Diagnostic yield of upper endoscopy in paediatric patients with Crohn's disease and ulcerative colitis. Subanalysis of the HUPIR registry

Marta Kovacs, Katalin Eszter Muller, Andras Arato, Peter Laszlo Lakatos, Judit B. Kovacs, Agnes Varkonyi, Eniko Solyom, Marianne Polgar, Eva Nemes, Ildiko Guthy, Istvan Tokodi, Gergely Toth, Agnes Horvath, Andras Tarnok, Erika Tomsits, Noemi Csoszanszky, Marta Balogh, Noemi Vasse, Piroska Bodin, Antal Dezso, Laszlo Gardos, Eva Micskey, Maria Papp, Daniel Szucs, Aron Cseh, Kriszta Molnar, Doloresz Szabo, Gabor Veres, on behalf of the Hungarian IBD Registry Group (HUPIR)

⁎ Corresponding author at: 1st Department of Paediatrics, Semmelweis University, 53 Bókay Street, 1083 Budapest, Hungary.
E-mail address: vergab@gyer1.sote.hu (G. Veres).

1 Both authors equally contributed to write this paper.

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1. Introduction

Inflammatory bowel disease (IBD) is chronic inflammatory disorders of the gastrointestinal tract that have been empirically defined by clinical, pathological, endoscopic and radiological features. The etiology of IBD is currently unknown. Inflammation is hypothesized to result of inappropriate activation of mucosal immunity by environmental factors in genetically susceptible individuals.\(^1,2\)

Crohn’s disease (CD) may present anywhere in the gastrointestinal tract. Ulcerative colitis (UC) is localized in the colon although mild inflammation can affect the terminal ileum (backwash ileitis). Recently, several studies have reported that macroscopic and histological lesions in the upper gastrointestinal tract (UGI) were present both in paediatric and adult patients with UC.\(^3,4\)

Recent study showed that up to 20\% of paediatric patients and 5–15\% of adult patients with colonic involvement had diagnostic difficulties whether they have UC or colonic CD.\(^9\) Upper endoscopy may help to establish the definitive diagnosis. \(^*\)ESPGHAN’s Porto Working Group has recommended routine upper endoscopy at the initial evaluation of children suspected to have IBD (except for undoubtedly distal UC).\(^10\) During endoscopy, multiple biopsies from all segments of the upper gastrointestinal tract (esophagus, stomach, and duodenum) are needed for a complete histological evaluation.\(^10,11\)

Recently, in a large North American multicentric study 8.8\% of adult patients with CD were reported to show macroscopic esophagogastroduodenal lesions.\(^12\) In two other population-based surveys performed in Denmark, 7\% and 8\% of the adult CD patients had UGI (extending to the terminal ileum) involvement.\(^13,14\) Furthermore, Lakatos et al. found L4 involvement in 2.4\% of the adult CD patients in Hungary.\(^15\)

The majority of the European and North-American studies as well as an Australian study reported higher UGI involvement in paediatric patients suffering from CD. Routinely (regardless of symptoms) performed esophagogastroduodenoscopy (EGD) revealed macroscopic lesions in 40–64\% of paediatric CD patients.\(^1,7\) Furthermore, microscopic lesions were found in more than 70\% of patients with CD.\(^3,4\) However, Heyman et al. reported lower prevalence of gastroduodenal CD. In this multicentric US study, the proportion of patients with gastroduodenal CD increased slightly with age: 5\% of children between 0 and 5 years, 10\% of patients between 6 and 12 years, and 13\% of children between 13 and 17 years.\(^16\) Furthermore, Ammoury and Pfepferkorn reported that isolated esophageal CD was observed in 20\% of patients.\(^17\)

At present, the real significance of EGD (diagnostic yield) at the diagnostic procedure of IBD is unknown. Therefore, the primary aim of the present prospective study was to assess the characteristics of macroscopic (specific and aspecific lesions) and microscopic abnormalities found at
EGD in paediatrics patients with IBD followed-up prospectively in the HUPIR registry from 1st of January 2007 to 31th of December 2009. The secondary aim of our study was to find associations between characteristic lesions of UGI and activity indexes, and laboratory parameters.

2. Methods

On behalf of the Hungarian Paediatric Gastroenterology Society, prospective nationwide registry of paediatric IBD was launched on the 1st of January, 2007 with the cooperation of 27 institutes (clinics, hospitals, and outpatient departments).

Questionnaires were filled in by paediatric gastroenterologists, who made the diagnosis of IBD. Newly diagnosed IBD patients younger than 18 years were registered. While we assume that most newly patients were registered, we did not track the number of those not enrolled. We analyzed the data of newly diagnosed paediatric IBD patients recorded in the period between the 1st of January 2007 and the 31st of December 2009 (36 months).

The recorded data were age, gender, weight, height, presenting symptoms, concomitant diseases, EIMs (extra-intestinal manifestation), familiarity (first-degree), perianal symptoms, localization and disease activity at presentation of IBD. Furthermore, data were obtained on the date of diagnosis, results of diagnostic procedures (including endoscopy, radiology and histology), laboratory findings, surgical interventions, and details of initial treatment. The survey obtained data anonymously.

Endoscopic (normal and abnormal), histological (normal, abnormal, and granuloma) and imaging findings (normal and abnormal) have been identified in all areas (including esophagus, stomach, duodenum, and jejunum) of the UGI tract. At diagnostics procedure, paediatric gastroenterologists were asked to give a detailed description of the noted endoscopic or histological lesions found at upper endoscopy. Erosion, ulcer and aphthous lesion as well as granuloma at histology were considered to provide diagnostic help for CD (Fig. 1). Macroscopic lesions such as erythema (focal or diffuse), chronic inflammation, focal antrum gastritis, and villous atrophy at histology were not considered for characteristic lesions for CD.

The diagnostic yield of EGD was calculated for CD on the basis of relevant macroscopic lesions (erosion, ulcer, and aphthous lesions) and the presence of granuloma in the UGI tract in patients with colonic involvement only (L2). Patients with granuloma in the colon were excluded because in these cases EGD serves no help in the diagnostic procedure.

According to the Porto criteria diagnosis of IBD was based on clinical history, physical examination, radiological studies, endoscopy and histology. However, EGD and imaging studies (small bowel follow through/SBFT or MRI) were not routinely performed in all patients. Every patient was reevaluated after 3 months and 12 months following the diagnosis: physicians had to confirm the diagnosis and report the therapy applied at that time.

Disease activity at baseline was determined using validated multi-item disease activity indexes, Paediatric Ulcerative Colitis Activity Index (PUCAI) and Paediatric Crohn's Disease Activity Index (PCDAI). Activity index $> 30$

Figure 1  Macroscopic lesions found at upper endoscopy in paediatric patients with Crohn’s disease. There was no drug intake nor Helicobacter infection suggesting the lesion is probably related to Crohn’s disease. Ulcers (arrows) in the peripyloric region of the antrum (A). Severe ulcer and inflammation involving the whole gastric region (B). Duodenal ulcers (arrows) in the bulbar region (C). Aphthous lesion as an early sign of Crohn’s disease (arrow) in the duodenal bulbar region (D).
defined as moderate-severe disease, between 11 and 30 a mild disease, and <10 defined as inactive disease.

Localization and phenotype of disease were based on the Montreal classification criteria. The extent of the disease was evaluated only for those patients who had undergone a complete bowel investigation (small and large bowel visualized for CD and large bowel was visualized up to the cecum for UC). Data of the registered patients were analyzed based on the diagnosis, endoscopic, histological and imaging findings as well as on the basis of disease localization and disease activity. Ethics committee permission was obtained, data were anonymously collected.

2.1. Statistical analysis

Statistical analysis was carried out using Graph Pad Prism 5 (GraphPad, San Diego CA, USA). χ²-Test and Fisher’s exact test were used to evaluate differences between CD and UC groups, as well as within subgroups of IBD patients according to disease localization. Spearman’s rank order correlation was calculated to test the association between clinical activity indexes (PCDAI and PUCAI) and CRP, hematocrit (Htc), platelet count (PLC), and serum iron (Se Fe) levels. Mann–Whitney-test was performed to statistically compare the values of PCDAI, PUCAI, CRP, Htc, PLC, and Se Fe levels as well as differences of age between in subgroups of IBD patients (CD or UC with vs. without macroscopic and histological findings). A p<0.05 was considered significant.

3. Results

3.1. Patients with EGD

420 patients with IBD were registered in the period between 1st of January 2007 and 31th of December 2009. The number of patients with CD was remarkably higher than the number of patients with UC [265 (63%) vs. 130 (31%), p=0.0001]. Fifty-four percent of the patients with IBD were male and 46% of them female. The mean age was 13.2 years (range: 1.2–18 years). Two hundred and thirty-seven (56%) patients (112 girls, 125 boys, mean age: 13.15 years, range: 1.17–18.01) underwent upper endoscopy. Demographic data of the patients and frequency of endoscopic lesions are shown in Table 1.

3.2. Endoscopic and histological findings and associations with either disease activity indexes or laboratory parameters in patients with IBD

Macroscopic lesions were found in 64% of patients with CD and in 40% of patients with UC (CD vs. UC p=0.0028). The gastric region was the most common site to show endoscopic lesions (CD: 51% and UC: 33%). In nearly 50% of CD patients had multiple site involvement (gastroduodenal and esophagogastroduodenal). Histological lesions were found in 71% of CD patients and in 48% of UC patients (CD vs. UC p=0.0035). Similarly, the gastric region was also the most common site of histological lesions (CD: 53% and UC: 40%). No biopsy was taken from the UGI of 23 (9%) patients who had endoscopic abnormalities. Abnormal histological findings with normal macroscopic lesions at upper endoscopy were found in 35 (15%) paediatric IBD patients (26 CD, 7 UC, and 2 IBD-U). Three of these patients had granuloma. Granuloma was identified in 12 (7%) children with CD in the UGI tract. In 8 (5%) patients granuloma was found only in this area. Nineteen percent (12/62) of all granulomas were found in the UGI tract and 13% (8/62) of these were solely there. However, only 1 (2%) patient with colitis had granulomas in the UGI tract, thereby changing the diagnosis from IBD-U to CD.

CRP and PLC values were significantly higher [p(CRP)=0.022, p(PLC)=0.034] and Se Fe levels were significantly lower (p=0.0296) in patients with macroscopic lesions than in patients without macroscopic lesions of UGI tract in CD. However, PCDAI and Htc values were not different in patients

| Table 1 | Demographic data, frequency of macroscopic-, and microscopic lesions in the upper gastrointestinal tract of paediatric patients with IBD registered in the Hungarian Pediatric IBD Registry (HUPIR) from 1st of January 2007 to 31th of December 2009. |
| Number of patients | 420 | 265 (63%) | 130 (31%) | 25 (6%) | <0.0001 |
| Median age at diagnosis, (years) | 13.2 (1.2–18) | 13.5 (1.2–18) | 12.7 (2.7–17.9) | 12.7 (1.6–17.2) | 0.089 |
| Male/female ratio | 227/193 (54/46%) | 126/109 (59/41%) | 60/70 (46/54%) | 11/14 (44/56%) | 0.018 |
| EGD | 237 (56%) | 176 (66%) | 48 (37%) | 13 (52%) | <0.0001 |
| Median age at diagnosis (range) | 13.2 yr (1.2–18 yr) | 13.2 yr (1.2–18 yr) | 12.6 yr (2.7–17.9 yr) | 13.9 yr (5.4–17.2 yr) | 0.310 |
| Male/female ratio | 125/112 (53/47%) | 101/75 (57/43%) | 19/29 (40/60%) | 5/8 (38/62%) | 0.034 |
| Macrscopic lesions n (%) | 140 (59%) | 113 (64%) | 19 (40%) | 8 (62%) | 0.003 |
| Esophagus | 38 (22%) | 2 (4%) | 1 (8%) | | 0.0048 |
| Stomach | 89 (51%) | 16 (33%) | 5 (38%) | | 0.035 |
| Duodenum | 72 (41%) | 6 (13%) | 4 (31%) | | 0.0002 |
| Histological inflammation | 155 (65%) | 125 (71%) | 23 (48%) | 7 (54%) | 0.004 |
| Esophagus | 52 (30%) | 7 (15%) | 2 (15%) | | 0.042 |
| Stomach | 93 (53%) | 19 (40%) | 4 (31%) | | 0.142 |
| Duodenum | 84 (48%) | 14 (29%) | 4 (31%) | | 0.023 |

EGD: esophagogastroduodenoscopy.
with macroscopic lesions and in patients without macroscopic lesions of UGI tract in CD. The histological findings were not associated with PCDAI and laboratory values in CD.

### 3.3. Diagnostic yield of EGD

The diagnostic significance of EGD in patients with CD is depicted in Table 2. Macroscopic and/or histological lesions were noted in 141 (80%) CD patients. Erosion, ulcer, aphthous lesions, cobblestoning and the presence of L4 granuloma were found in 55 (31%) CD patients. Nevertheless, the majority (65%) of our CD patients had ileal (isolated ileal or ileo-colonic) involvement. When we evaluated these findings in the subgroup of patients with colitis (L2) without colonic granuloma, EGD helped to establish the final diagnosis in 16 (9%) CD patients (Fig. 2). However, in some of these 16 patients, CD could have been diagnosed solely on the specific colonic appearance without EGD. On the basis of the above criteria the diagnostic yield of EGD was 9% (16/176) for CD, 26% (16/61) for CD with colitis, 36% (16/44) for CD with colitis without granuloma in the colon and 7% (16/237) for IBD. Macroscopic and microscopic lesions were unspecific in UC patients and did not help to establish the diagnosis.

### 3.4. Location of CD

We analyzed the extent of disease in accordance with Montreal criteria in 143 paediatric patients with CD. UGI and ileocolonic involvement, the so-called "panenteric" phenotype (L3 + L4) was found in 42% of all CD patients and in 80% of patients with UGI involvement. In younger patients (under 8 years and between 8 and 14 years) L3 + L4 involvement was higher than in patients older than 14 years, although the difference was not statistically significant. There were no patients with isolated UGI involvement.

### 3.5. Disease activity and laboratory parameters

Disease activity index was available in 85 CD patients with UGI involvement. The majority of patients had moderate to severe disease activity. The mean PCDAI was 33.0 (range: 7.5–67.5) in CD. We did not find significant differences in the activity index values of CD patients with UGI involvement and patients not showing UGI involvement (Table 3). Analyzing the association between localization and disease activity in CD children with L4 involvement (n=41), mean PCDAI was the highest in patients with L3+L4 involvement. Nevertheless, the difference between subgroups of IBD patients concerning disease localization did not reach significance.

PCDAI correlated positively with CRP (n=103, R: 0.46, p<0.0001), with Htc (R: 0.34, p<0.0001), with PLC (R: 0.37, p=0.0001) and with low level of Se Fe (R: −0.26, p=0.0092) in patients with CD.

### 4. Discussion

According to data of the Hungarian Paediatric IBD Registry (HUPIR), macroscopic lesions were found in the UGI tract in 2/3 (64%) of paediatric patients with CD between 1st of January 2007 and 31th of December 2009. Nine percent of patients had characteristic signs for CD (ulcer, erosion, aphthous lesion, and granuloma) contributing significantly to the diagnostic workup (diagnostic yield). In nearly 50% of UC patients milder macroscopic and/or microscopic abnormalities were observed, but these lesions were unspecific and did not provide diagnostic help.

Comparison of our results with previously published data is difficult due to the fact that there is no uniform diagnostic criteria and classification of IBD. In contrast to the previous Vienna classification, the Montreal classification system does not focus only on isolated UGI involvement, but it also pays attention to the site of gastrointestinal involvement which coexists with more distal diseases. Nevertheless, a consensus regarding the definition of UGI involvement is still lacking. Recently, the Paris classification was introduced to improve the characterization e.g. of small intestinal involvement (L4a and L4b) in paediatric patients with IBD. Due to the prospective nature of our study Montreal classification was applied.

High frequency of UGI involvement in patients with IBD was reported in some previous studies. Abnormal endoscopic findings have been described in 40–64% of CD and in 13–50% of UC children. Moreover, histological inflammation has been reported in 70–90% of paediatric patients with CD and in nearly 50% of patients with UC. In these studies biopsies were taken routinely from 3 to 5 areas of the gastrointestinal tract (esophagus, stomach, and duodenum) and, additionally from abnormal looking mucosa in children with suspectable IBD. In a prospective US study – as opposed to these publications – the occurrence of UGI involvement was

<table>
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<th>Table 2</th>
<th>Frequency of characteristic macroscopic lesions, granulomas, and all macroscopic lesions in paediatric patients with Crohn’s disease.</th>
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<tbody>
<tr>
<td>EGD in children with CD (n=176)</td>
<td>All macroscopic lesions n (%)</td>
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<tr>
<td>Characteristic macroscopic lesions n (%)</td>
<td>51 (29%)</td>
</tr>
<tr>
<td>Erosion</td>
<td>24 (14%)</td>
</tr>
<tr>
<td>Ulcer</td>
<td>23 (13%)</td>
</tr>
<tr>
<td>Aphthous lesion</td>
<td>15 (9%)</td>
</tr>
<tr>
<td>Cobblestoning</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Granulomas</td>
<td>4 (2%) all 12 (7%) a</td>
</tr>
<tr>
<td>Total</td>
<td>55 (31%)</td>
</tr>
</tbody>
</table>

In cases of granulomas 8 out of 12 patients had erosions, ulcers, aphthous lesion or cobblestoning, 1 patient had mild inflammation (mucosal erythema and edema), and 3 patients had endoscopically normal-looking mucosa.
Figure 2  A. The diagnostic yield of EGD for CD on the basis of macroscopic lesions (erosion, ulcer, aphthous lesions) and the presence of granulomas in the UGI tract considering colonic disease localization without granuloma in the colon. B. Macroscopic findings of UC patients on EGD.
considerably lower according to the data of PediIBD (Pediatric Inflammatory Bowel Disease Consortium) which involved 6 regional IBD centers. Based on the data of 798 paediatric patients with CD gastroduodenal involvement was found in 5% of children between 0 and 5 years, in 10% of patients between 6 and 12 years, and in 13% of children between 13 and 17 years.16

In our study, the prevalence of endoscopic and histological findings of UGI tract in children with IBD was similar to published paediatric reports. However, Heyman and his colleagues reported lower prevalence of gastroduodenal involvement16 which could be explained by different diagnostic criteria used in this study.

According to previous data endoscopic and histological appearance of the UGI tract (e.g. the presence of aphthoid ulcers or giant cell granulomas) may confirm the diagnosis of CD in up to 25% of cases.5,24 In a prospective study published by Castellaneta et al., the significance of EGD was 20% (n=11/54) on the basis of granulomas of the UGI tract, however, in this study 4 patients had ileo-colonic disease.5 In our present study CD characteristic lesions at upper endoscopy (erosion, ulcus, aphthous lesion, and granuloma) were noted in about one third (31%) of patients with CD, nevertheless, the diagnostic yield of EGD was only 9% for CD.

Our findings confirm that endoscopic and histological abnormalities of the UGI tract are common not only in CD but also in children with UC. In 1997 Kaufman et al. reported a case series of 5 children with colitis who had been initially diagnosed with CD on the basis of UGI involvement and chronic active gastritis.25 However, subsequent clinical follow-up verified that these children had UC. Since then, many studies reported UGI involvement in UC, but the established lesions were unspecific and they might even suggest the intensification of the physiological inflammation which is always present in the gastrointestinal tract. The cause of a more severe inflammation in the UGI tract of UC patients is not clear. Probably, there are immunologic factors associated with the underlying disease which have been unknown so far. Secondary immune response to yet-unknown factors associated with the disease may be responsible for these lesions.5,26

Gastroduodenal inflammation may occur both in CD and UC. However, histological lesions in the UGI tract are unspecific and less severe in UC than in CD.3,6,27 Regarding unspecific, mild-moderate gastritis, no significant difference has been found in the two patients' groups. Focally enhanced gastritis may also occur in both diseases although it is more common in CD. Some studies reported that prevalence of focally enhanced gastritis was 43–76% in CD and 12–20% in UC.28–30 We had no opportunity to carry out a detailed analysis of histological examinations in every patient, because only normal histological appearance or histological abnormalities or the presence of granulomas were recorded on the questionnaires. In our study according to the available findings, chronic gastritis and duodenitis as well as focally enhanced gastritis prevailed in CD and mild superficial gastritis and duodenitis in UC.

Histological lesions (in three children even granuloma) were found in 35 (15%) patients with IBD when mucosa looked endoscopically normal. This underlines the importance of taking biopsies from each segment of the UGI tract, even if endoscopic findings do not indicate any abnormalities.4,10,31

In our study 19% of all granulomas were found in the UGI tract and 13% of these were localized only here. However, only 1 (2%) patient with colitis had granulomas in the UGI tract, thereby changing the diagnosis from IBDU to CD. According to published data, granuloma is common in the UGI tract of paediatric patients with CD (24–42%). However, it is highly dependent on the number of biopsies and the number of serial sections made by the pathologist6,9,29 as highlighted in a study from Philadelphia where 13.4% of the paediatric patients with CD had isolated UGI granuloma.9 Apart from IBD, granulomatous inflammation of the stomach may be caused by a number of other factors, including Helicobacter pylori (H. pylori) infection, adenocarcinoma of the stomach, sarcoidosis, and idiopathic granulomatous gastritis.32,33 However, the presence of H. pylori should not exclude a diagnosis of IBD.

In our study we found the presence of granuloma slightly lower than in these reports. This is due to the fact that biopsies were not taken in every patient and from each segment of UGI tract.

In addition, we investigated the extent of the disease in children with CD. Recent studies from Scotland and Hungary reported that "panenteric" phenotype (L3 + L4: ileocolonic and UGI involvement) was more common in children than in adult patients (43 vs. 3% and 45% vs. 28%).34,35 Based on population data from Denmark, proximal and larger extent of involved bowel segment were significantly more common in children than in adults.14 In accordance with these findings we observed similar phenomenon as "panenteric" phenotype was the most common (42%) in patients with CD. Furthermore, L3 + L4 involvement in young patients was also higher.

In accordance with the results of Tilakaratne et al. in our present study CRP correlated positively with PCDAI in patients with CD.36 Children with active disease had significantly higher CRP values compared to children with inactive disease. In contrast, in a recent Finnish study the CRP could not differentiate between active or quiescent disease in children with IBD (CD [n=27] or UC [n=33]).37 However, in the above-mentioned Australian36 and in our study the number of CD patients (n=63 [with 100 visits] and n=103) was higher than in the Finnish study (n=27). Furthermore, it should be noted that in our study a new association between PCDAI and 3 laboratory parameters (PLC, Htc, and Se Fe) were found in patients with CD. In concordance with our findings Henriksen et al. described

### Table 3

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<tr>
<th>Disease activity indexes in patients with Crohn's disease (PCDAI) who had upper endoscopy.</th>
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<tr>
<td>CD (PCDAI)</td>
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<tr>
<td>UGI+ a (n=85)</td>
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<tr>
<td>UGI− b (n=19)</td>
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<tr>
<td>Mild (n)</td>
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<tr>
<td>4</td>
</tr>
<tr>
<td>Moderate (n)</td>
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<tr>
<td>41</td>
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<tr>
<td>Severe (n)</td>
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<tr>
<td>40</td>
</tr>
<tr>
<td>Mean activity indexes (range)</td>
</tr>
<tr>
<td>33.0 (7.5–67.5)</td>
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<tr>
<td>33.0 (15–52.5)</td>
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<tr>
<td>P (UGI+ vs. UGI−)</td>
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<td>0.8298</td>
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No statistically significant differences were noted.

a Known activity index in patients with upper gastrointestinal involvement (macroscopic and/or histological findings): CD: 85/136.

b Available activity index in patients without upper gastrointestinal involvement: CD:19/40.
that patients with CD had a stronger CRP response than those with UC. 38

In addition, an association between CRP, PLC, and Se Fe values and endoscopic lesions of UGI tract in children with CD was observed. In accordance with our results, Solem et al. reported that CRP elevation was associated with clinical disease activity and endoscopic findings in CD. 39

Of note, our study has some limitations. First, according to Porto Criteria upper endoscopy is recommended in all patients with suspected IBD. Nevertheless, in this study 56% (n=237) of patients with IBD had EGD. This percentage is not too high, however, our study population and different centers represent a whole country may be more realistic for the everyday practice. In Hungary there are 9 IBD centres which perform EGD as a part of the protocol. Subgroup analyses showed that these 9 centres performed EGD in 88% of the patients (140/164 patients) throughout the study. It is of interest, that specific UGI lesions (ulcer, aphtha, and erosion) were present 35.5% of patients (38/107 patients) suggesting that there is no significant selection bias. The rate of L4 was the same in these centres. It should be noted that Porto Criteria is a logical approach in the diagnosis of IBD but it has been never validated. In a patient with pure colonic involvement and duodenal ulcer may suggest Crohn’s colitis, however, different causes of ulcer (esp. H. pylori) should be excluded. This phenomenon is related to our second limitation. In our study, H. pylori has been systematically investigated in gastric biopsies, but histology has low sensitivity. Urea breath test has a higher diagnostic yield investigated in gastric biopsies, but histology has low sensitivity. Urea breath test has a higher diagnostic yield.

In conclusion, we found frequent UGI involvement in paediatric patients with CD and UC, but abnormalities observed in UC were un specific. The specific findings (ulcer, erosion, aphtha lesions, and granuloma) were noted in about one third of patients with CD, however, EGD helped to establish the final diagnosis only in 9% of CD patients (diagnostic yield, 9%). Due to a relatively low side effect of performing an upper endoscopy in the diagnostic procedure in paediatric patients with IBD upper endoscopy is recommended.

References