic workup in new PIBD patients at diagnosis and during follow-up. We postulate that a diagnosis of IBD-U is less likely if a patient undergoes full endoscopy plus small bowel radiology. Furthermore, the revised Porto criteria will guide clinicians in distinguishing between UC (including the atypical phenotype), Crohn's colitis, and IBD-U.[6] Implementation of the newly defined diagnostic criteria will further reduce the rate of IBD-U in the future.

REFERENCES

1. Sawczenko A, Sandhu BK. Presenting features of inflammatory bowel disease in Great Britain and Ireland. *Arch Dis Child.* 2003; 88:995–1000.
2. IBD Working Group of ESPGHAN. Inflammatory bowel disease in children and adolescents: recommendations for diagnosis—the Porto criteria. *J Pediatr Gastroenterol Nutr.* 2005;41:1–7.
3. Geboes K, De Hertogh G. Indeterminate colitis. *Inflamm Bowel Dis.* 2003;9: 324–331.
4. Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut.* 2006;55:749–753.
5. Levine A, de Bie CI, Turner D, et al. Atypical disease phenotypes in pediatric ulcerative colitis: 5-year analyses of the EUROKIDS Registry. *Inflamm Bowel Dis.* 2012;19:1–8.

6. Levine A, Koletzko S, Turner D, et al. The ESPGHAN revised Porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr.* 2014;58:795–806.
7. Rimola J, Ordás I, Rodriguez S, et al. Magnetic resonance imaging for evaluation of Crohn's disease: validation of parameters of severity and quantitative index of activity. *Inflamm Bowel Dis.* 2011;17:1759–1768.
8. Pariente B, Cosnes J, Danese S, et al. Development of the Crohn's disease digestive damage score, the Lémann score. *Inflamm Bowel Dis.* 2011;17: 1415–1422.
9. Ruemmele FM, Hyams JS, Otley A, et al. Outcome measures for clinical trials in paediatric IBD: an evidence-based, expert-driven practical statement paper of the paediatric ECCO committee. *Gut*. 2015;64:438–446.
10. Turner D, Schünemann HJ, Griffith LE, et al. The minimal detectable change cannot reliably replace the minimal important difference. *J Clin Epidemiol.* 2010;63:28–36.
11. de Bie CI, Buderus S, Sandhu B, et al. Diagnostic workup of paediatric patients with inflammatory bowel disease in Europe: results of a 5-year audit of the EUROKIDS registry. *J Pediatr Gastroenterol Nutr.* 2012;54: 374–380.
12. de Bie CI, Paerregaard A, Kolacek S, et al. Disease phenotype at diagnosis in pediatric Crohn's disease: 5-year analyses of the EUROKIDS registry. *Inflamm Bowel Dis.* 2013;19:378–385.
13. Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis.* 2011;17:1314–1321.
14. Henderson P, Hansen R, Cameron FL, et al. Rising incidence of pediatric inflammatory bowel disease in Scotland. *Inflamm Bowel Dis*. 2012; 18:999–1005.
15. Müller KE, Lakatos PL, Arató A, et al. Incidence, Paris classification and follow-up in a nationwide, incident cohort of pediatric patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2013;57:576–582.
16. Martín-de-Carpi J, Rodríguez A, Ramos E, et al. Increasing incidence of pediatric inflammatory bowel disease in Spain (1996-2009): the SPIRIT registry. *Inflamm Bowel Dis.* 2013;19:73–80.
17. Castro M, Papadatou B, Baldassare M, et al. Inflammatory bowel disease in children and adolescents in Italy: data from the pediatric national IBD register (1996-2003). *Inflamm Bowel Dis.* 2008;14:1246–1252.
18. Heyman MB, Kirschner BS, Gold BD, et al. Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. *J Pediatr.* 2005;146:35–40.
19. Hope B, Shahdadpuri R, Dunne C, et al. Rapid rise in incidence of Irish paediatric inflammatory bowel disease. *Arch Dis Child.* 2012;97:590–594.
20. Prenzel F, Uhlig HH. Frequency of indeterminate colitis in children and adults with IBD—a meta analysis. *J Crohns Colitis.* 2009;3:277–281.
21. Martín-de-Carpi J, Rodríguez A, Ramos E, et al. The complete picture of changing pediatric inflammatory bowel disease incidence in Spain in 25 years (1985–2009): the EXPERIENCE registry. *J Crohns Colitis.* 2014;8: 763–769.
22. Turunen P, Kolho KL, Auvinen A, et al. Incidence of inflammatory bowel disease in Finnish children, 1987-2003. *Inflamm Bowel Dis.* 2006;12:677–683.
23. Mamula P, Telega GW, Markowitz JE, et al. Inflammatory bowel disease in children 5 years of age and younger. *Am J Gastroenterol.* 2002;97: 2005–2010.
24. Aloi M, Lionetti P, Barabino A, et al. Phenotype and disease course of early-onset pediatric inflammatory bowel disease. *Inflamm Bowel Dis.* 2014;20:597–605.