**Endoscopic and Histological Assessment of Paediatric Inflammatory Bowel Disease over a three year follow-up period**

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**Conflicts of interest**

There are no conflicts of interest to declare

**Funding**

JJA is supported by a University of Southampton NIHR academic clinical fellow and has been awarded an Action Medical Research, research training fellowship. TC is supported by a Crohn's in children research association (CICRA) fellowship. EM is supported by a Hilary Marsden IfLS scholarship.

**Abstract**

**Objectives-** Discrepancies between Inflammatory bowel disease (IBD) endoscopic/histological extent are documented at diagnosis. It is unclear whether these differences persist through disease course, with potential impact on categorisation and management. We aimed to analyse the progression of disease over a 3-year period.

**Methods-**Patients aged <17 years, diagnosed between 2010-2013 at Southampton Children’s Hospital and followed-up for 3 years were eligible. Primary outcome was disease extent at diagnosis and follow-up. Data are presented as percentage of patients undergoing endoscopy. Paris classification (PC) and PC using histological, rather than endoscopic disease, were determined.

**Results-**One-hundred-and-twenty-five patients were included, 66 male; Crohn’s disease (CD) 74, ulcerative colitis (UC) 40, IBD unclassified (IBDU) 11. All had endoscopy at diagnosis. One-hundred-and-two patients underwent ≥ 1 repeat endoscopies.

Disease extent reduced from diagnosis to first follow-up endoscopy for both endoscopic and histological disease extent (CD/UC/IBDU, all p= <0.00006). Histological extent remained greater than endoscopic in CD with significant differences in stomach, ileum and large bowel at all follow-up points (p=<0.045). Endoscopic matched histological extent in UC/IBDU. Applying a modified PC resulted in significant changes for CD (L3- 27.4% to 53.2%, p=0.006, L3 + L4A- 21% to 50%, p=0.001 and upper-GI disease- 50% to 80.6%, p=0.0006) but not UC/IBDU. CD height (-0.37 to -0.25) and weight (-1.09 to -0.19) standard-deviation-scores increased from diagnosis to follow-up.

**Conclusions-**Histological disease is greater than endoscopic extent at diagnosis and during follow-up in CD, although not in UC/IBDU. Classification of disease extent in CD should be based on both endoscopic *and* histological criteria.

**Key words**

Inflammatory bowel disease; paediatric; Paris classification; Crohn’s disease; Ulcerative colitis

**What is known?**

* In paediatric inflammatory bowel disease severity and extent of disease influences management.
* Discrepancies between endoscopic disease extent and histological disease extent are documented at diagnosis but it is unknown if these persist through the disease course.

**What is new?**

* Histological disease extent is greater than endoscopic extent during follow-up in Crohn’s disease, but this is not in observed in ulcerative colitis or inflammatory bowel disease unclassified.
* It may be helpful for classification of disease extent in Crohn’s disease to be based on both endoscopic and histological criteria, a modified Paris classification.

**Introduction**

Paediatric inflammatory bowel disease (PIBD), comprising Crohn’s disease (CD), ulcerative colitis (UC) and inflammatory bowel disease unclassified (IBDU) is a chronic, relapsing condition typically presenting with severe and extensive disease in children (1, 2).

The progression of both endoscopic and histological disease in relation to treatment is likely to be valuable in order to better understand the efficacy of treatment, and in particular to assess disease control by seeing if mucosal healing is achieved (3, 4). The impact of newer therapies on mucosal healing, growth and relapse rates are positive but further data are needed in paediatric cohorts (5). There is increasing interest in the differences between endoscopic and histological disease extent (2, 6, 7). It is now accepted that histological disease is far more extensive than endoscopic disease extent at diagnosis, however only Paris classification of endoscopic disease is a validated tool for subclassification of disease and it does not consider histological disease (8). Endoscopic and histological disease extent from diagnosis through follow-up is less well documented with studies focusing on Paris classification in isolation (9-11). If mucosal healing is the aim of therapy then it is important that patients are not ‘underclassified’ based on endoscopic findings only as this may lead to under-treatment.

In this study, we detail the 3 year follow-up from diagnosis of a previously described cohort of PIBD patients and analyse the endoscopic and histological disease progression and assess any differences between endoscopic and histological disease extent over this time period. We apply a modified Paris classification of disease based only on histological disease extent to these data (excluding small bowel imaging).

**Methods**

Patients were identified from the Paediatric Gastroenterology service database at Southampton Children’s Hospital. All patients had previously been studied at diagnosis and were selected for inclusion in this study based on these criteria (2). Patients were diagnosed from January 1st, 2010 to December 31st, 2013. All were aged less than 17 years at the point of diagnosis and all were diagnosed according to the Porto criteria (12) with IBDU patients categorised according to revised Porto criteria and ESPGHAN/NASPGHAN guidelines (13). The most up to date diagnostic criteria was used at each time point.

Data for a 3 year follow-up period were collected by two individuals (JJA, QB) on a standardised proforma and all were cross-checked by the second clinician. Repeat endoscopy was performed for consideration of treatment escalation or assessment of assessment of the efficacy of anti-TNF agents in patients on these treatments. All endoscopic and histological data were collected from prospectively entered standardised electronic records at Southampton Children’s Hospital. Where patients had undergone more than 2 endoscopies during the follow-up period the first and last endoscopy data were analysed. Disease extent at diagnosis was compared to disease extent at first and most recent follow-up endoscopy. Treatment and surgical data were collected for each treatment/surgery used in follow-up period from electronic clinic letters. Growth data were collected from 2.5-3.5 years after diagnosis. Radiological data were not examined in this study.

Endoscopic disease extent was determined by a group of 4 paediatric gastroenterologists (RMB, NA, TC, AB) in line with Paris classification (8). A standardised system of taking biopsies was applied; 2 oesophageal, 2 gastric (including antral), and 2 duodenal biopsies plus 3 to 4 ileal biopsies and a colonic series (from caecum to rectum) of >8 biopsies. Histological diagnosis was based on the presence of inflammatory changes in the mucosa (acute or chronic gastritis/duodenitis/oesophagitis, cryptitis, crypt abscesses, and granulomas), architectural abnormalities (crypt distortion, crypt branching, and crypt atrophy), and epithelial abnormalities such as mucin depletion and metaplasia, alongside surface irregularities (epithelial active/regenerative changes).

The primary outcome was percentage of patients with endoscopic or histological disease at a specific location. Secondary outcomes were percentage of patients with specific Paris classification/modified Paris classification.

This retrospective study was approved and registered with the Clinical Effectiveness and Governance teams at the University Hospital Southampton NHS trust. Data are presented as percentage of patients undergoing endoscopy to that anatomical location (restriction of procedure results in more distal location data than proximal data). Statistical analysis was conducted using Fisher’s exact test (SPSS v23. IBM).

**Results**

Of 172 eligible patients identified, 125 were included and followed-up. All 47 excluded patients had transitioned to adult services or moved out of area within the 3 year follow-up period (supplementary figure 1). Median age at diagnosis 12.5 years, 66 boys; CD 74, UC 40, IBDU 11. A single patient initially classified at ulcerative colitis was re-diagnosed at Crohn’s disease following further investigations (12).

The mean time to first repeat endoscopy was 1.2 years for Crohn’s disease, 1.9 years for ulcerative colitis and 1.9 years for IBDU. Five patients (1 CD, 3 UC and 1 IBDU) underwent lower GI endoscopy only. Ileoscopy was achieved in 84% of patients undertaking colonoscopy.

Crohn’s disease

Sixty-two patients had ≥ 1 follow-up (FU) endoscopy, 39 had ≥ 2 FU endoscopies.

*Upper GI endoscopy*

At first follow-up endoscopy there was endoscopic involvement of the oesophagus in 9.8%, the stomach 37.7% and the duodenum 27.9%. Histological involvement of the oesophagus was seen in 24.6%, the stomach in 78.7% and the duodenum in 24.6%.

At most recent follow-up endoscopy (mean time from diagnosis, 2.3 years) there was endoscopic involvement of the oesophagus in 10.5%, the stomach 15.8% and the duodenum 18.4%. Histological involvement of the oesophagus was observed in 28.9%, the stomach 71.1% and the duodenum 18.4% (table 1).

*Lower GI endoscopy*

At first follow-up endoscopy there was endoscopic involvement of the rectum in 53.2%, descending colon 53.2%, transverse colon 45.9% and the ascending colon 47.5%. There was ileal disease in 46.5%. Histological involvement of the rectum was seen in 71%, the descending colon 71%, the transverse colon 72.6% and the ascending colon 72.1%. There was histological ileal disease in 78.4% of patients.

At most recent follow-up endoscopy endoscopic involvement of the rectum was observed in 38.5%, descending colon 41%, transverse colon 25.7% and the ascending colon 29.4%. There was ileal disease in 25%. Histological involvement of the rectum was seen in 69.2%, the descending colon 69.2%, the transverse colon 62.9% and the ascending colon 62.9%. There was histological ileal disease in 66.7% (table 1).

*Disease progression*

Disease extent reduced from diagnosis to first and most recent follow-up endoscopy for both endoscopic disease extent and histological disease extent at all sites (excluding the duodenum)(table 2). Despite overall disease extent reducing there was increased discrepancy between endoscopic and histological disease from diagnosis through to most recent follow-up. This was most pronounced throughout the lower GI tract (table 1 and 2).

*Paris classification*

The Paris classification of disease was applied to endoscopic and histological disease location as previously described (2). A (modified) histological Paris classification demonstrated a statistically significant increase of 25.8% in total L3 disease (p= 0.006), a statistically significant increase of 29% in L3 + L4A disease (p= 0.001) and a statistically significant increase of 30.6% in total upper GI involvement (L4 disease) (p= 0.0006), as compared to endoscopic Paris classification (table 3).

*Growth*

Follow-up growth data (height, weight and BMI SDS) were available for 66/74 (89.2%) patients. At diagnosis the median height SDS -0.37, median weight SDS -1.09 and BMI SDS -1.39. At follow-up median height SDS -0.25, median weight SDS -0.19 and median BMI SDS 0.11 (figure 1).

*Medications*

At initial follow-up endoscopy (n= 62 patients) 41.9% of patients were on a 5ASA preparation, 56.5% a thiopurine, 3.2% a biological agent and 9.7% on no maintenance medication; 19.4% were on 2 maintenance medications. At most recent follow-up endoscopy (n= 39 patients) 41.0% of patients were on a 5ASA preparation, 79.5% a thiopurine, 61.5% a biological agent and 5.1% were on no maintenance medication; 74.4% were on 2 maintenance medications.

At 3 year follow-up (74 patients), 47.3% of all patients were on a biological agent (mean time to commencing treatment from diagnosis, 1.3 years). During follow-up 53.4% of patients had been on/are currently on a 5ASA preparation (mean time to starting from diagnosis, 0.4 years) and 85.1% had been on/are currently on a thiopurine agent (mean time to starting from diagnosis, 0.6 years).

During follow-up 14 patients underwent surgery (23.3%), 10 of these procedures were resections and 4 were perianal (seton placement etc.).

*Predictors of disease extent*

The presence of granuloma at diagnosis was assessed as a predictor for disease outcome (histological or endoscopic disease extent). Supplementary table 1. Granuloma seen at diagnosis was associated with more extensive histological colonic disease (p=0.024) but not endoscopic disease at follow-up.

Ulcerative colitis

Thirty patients had ≥ 1 FU endoscopy, 12 had ≥ FU 2 endoscopies.

*Upper GI endoscopy*

At first follow-up endoscopy there was endoscopic involvement of the oesophagus in 10.7%, the stomach in 10.7% and the duodenum in 10.7% of patients. There was histological involvement of the oesophagus in 7.4%, the stomach 33.3% and the duodenum 3.7%. At most recent follow-up endoscopy (mean time from diagnosis, 2.9 years) endoscopic involvement of the oesophagus was seen in 9.1%, the stomach 9.1% and the duodenum 27.3%. Histological involvement of the oesophagus was observed in 18.2%, the stomach 27.3% and the duodenum 27.3% (table 1).

*Lower GI endoscopy*

At first follow-up endoscopy there was endoscopic involvement of the rectum in 66.7%, descending colon in 56.7%, transverse colon in 30% and the ascending colon in 23.3%. There was ileal disease in no patients. Histological involvement of the rectum was seen in 65.5%, the descending colon 39.3%, the transverse colon 31.1% and the ascending colon 27.6%. Histological ileal disease was observed in no patients. At most recent follow-up endoscopy there was endoscopic involvement of the rectum in 83.3%, descending colon 66.7%, transverse colon 58.3% and the ascending colon 41.7%. Ileal disease was rare, seen in 9.1% of patients. There was histological involvement of the rectum in 100%, the descending colon 83.3%, the transverse colon 58.3% and the ascending colon 41.7%. Histological ileal disease was observed in 9.1% (table 1).

*Disease progression*

Disease extent reduced from diagnosis to initial follow-up endoscopy for both endoscopic disease extent and histological disease extent at all sites (excluding the oesophagus and duodenum). At most recent follow-up endoscopic disease extent was less than at diagnosis and highly comparable to initial follow-up (with moderately greater lower GI disease extent). Upper GI histological disease extent was generally greater at most recent follow-up, whereas lower GI disease was highly comparable to initial follow-up (table 2).

*Paris classification*

The Paris classification of disease were applied to endoscopic and histological disease location as previously described (2). Modified histological Paris classification demonstrated an increase of 14.5% in total E1 disease and an increase of 7.6% in E4 disease, as compared to endoscopic Paris classification (table 3).

*Growth*

Follow-up growth data (height, weight and BMI SDS) were available for 35/40 (87.5%). At diagnosis the median height SDS 0.53, median weight SDS 0.14 and BMI SDS 0.36. At follow-up median height SDS 0.33, median weight SDS 0.96 and median BMI SDS 1.02.

*Medications*

At first follow-up endoscopy (n= 30 patients) 70% of patients were on a 5ASA preparation, 53.3% a thiopurine, 3.3% a biological agent and 16.7% were on no maintenance medication; 43.3% were on 2 maintenance medications. At the most recent follow-up endoscopy (n= 12 patients) 41.7% of patients were on a 5ASA preparation, 58.3% a thiopurine, 16.7% a biological agent and 16.7% were on no maintenance medication; 50% were on 2 maintenance medications.

During follow-up 2 patients underwent surgery (6.7%), both procedures were resections.

Inflammatory bowel disease unclassified

Ten patients had ≥ 1 FU-endoscopy (9 had undergone upper GI endoscopy), 4 had ≥ 2 FU endoscopies.

*Upper GI endoscopy*

At first follow-up upper GI endoscopy (n=9) there was endoscopic involvement of the oesophagus in 11.1%, the stomach in 37.5% and the duodenum in 22.2% of patients. There was histological involvement of the oesophagus in 11.1%, the stomach in 11.1% and the duodenum in no patients (table 1). Most recent follow-up data (for 4 patients undergoing a 2nd endoscopy) can be seen in table 1.

*Lower GI endoscopy*

At first follow-up lower GI endoscopy (n=10) there was endoscopic involvement of the rectum in 30%, descending colon in 30%, transverse colon in 20% and the ascending colon in 20% of patients. No ileal disease was seen. There was histological involvement of the rectum in 60%, the descending colon in 40%, the transverse colon in 30% and the ascending colon in 40% of patients. Histological ileal disease was observed in 20% of patients (table 1). Most recent follow-up data (for 4 patients undergoing a 2nd endoscopy) can be seen in table 1.

*Disease progression*

Disease extent reduced from diagnosis to initial follow-up endoscopy for both endoscopic disease extent and histological disease extent at all sites (excluding the duodenum) (table 2).

*Growth*

Follow-up growth data (height, weight and BMI SDS) were available for 11/12 (91.7%) patients. At diagnosis the median height SDS 0.08, median weight SDS -0.15 and BMI SDS -0.08. At follow-up median height SDS -0.05, median weight SDS 0.04 and median BMI SDS -0.16.

*Medications*

At initial follow-up endoscopy (n= 10 patients) 50% of patients were on a 5ASA preparation, 50% a thiopurine, none were on a biological agent and 20% were on no maintenance medication; 20% were on 2 maintenance medications. At the most recent follow-up endoscopy (n= 4 patients) no patients were on a biological therapy.

**Discussion**

Follow-up data in PIBD patients is vital to plan and assess response to treatment, with a potential shift towards achieving mucosal healing as a true definition of remission (14, 15). This study demonstrates statistically significant reductions in both endoscopic and histological disease extent from diagnosis to all follow-up points in Crohn’s disease, ulcerative colitis (excluding endoscopic disease at 2nd FU) and IBDU. Less extensive disease throughout the GI tract demonstrates effective treatment leading to macroscopic and microscopic healing. However in Crohn’s disease there are still areas of the bowel with significant active disease, and there is a discrepancy between endoscopic and histological disease extent which increases from diagnosis through follow-up. The lower GI tract has high levels of histological involvement at follow-up (ileal disease in 66.7-78.4% of patients and colonic disease in 62.9-72.6% of patients). This histological extent in not captured by the Paris classification and increased with time leading to potentially underreported disease extent during follow-up.

This discrepancy is less evident in ulcerative colitis and IBDU at follow-up compared to diagnosis (table 1). However in Crohn’s disease there are statistically significant increases in disease extent in the stomach, ileum and throughout the large bowel at all time points studied, compared to diagnosis. It is possible this reflects the transmural and systemic inflammation seen in Crohn’s disease not observed in UC or IBDU. Granulomatous disease (upper or lower GI) was present in 66.1% of initial follow-up endoscopy cases and 56.4% of most recent follow-up endoscopy cases. This is comparable to 63.8% at diagnosis and remains in line with the upper estimates (36-66%) of the presence of granulomatous disease (16, 17).

At all follow-up points there remains a significant proportion of UC patients (27.3-33.3%) with inflammatory gastritis, previous studies have demonstrated this at diagnosis and here we detail a persistence through follow-up (18, 19). Upper GI involvement remains more common in CD, with a 55.3-78.7% of patients having histologically confirmed gastric inflammation at follow-up.

Van Limbergen *et al* detailed the 2 year endoscopic follow-up of PIBD patients, finding 39% of patients had an extension of disease during this time frame (20). In CD, L3 disease was present in 16.3% of cases with L3 +L4A disease present in 43.9% at 2 year follow-up. Our study reports 6.5% of patients had L3 disease and 21% had L3 + L4A disease. In UC patients, 82.2% had extensive disease (E3 on Montreal classification, E4 on Paris classification), in our study 20% of patients had E4 disease at initial follow-up. Vernier-Massouille *et al* also described disease extension in 31% of paediatric patients with CD in 2008 (11). It may be that the apparent reduction in disease extent during follow-up during this 10 year period is due to more aggressive immunosuppression and the increasing use of biological therapies as directed by ESPGHAN/NASPGHAN guidelines (21, 22). In comparison to Van Limbergen *et al’s* study there was introduction of immunomodulatory agents at an earlier time point in this study with only 46% of children with CD on these medication within 1 year compared to 71.6% in this study. Rinawi *et al* demonstrated 28% of Crohn’s disease patients progressing to more extensive macroscopic disease over a 10 year follow-up period; although microscopic disease extent was not reassessed it’s presence at diagnosis appeared to be associated with more macroscopic disease extension during follow-up (23).

Whilst the Paris classification of disease remains an important and validated tool for classification of disease it only accounts for endoscopic disease extent. The data presented here makes a further case for the inclusion of histological disease extent in a modified Paris classification (and therefore a modified Montreal classification). In CD there is a persistent and statistically significant difference between the classical Paris classification and the modified (histological) classification, characterised by increased extensive disease (L3 + L4A) and upper GI involvement. There is a greater discrepancy at follow-up between classical and modified histological Paris classification (table 3). If mucosal healing is the aim of therapy then it is vital that patients are not ‘underclassified’ based on endoscopic findings only as this may lead to under-treatment. The role of histological disease extent on disease phenotype, progression and outcome remains uncertain and prospective longitudinal cohort studies are vital to provide an evidence base for the ultimate goal of treatment (endoscopic vs histological vs transmural healing). Additional consideration of the role of transmural healing in Crohn’s disease must be made through future studies, in addition to assessing outcome compared to mucosal and macroscopic healing.

Patients were studied at diagnosis and follow-up utilising prospectively entered data collected. All uncertain results were discussed contemporaneously at a multi-disciplinary meeting of paediatric gastroenterologists and paediatric pathologists, however inter-observer bias cannot be completely excluded from this study and is a potential weakness. Additionally there will be an intrinsic bias towards inclusion of more extensive disease in this study as those patients with worse disease/symptoms are more likely to undergo repeat endoscopy. All endoscopies were performed by a team of 4 consultant paediatric gastroenterologists using a structured biopsy system. This study focuses on disease extent as described through endoscopy and histology, Paris classification requires small bowel imaging to fully assess disease distribution however this study does not include small bowel disease diagnosed by capsule endoscopy or radiological imaging where histological evidence of disease is not simultaneously available.

Conclusion

This study provides new data detailing the location of disease in PIBD over a 3 year follow-up period. Histological disease extent remains greater than endoscopic disease extent throughout follow-up and the discrepancy increases in Crohn’s disease, but there is no significant difference in ulcerative colitis or IBDU, although fewer patients were studied. This study suggests that as histological disease extent is frequently greater than endoscopic disease extent that this should be considered when disease is classified particularly as contemporary treatment regimens are often aimed at achieving mucosal healing and long term remission.

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**Tables and Figures**

Table 1- Comparison of Endoscopy and Histological disease activity for CD, UC and IBDU. Values expressed as percentage of patients with disease that underwent endoscopy to that anatomical location for endoscopic disease and percentage patients with disease on histology for histological disease.

Table 2- Comparison of disease extent at diagnosis and follow-up for CD, UC and IBDU. Data at diagnosis taken from Ashton et al, 2016. Values expressed as percentage of patients with disease that underwent endoscopy to that anatomical location for endoscopic disease and percentage patients with disease on histology for histological disease.

Table 3- Comparison of Endoscopic verses Histological disease- Paris classification of disease location from diagnosis to initial follow-up

Figure 1- Standard Deviation Scores at Diagnosis and 3 year follow-Up in Crohn’s Disease. Data at diagnosis taken from Ashton et al (24).

Supplementary Figure 1- Number of patients undergoing repeat endoscopy during 3 year follow-up.