Improved Medical Treatment and Surgical Surveillance of Children and Adolescents with Ulcerative Colitis in the United Kingdom

Inflammatory Bowel Diseases

Improved medical treatment and surgical surveillance of children and adolescents with ulcerative colitis in the United Kingdom

--Manuscript Draft--

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Abstract:	Background: Paediatric ulcerative colitis (UC) presents at an earlier age and increasing prevalence. Our aim was to examine morbidity, steroid sparing strategies, and surgical outcome in children with active UC. Methods: A national prospective audit was conducted for the inpatient period of all children with ulcerative colitis for medical or surgical treatment in the UK over one year. 32 participating centres recruited 224 children in 298 admissions, comparisons over 6 years were made with previous audits. Results: Over six years, recording of PUCAI score (median 65)(23% to 55%, p<0.001),

	guidelines for acute severe colitis (43% to 77%, p 0.04), and ileal pouch surgery registration (4% to 56%, p<0.001) have increased. Corticosteroids were given in 183/298 episodes (61%) with 61/183 (33%) not responding and requiring second line therapy or surgery. Of those treated with anti-TNFalpha (16/61, 26%), 3/16 (18.8%) failed to respond and required colectomy. Prescription of rescue therapy (26% to 49%, p=0.04) and proportion of anti-TNFalpha (20% to 53%, p=0.03) had increased, colectomy rate (23.7% to 15%) was not significantly reduced (p=0.5). Subtotal colectomy was the most common surgery performed (n=40), and surgical complications from all procedures occurred in 33%. In 215/224 (96%) iron deficiency anaemia was detected and in 51% treated, orally (50.2%) or intravenously (49.8%). Conclusions: A third of children were not responsive to steroids, and a quarter of these were treated with anti-TNFalpha. Colectomy was required in 41/298 (13.7%) of all admissions. Our national audit programme indicates effectiveness of actions taken to reduce steroid dependency, surgery, and iron deficiency.

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To the Editors of Inflammatory Bowel Diseases,

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Dear Professor Lashner,
Dear Professor Cominelli,

Re: IBD-D-17-00570 entitled "Improved medical treatment and surgical surveillance of children and adolescents with ulcerative colitis in the United Kingdom"

We are delighted that you find our paper acceptable to publication in Inflammatory Bowel Diseases pending appropriate revision to address your reviewers' comments.

In response to the helpful and constructive suggestions from the three reviewers, we have specifically addressed all issues in our structured response and hereby submit our revised manuscript.

We believe that the amendments in response to the reviewers' comments have further improved the quality of our paper.

We are looking very much forward to your decision,

With kind regards,

Yours sincerely

Marcus KH Auth, M.D., P.D.

Consultant Paediatric Gastroenterologist

Reviewer #1:

Dear reviewer,
Thank you very much for your helpful and constructive comments, which we have all addressed in itemised form below and in our specifically revised manuscript:

1. The expression "Young UC patients" is extremely ambiguous. The absence of age restriction affects the analysis result. At least the age distribution of the patients should be demonstrated. Especially, the information of very early onset UC patient is important. Is the percentage of them changing in survey of each era? In very early onset UC patients, are there features in treatment contents and surgery rates compared with other pediatric UC patients?

We have added the fully available biometric data including age distribution (median with IQR) and gender to Materials and Methods. We fully agree with the reviewer that the information of very early onset UC patients is important, and have added the biometric data to this audit. Unfortunately we had no access to the full biometric data from the previous audit rounds to elucidate if the percentage has changed over the years, or to investigate difference on medical and surgical treatment of children initially presenting with VEOIBD or later onset IBD in this audit.
We hope that the reviewer agrees that we have not discussed this issue formally in the discussion as we are not presenting the data in this manuscript.

Materials and Methods:
32 sites in the UK (total UK population 64.1 million in 2013, Office for national Statistics) entered clinical data on up to 50 consecutive admissions of children between less than 3 and up to 18 years between 1 January and 31 December 2013.

Table 1:

Patient demographics and characteristics

		Median (IQR) **% (numerical)**
Age	**Total n=224 children**	14 (11, 15) years
Age distribution	**< 3**	0.9% (2/224)
	< 6 years	3.6% (8/224)
	6 -18 years	95.5% (214/224)

2. In Table1, ileal pouch surgery entered on registry significantly increased in round 4. Is this due to an increase in facilities with UC surgeon or due to the increasing number of pediatric UC patients with surgical indications? Does the actual surgical rate in pediatric UC in UK increase compared to the past? Does increase of anti-TNF use affect colectomy rate?

The number of ileal pouch surgery performed (n=16) was not higher than on the previous audit (n=23), however patient's details were collected on a national surgical database (1/23, 4.3% of n=23 in round 3; versus 9/16, 56% of n-16 in round 4).
To answer the first part of the questions, our surgical colleagues have previously conducted national and regional surveys among all UK paediatric surgeons with a sub-specialist interest in IBD:
Smith NP, Ba'ath ME, Perry D, Morgan LE, Lamont GL, Baillie CT. BAPS UK inflammatory bowel disease surgical practice survey. J Pediatr Surg. 2007 Feb;42(2):296-9.

"Annual consultant caseload was requested for colonoscopy, J-pouch ileoanal anastomosis (IPAA) for ulcerative colitis, and strictureplasty (Crohn's disease). The median experience with IPAA was 0.9 cases per year of consultant practice (range, 0-3.7), and 12.5% of surgeons had limited experience of revision pouch surgery. The majority have arrangements for joint operating with adult surgeons for IPAA. Experience with IPAA is limited for most surgeons. Whether children should undergo elective IPAA independent of experienced adult practitioners, who naturally assume responsibility after transition, requires careful debate."

As we have not collected follow-up data in this audit, it is possible that more patients may undergo ileal pouch surgery after transition to the adult units, keeping in mind that in this audit 90% of units were found to have transitional care in place (Table 1). Because we have been asked by all reviewers to condense the discussion in our manuscript, we have not quoted this data, but provided a short explanation in the results section and discussion:

For the first time in this audit, all medical and surgical admissions were captured for this IBD cohort over a year, and surgical data such as ileal pouch surgery were captured systematically to monitor both frequency (table 3) and outcome (tables 4+5).

Because participating centres had been asked in previous audits to enter up to 20 consecutive medical and surgical admissions per centre, we are unable to elucidate if the overall surgical rate in paediatric UC has increased over the years.
We thank the reviewer for the important question if the use of anti-TNFalpha reduces the colectomy rate. We have now provided the number of colectomies for steroid failure and compared these to the previous audits. A slight reduction of the colectomy rate versus the first audit round was not significant. On the contrary, the numbers of patients who received anti-TNFalpha for rescue therapy has increased significantly for rescue therapy (20% to 53%, p=0.03 from 2008/2010 to 2012/2014) and for maintenance from 5% to 14% (p=0.02) from 2010-2012.

Because of the relevance of the finding, we have added a statement in the abstract, results section and discussion, and have added colectomy rates and p-values under proportion of TNF-alpha usage in table 3:

Abstract:
Prescription of rescue therapy (26% to 49%, p=0.04) and proportion of anti-TNFalpha (20% to 53%, p=0.03) had increased, colectomy rate (23.7% to 15%) was not significantly reduced (p=0.5).

Results:

A comparison of this audit documenting improvements to the previous 2 national audit rounds is shown in table 3 highlighting significant increases in guideline use, PUCAI recording, Clostridium difficile (C. difficile) analysis, anti-TNFalpha use, and colectomy rate.

…

Comparison of the audits rounds illustrates an increasing number of patients receiving anti-TNFalpha for rescue and maintenance therapy, but a similar proportion of children with UC requiring colectomy (table 3).

Table3:

Variables examined	**Round 2** **2008-10**	**Round 3** **2010-12**	**Round 4** **2012-14**	χ^2 test, p-value
Plans for maintenance anti-TNFalpha	Not asked	5% (11/173)	14% (24/177)	0.02
Colectomy rate in steroid failures	23.7% (9/38)	15.2% (5/33)	15% (9/61)	0.50

Discussion:

Along with an increasing number of patients treated with anti-TNFalpha, fewer children required colectomy, although this did not reach statistical significance. For future studies, it would be valuable to examine how patients perceived the preparation and timing of colectomy with regard to their quality of life, impact on growth, puberty, and psychosocial development.

3. In Figure 4, thiopurine was used as a steroid sparing management (28/45). Condition of EBV infection should be concerned when we use thiopurine in pediatric patients. EBV titer was examined? How many centres did check EBV infection status prior to thiopurine use?

We agree with a reviewer on that point and since the audit was conducted, we and many other paediatric centres included EBV titer/EBV infection status routinely into our IBD protocol for new and existing patients. For this audit, no information had been collected how many centres assessed the EBV status before commencing thiopurines. We have forwarded this topic to the national IBD working group to address this formally in future audits and guidelines.

4. Discussion part is too long. The authors should focus more and discuss them compactly.

We agree with the reviewer and have condensed the discussion substantially from 9 to 6 pages. We have focussed on the most important findings in relation to what has been previously shown and have concluded our main findings at the end.

Reviewer #2:

Dear reviewer,
Thank you very much for your helpful and constructive comments, which we have all addressed in itemised form below and in our specifically revised manuscript:

The strengths of this study is that it is a detailed description of over 200 admissions for ASUC in children and provides reasonably contemporary outcome data. Weakness include the lack of clarity whether data at the sites were collected retrospectively, description of outcomes from over 3 years ago, and lack of focus in the discussion.

We thank the reviewer for the valuable comment and suggestions. Data were collected in the year of the audit in the individual centres with a deadline set for data entries for each patient. Analysis was then conducted by the Royal College of Physicians (RCPCH) and a generic report was prepared by the national audit leads with additional columns for each participating centre. The authors of this manuscript then compared results of this audit with previous audits and retrieved further raw data from the original dataset, once they had support from a designated statistician. Because of the substantial work involved, this process was divided between the first authors (MA and SB) and the audit team, and involved a critical and constructive reviewing process from the many centres and experts involved.
While we share the view that it is preferable to publish data as soon as possible, we believe that the strength of our paper, i.e. representative participation from 32 centres with 298 paediatric admissions, outweighs the delay mentioned.

Specific Comments:
1. Patient characteristics are described in page 8 starting line 9, but there should be a detailed "Table 1" with the characteristics of the patients (age, gender, Paris classification, medications at admission, time since diagnosis, etc)

We fully agree and consequently have generated a detailed Table 1 with those characteristics:

Table 1:

Patient demongraphics and characteristics

		Median (IQR) **% (numerical)**
Age	**Total n=224 children**	14 (11, 15) years

Age distribution	**< 3**	0.9% (2/224)
	< 6 years	3.6% (8/224)
	6 -18 years	95.5% (214/224)
Gender	**Female 50.4% (113/224)**	Male 49.6% (111/224)
Paris classification	**Proctitis (E1)**	3% (8/298)
	Left sided (E2)	18% (54/298)
	Extensive (E3)	17% (52/298)
	Pan colitis (E4)	51% (151/298)
	Unknown	11% (33/298)
Medication of patients not admitted from clinic	**5-ASA**	52% (53/103)
	Steroids	52% (53/103)
	Topical	52% (53/103)
	Thiopurine	52% (53/103)
Ambulatory disease management	**Days prior to admission**	26 (7, 61) days
Previous admissions	**Admitted for UC in previous 2 years**	41% (92/212)
PUCAI	**On admission**	60 (50, 70)
	On discharge	15 (7.5, 25)
Length of stay		6 (3, 10) days
Type of admission	**Newly diagnosed severe UC**	18% (55/298)
	Emergency admissions for established UC	44% (131/298)

	Elective medical or surgical admissions for known UC	27% (52/298)
	Transfer from other sites	11% (36/298)
Comorbidity	**None**	82% (245/298)
	Cardiovascular	0.3% (1/298)
	Respiratory	4% (11/298)
	Diabetes	1% (4/298)
	IBD related liver disease	7% (20/298)
	Active cancer	0.7% (2/298)
	Other	6% (17/298)
Admissions	**n=298 admissions**	13 (11, 14) years)

2. It appears a major conclusion is that by conducting these audits, sites improve in quality improvement measures and while these measures are detailed in Table 1, there is little mention of the measures specifically in the results (more on patient characteristics and treatment).

Quality improvement measures have been applied to outpatient and inpatient management of these patients, and different audit rounds have focussed on different aspects of the overall management, e.g. provision of specialist nurses and dieticians with telephone and clinic access. As markers for quality improvement, in this paper we have presented results for steroid dependency, treatment of iron deficiency anaemia, and colectomy rate. Other quality measures from the full audit report (ref. 17), such as proportion of bone protection prescribed (addressed for the first time in this audit round), were not presented here to keep the focus and manuscript length concise.
Following the reviewer's advice, we have the following paragraphs about quality improvement.

As explained in question 1, we have added a new table (new table 1), which summarises measures taken, e.g. recognition of disease activity by applying PUCAI scores, attempts to reduce waiting time from symptom presentation to treatment by availability of specialist nurse, reduction of steroid side effects by prescription of second-line treatments, etc. We have added colectomy rate into the amended new table 3, and have discussed the effect of these measures taken:

Table 1:
Patient demographics and characteristics

(please refer to table above in question 1)

Results:

Comparison to previous audits

A comparison of this audit documenting improvements to the previous 2 national audit rounds is shown in table 3 highlighting significant increases in guideline use, PUCAI recording, Clostridium difficile (C. difficile) analysis, anti-TNFalpha use, and colectomy rate.

Quality improvement

The national and local efforts to improve service provision by implementing action plans from previous audits is reflected in table 3, indicating increase of clinical nurse specialists, establishment of guidelines for ASC, recording of PUCAI score, transitional care plans, and other (table 3). The high proportion of patients seen within 7 days reflects improvements in surveillance and efficacy of specialist service response for children with UC.

Table 3:

Comparison of the paediatric data in 3 rounds of the national UK inflammatory bowel disease (IBD) audits

Variables examined	**Round 2** **2008-10**	**Round 3** **2010-12**	**Round 4** **2012-14**	χ^2 test, p-value
Relapsing patients seen within 7 days	87% (20/23)	91% (21/23)	94% (29/31)	0.71
Colectomy rate in steroid failures	23.7% (9/38)	15.2% (5/33)	15% (9/61)	0.50

Some of the measure in table 1 are difficult to understand including "Relapsing patient seen within 7 days" (7 days from when, when are they assessed to be relapsing - and also this is not a patient specific metric) - in general the quality indicators should be better defined.

The quality indicators from Table 1 were chosen by national adult and paediatric leads, sometimes as part of overarching national quality improvement programs e.g. for waiting times or transition arrangments, and published in national IBD standards. As suggested by the reviewer, we have provided an explanation for measures presented in table 1 (now table3) and the reference link to the national IBD standards:

Results:

Quality improvement

Based on agreed national IBD standards, the concept for service improvements was to implement local actions identified as problems in previous audits (7). This is illustrated in table 3, indicating increase of clinical nurse specialists (who provide direct and continuous contact and advice), establishment of guidelines for ASC (to reduce treatment variability and

provide adherence to evidence-based protocols), recording of PUCAI score (to reduce bias in assessment of disease activity and treatment), transitional care plans (to facilitate continuity of specialist care), and other (table 3) (7). It had been recognised in previous audits that GPs in the UK were unfamiliar in the management of children with IBD, therefore the high proportion of patients seen within 7 days reflects improvements in surveillance and efficacy of a more rapid specialist service response for children with UC.

3. The discussion is simply too long and diffuse at 9 pages. Should really be 4-6 pages. There is a lot of data in this paper but the authors would better serve the reader by narrowing down on what they feel the most important findings are, how it fits with what has previously been shown, and conclude with the main conclusions.

We agree with the reviewer and have condensed the discussion substantially from 9 to 6 pages. We have focussed on the most important findings in relation to what has been previously shown and have concluded our main findings at the end.

Reviewer #3:

Dear reviewer,
Thank you very much for your helpful and constructive comments, which we have all addressed in itemised form below and in our specifically revised manuscript:

Anyhow, the results and discussion sections are not well balanced; in fact, the result section is quite short, even though crowded with data, giving lots of interesting information that may, however, be difficult to be the fully extrapolated from the text by the readers. I would suggest expanding this section, in order to "dilute" the data for easier reading. On the contrary, the discussion is very long and should be shortened.

We agree with the reviewer that some of the results data could be better illustrated. Accordingly, to dilute some of the data for the readers, we have added table 1 which illustrates patient demographics and some of the text section of the results from this audit.
In further response, we have condensed the discussion substantially from 9 to 6 pages. We have focussed on the most important findings in relation to what has been previously shown and have concluded our main findings at the end.

Table 1:
Patient demographics and characteristics

		Median (IQR) **% (numerical)**
Age	**Total n=224 children**	14 (11, 15) years
Age distribution	**< 3**	0.9% (2/224)
	< 6 years	3.6% (8/224)
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Paris classification	**Proctitis (E1)**	3% (8/298)
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	Steroids	52% (53/103)
	Topical	52% (53/103)
	Thiopurine	52% (53/103)
Ambulatory disease management	**Days prior to admission**	26 (7, 61) days
Previous admissions	**Admitted for UC in previous 2 years**	41% (92/212)
PUCAI	**On admission**	60 (50, 70)
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Length of stay		6 (3, 10) days
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	Elective medical or surgical admissions for known UC	27% (52/298)
	Transfer from other sites	11% (36/298)
Comorbidity	**None**	82% (245/298)
	Cardiovascular	0.3% (1/298)
	Respiratory	4% (11/298)
	Diabetes	1% (4/298)
	IBD related liver disease	7% (20/298)

	Active cancer	0.7% (2/298)
	Other	6% (17/298)
Admissions	**n=298 admissions**	13 (11, 14) years)

Another critical point is that two centers (Liverpool and Newcastle) enrolled almost half of patients (41%); indeed, this issue greatly reduces the statistical weight of those centers, which have contributed with smaller number of patients. It would be interesting to have a table showing the number of patients enrolled by each single center. In addition, it may be worthy to show whether or not there are discrepancies in caring strategies in the different centers, according to the center size.

In response to the reviewer's suggestions, we have added a table with number of patients enrolled by each single centre (table 2). 13 centres entered more, and 15 centres more than the median. One purpose of the audit was to capture the real-life patient experience throughout the country, acknowledging existing variation in commissioning and service provision, to identify and address regional areas for development.
As briefly outlined in the discussion, Liverpool and Newcastle had no discrepant caring strategies, apart from Liverpool (50/298 admissions) using high dose intravenous steroids as first line treatment in acute severe colitis, and their experiences have been published before (reference 22) and are briefly discussed. As explained in the results section, Newcastle and Liverpool had a larger IBD population and had medical care arrangements to admit patients from their population directly into their (tertiary) hospitals. We acknowledged that in table 2, results and discussion.

Table 2: National recruitment of children with UC admitted over 1 year

Centre	**City**	**Admissions**
Alder Hey Children's Hospital	Liverpool	16.8% (50/298)
Great North Children's Hospital	Newcastle upon Tyne	12.1% (36/298)
Chelsea and Westminster Hospital, Children's Services	London	5.7% (17/298)

Birmingham Children's Hospital	Birmingham	5.4% (16/298)
Royal Hospital for Children Glasgow	Glasgow	5.4% (16/298)
Royal London Children's Hospital, Barts Health	London	5.0% (15/298)
Southampton Children's Hospital	Southampton	4.7% (14/298)
Leicester Royal Infirmary Children's Hospital	Leicester	4.0% (12/298)
Royal Bristol Hospital for Sick Children	Bristol	3.7% (11/298)
King's College Hospital	London	3.7% (11/298)
Children's Hospital, John Radcliffe	Oxford	3.4% (10/298)
Leeds General Infirmary	Leeds	2.7% (8/298)
University Hospitals of North Midlands	Stoke	2.7% (8/298)
Royal Hospital for Sick Children Edinburgh	Edinburgh	2.0% (6/298)
Nottingham Children's Hospital	Nottingham	2.0% (6/298)
Royal Free Hospital	London	2.0% (6/298)
Queen Mary's Hospital for Children	St Epsom and Helier	2.0% (6/298)
St George's Hospital	London	2.0% (6/298)

Morriston Hospital	Swansea	1.7% (5/298)
Addenbrooke's Hospital	Cambridge	1.7% (5/298)
Tunbridge Wells Hospital	Maidstone	1.7% (5/298)
Royal Aberdeen Children's Hospital	Aberdeen	1.3% (4/298)
Royal Belfast Hospital for Sick Children	Belfast	1.3% (4/298)
Royal Devon and Exeter Hospital	Exeter	1.3% (4/298)
Great Ormond Street Hospital	London	1.3% (4/298)
Luton and Dunstable University Hospital	Luton	1% (3/298)
Sheffield Children's Hospital	Sheffield	1% (3/298)
Noah's Ark Children's Hospital	Cardiff	0.7% (2/298)
Jenny Lind Children's Hospital	Norwich	0.7% (2/298)
University Hospital of North Tees	Hartlepool	0.03% (1/298)
The Children's Hospital Lewisham	Lewisham	0.03% (1/298)
Royal Manchester Children's Hospital	Manchester	0.03% (1/298)
Queen's Hospital Burton	Burton	0% (0/298)

Results:

The mode of admission (elective versus emergency) was higher electively in Liverpool/Newcastle (20/86, 23%) versus others (23/212, 11%)(p=0.004) and respectively Liverpool/Newcastle had a lower rate of emergency admissions (30/86, 35%) versus other centres (102/212, 48%) (p=0.037). A slightly higher rate of readmissions of children with UC

in Liverpool/Newcastle in the previous two years (54/86, 63%) versus others (112/212, 53%) was statistically not significant (p=0.12), and if patients had to be admitted for surgery or had surgery performed their proportion was similar in Liverpool/Newcastle to the other centres.
Although not formally asked in the audit questionnaire, we further interviewed participating centres if there was a treatment difference regarding steroid application, steroid sparing, 2nd line therapy, or use of biologics. In their region, children requiring inpatient treatment for UC were always admitted in Liverpool and Newcastle, while it was practice in some other tertiary centres to arrange admission and treatment for less severe UC in secondary hospitals from their network. In acute severe colitis (PUCAI score 65-85) , the Liverpool centre administered i.v. steroids as high dose bolus (20mg/kg), but applied similar second line treatment and steroid reduction scheme as other units.

Discussion:
Notably, an alternative treatment for successful treatment of ASC published recently by the Liverpool centre, was applied in 5% (15/298) of children admitted in this audit (22). Based on a short-term course of high dose (20mg/kg) iv methylprednisolone, with this protocol the steroid dependency rate had been reported before as 21% after 6 months and 0% after 1 year (22).
…
In contrast to other published national reports, which were limited to tertiary centres (14, 19,30), our audit was truly representative for the national practice including 9% of patients with severe UC managed in non-specialised sites. We observed a wide range in the catchment area, size of the IBD population, and referral pattern within regional networks over the audit period. The audit illustrated variation in areas of service provision (e.g. risk assessment by a nutritional screen) or compliance to quality standards (e.g. prescription of bone protection), which enables each individual hospital to benchmark against the national median and IQR (7, 17).

Furthermore, we examined key indicators of care provisions in hospitals admitting between 6 (2%, 6/298) and 50 admissions, which comprised 85.2% (254/298) admissions. These included 7 variables: (i) Seen by a paediatric IBD nurse during admission in patients admitted as an emergency, (ii) Recording of PUCAI score on Day 1 of emergency admissions, (iii) Stool sample sent for standard stool culture (SSC), where the patient had diarrhoea, (iv) Stool sample sent for Clostridium difficile toxin (CDT), where the patient had diarrhoea, (v) Nutritional screen (risk assessment) undertaken during admission, (vi) Bone protection prescribed in those discharged home on steroids, (vii) Clear plan to follow up the patient that was recorded in the notes at discharge. This yielded a wide range of individual hospital's fulfilment from 0% to 100%, which revealed gaps both in larger and smaller recruitment sites. Data from this audit did not suggest fundamental discrepancies between centres of different sites, but comparison of different rounds of audits suggested that participation in the audit contributed to improving delivery of nationally agreed protocols and standards.

As hospitals with 0-5 admissions (14.8%, 44/298 from all admissions) had not been sub-analysed by the audit leads individually, unfortunately we are unable to calculate discrepancy of treatments according to centre size between all centres.

Together with the results on anaemia, Authors may want to add, if possible, data on other extra-intestinal manifestations, about their distribution and therapies.

We have added data on extra-intestinal manifestations in an additional table 1:

Comorbidity	**None**	82% (245/298)
	Cardiovascular	0.3% (1/298)
	Respiratory	4% (11/298)
	Diabetes	1% (4/298)
	IBD related liver disease	7% (20/298)
	Active cancer	0.7% (2/298)
	Other	6% (17/298)

This was asked the first time in the national audit and unfortunately no further questions had been asked about distribution and therapies. However, our centre has addressed the issue of paediatric primary sclerosing cholangitis in a global multi-centre paper published recently (Deneau MR, et al. The natural history of primary sclerosing cholangitis in 781 children: A multicenter, international collaboration. Hepatology. 2017 Aug;66(2):518-527. doi: 10.1002/hep.29204. Epub 2017 Jun 26.).

3. The discussion is simply too long and diffuse at 9 pages. Should really be 4-6 pages. There is a lot of data in this paper but the authors would better serve the reader by narrowing down on what they feel the most important findings are, how it fits with what has previously been shown, and conclude with the main conclusions.

We fully agree with the reviewer. Accordingly, we have condensed the discussion substantially from 9 to 6 pages and have rewritten some paragraphs e.g. for analysis of surgery or for geographical differences. We have focussed on the most important findings in relation to what has been previously shown and have concluded our main findings at the end:

Conclusions:
Over 6 years, progress has been made that nearly all centres providing secondary and tertiary gastroenterology contributed to the national audit rounds, applying agreed quality standards of PUCAI score, guidelines for acute severe colitis, and ileal pouch surgery

registration. Nearly all children admitted had iron deficiency anaemia and half of them were prescribed oral or intravenous iron therapy, both considered as effective. More than half of inpatients with UC required iv steroids and of those one third were not responding and requiring second line therapy or surgery.

More than half children with rescue therapy received anti-TNFalpha, and nearly 20% of those failed to respond and required colectomy. Although prescription of rescue therapy (50%) and proportion of anti-TNFalpha (50% of those) had significantly increased, over a period of 6 years the reduction of colectomy rate (15%) had not reached statistical significance. Subtotal colectomy was required in 13.7% of patients admitted, nearly half of them admitted non-electively, and complications occurred in one third of surgical patients with UC.

Our national audit programme has proven effective to reduce steroid side-effects and iron deficiency anaemia in children with UC. Although over 6 years in the era of biologics there was a trend of decreasing colectomy rates, nearly half of children requiring colectomy had to be operated non-electively, indicating the importance of early recognition, optimising treatment, and collaborative gastro-surgical assessment.

IMPROVED MEDICAL TREATMENT AND SURGICAL SURVEILLANCE OF CHILDREN AND ADOLESCENTS WITH ULCERATIVE COLITIS IN THE UNITED KINGDOM

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Abstract

Background:

Paediatric ulcerative colitis (UC) presents at an earlier age and increasing prevalence. Our aim was to examine morbidity, steroid sparing strategies, and surgical outcome in children with active UC.

Methods:

A national prospective audit was conducted for the inpatient period of all children with ulcerative colitis for medical or surgical treatment in the UK over one year. 32 participating centres recruited 224 children in 298 admissions, comparisons over 6 years were made with previous audits.

Results:

Over six years, recording of PUCAI score (median 65)(23% to 55%, p<0.001), guidelines for acute severe colitis (43% to 77%, p 0.04), and ileal pouch surgery registration (4% to 56%, p<0.001) have increased.

Corticosteroids were given in 183/298 episodes (61%) with 61/183 (33%) not responding and requiring second line therapy or surgery. Of those treated with anti-TNFalpha (16/61, 26%), 3/16 (18.8%) failed to respond and required colectomy. Prescription of rescue therapy (26% to 49%, p=0.04) and proportion of anti-TNFalpha (20% to 53%, p=0.03) had increased, colectomy rate (23.7% to 15%) was not significantly reduced (p=0.5).

Subtotal colectomy was the most common surgery performed (n=40), and surgical complications from all procedures occurred in 33%. In 215/224 (96%) iron deficiency anaemia was detected and in 51% treated, orally (50.2%) or intravenously (49.8%).

Conclusions:

A third of children were not responsive to steroids, and a quarter of these were treated with anti-TNFalpha. Colectomy was required in 41/298 (13.7%) of all admissions. Our national audit programme indicates effectiveness of actions taken to reduce steroid dependency, surgery, and iron deficiency.

Key words:

Ulcerative colitis, anti-TNFalpha, colectomy, iron deficiency, steroid dependency.

Background:

Ulcerative colitis (UC) developing in the paediatric age range tends to be more extensive and severe than seen in adult patients with higher colectomy rates (1). Recent advances in standardising (with the aim of improving) care of young people with UC include the development and validation of a simple clinical scoring system for disease activity, the Pediatric UC Activity Index (PUCAI) (2,3) together with publication of evidence based guidelines for the management of paediatric UC and acute severe ulcerative colitis (ASC) (4,5). UK national standards of care for adults, children and young people with UC have also been outlined by the National Institute for Health and Care Excellence (NICE) (6) and the UK IBD Standards (7).

A modest increase in the incidence of paediatric UC has been reported (8-10). The disease adversely affects quality of life (11,12) and the three-month, per-patient cost for UC was calculated at £1211 in 2010 (13), with the majority of this cost attributed to inpatient stays. It is therefore important both on a patient level and national level to understand details of inpatient care required by children and young people with UC.

Majority of inpatient care of young people with UC is for the management of ASC, a potentially life threatening condition. Approximately 70% of children with ASC respond to intravenous steroids and in those non-responsive to steroids therapeutic options are either surgical colectomy or second line rescue medical therapy (Cyclosporin, Tacrolimus, Infliximab). Historically rates of rescue medical therapy were low (26%) and colectomy rates high (30-70%) (14,15) but this pattern is changing towards most children, in the absence of a surgical

abdomen or toxic megacolon, being offered medical rescue therapy (4,5) reducing the short term colectomy rates in ASC to 10-20% (15,16).

A national IBD audit has been undertaken on 4 occasions in the UK. The first round did not include paediatric sites and was published in 2006. The subsequent audits - round 2 (2008), round 3 (2010) and round 4 (2013) have all included paediatric sites. UK IBD audit paediatric data from 2008 and 2010 have been compared in a previous publication (14) and showed improvements in some elements of inpatient care of children with UC, including centres delivering higher rates of rescue therapy in patients who did not respond to steroids. However round 2 and 3 audits were of the total paediatric inflammatory bowel disease population and therefore had proportionally small numbers of children with UC.

The fourth round of the UK IBD 2013 audit focussed exclusively on the inpatient care provided to young people admitted to children's hospitals in the UK for treatment of UC, including those undergoing surgery. A report on this and previous audits was generated from the Royal College of Physicians to enable hospitals and paediatric services to implement action plans and changes and benchmark their centre against national standards (17).

We aim to examine morbidity and escalation treatment for children with active UC, steroid sparing strategies, proportion of second line treatment and surgical outcome, highlighting geographical differences, areas of improving practice and areas for future development.

Materials and Methods:

Following prospective identification and notification of 35 secondary and tertiary hospital sites with a defined IBD lead, via a secure web-based data collection tool, 32 sites in the UK (total UK population 64.1 million in 2013, Office for national Statistics) entered clinical data on up to 50 consecutive admissions of children between less than 3 and up to 18 years between 1 January and 31 December 2013 (table 1). The vast majority of sites took part with 24/25 specialist paediatric sites and 8/10 non-specialist sites giving an overall UK site participation rate of 32/35 (94%) (table 2). The primary reason for the admission had to be for the treatment of UC and each admission must have been longer than 24 hours, thus excluding patients admitted only for endoscopy. Newly diagnosed cases, established diagnoses as well as multiple admissions of the same patient could be included. There were no age restrictions but patients had to be admitted to a paediatric centre for inclusion in the paediatric audit. It was predicted that very few UK paediatric sites would reach 50 admissions for UC over the course of a year so this methodology would therefore theoretically encompass 100% of their inpatient UC case load. A small number of questions also addressed the outpatient care provided to each patient prior to their admission to hospital.

Disease extent was defined using the Paris Classification (18) (table 1). Disease activity was assessed using the PUCAI score which is a validated, non-invasive, multi-item measure of disease activity with established cut-off values for remission (10 points), mild (10–34 points), moderate (35–64 points), and severe disease (65–85 points) (2,3). All data analysis including statistical analysis was performed by statisticians (LJW, HE, AP). Data are present as n (%) for categorical data or median interquartile range [IQR]) for continuous data. Analysis was

conducted using either a chi-square test, Fisher's exact test, or Mann–Whitney test as appropriate. $P < 0.05$ was taken to indicate statistical significance. All analysis was performed using Stata 11 (StataCorp LLC, College Station, Texas 77845-4512, USA).

Ethical considerations:

Ethical permission was not required as this was an audit of clinical practice and all data was anonymised.

Results:

Demographics and disease localisation

Demographics, disease location, ambulatory time and disease activity are summarised in table 1. The proportion of children admitted in non-specialised paediatric sites was 9% (27/298) (table 2).

Comparison to previous audits

A comparison of this audit documenting improvements to the previous 2 national audit rounds is shown in table 3 highlighting significant increases in guideline use, PUCAI recording, Clostridium difficile (C. difficile) analysis, anti-TNFalpha use, and colectomy rate.

Patient distribution

The median number of children entered per site was 6 (IQR 3,9). There were 2 outliers with regard to number of children entered, Liverpool and Newcastle, entering 50 and 36, respectively. These 2 centres together entered 41% of all cases (see further below).

Excluding multiple admissions of the same child, 25% (55/224) were first presentations of UC. Considering previous admissions (41%), 17% had been readmitted within 30 days. The majority (61%) of patients with established UC were felt to have active disease when seen in an outpatient appointment prior to the admission and were admitted from clinic (27%), had their treatment changed (19%), but 54% were neither admitted to hospital nor had their treatment changed at that time. Standard stool cultures were sent off in 69% (85/123) of children with diarrhoea, with 8% (7/85) reported as positive, and stool cultures sent off for C. difficile in 60% (74/123) were reported as positive in 3% (2/74) (table 3).

68% of the children admitted with UC had extensive disease (E3 and E4), and 49% of total admissions had more than 6 bloody or loose stools per day (table 1). PUCAI was documented or not considered applicable in n=184 (61%) and not recorded in the remaining 114 (38%). Of those in whom it was recorded (n=135) the median score on their first admission was 65 (IQR 55,70).

Quality improvement

Based on agreed national IBD standards, the concept for service improvements was to implement local actions identified as problems in previous audits (7, 14). This is illustrated in table 3, indicating increase of clinical nurse specialists (who provide direct and continuous contact and advice), establishment of guidelines for ASC (to reduce treatment variability and adherence to evidence-based protocols), recording of PUCAI score (to reduce bias in assessment of disease activity and treatment), transitional care plans (to facilitate continuity of specialist care), and other (table 3) (7). It had been recognised in previous audits that GPs in the UK were unfamiliar in the management of children with IBD, therefore the high proportion of patients seen within 7 days reflects improvements in surveillance and efficacy of a more rapid specialist service response for children with UC.

Medical treatment

183/298 (61%) of admissions received steroid therapy, 138/183 (75%) intravenous and 45/183 (25%) orally. The progression on treatment for all patients, excluding the elective surgical admissions, is detailed in Figure 1. Of those receiving intravenous steroid therapy 2/3 had methylprednisolone and 1/3 hydrocortisone. Excluding readmissions (n=74) and newly diagnosed cases (n=55), 45/169 children (26%) received steroids for greater than 3 months in the previous 12 months. Steroid sparing agents were tried in this group, (Figure 2), but in 24%

only 5-aminosalicylic acid (5-ASA) or no steroid sparing agents (11/45) had been used. Of the 34 children who had received steroid sparing therapy it was stopped due to lack of effect (8/34) or intolerance (2/34). In the remainder (24/34) it was continued but the child still required admission for active disease.

Iron deficiency anaemia

Anaemia was a significant finding in the group of children admitted with active UC. The median haemoglobin (g/dl) at first admission was 10.9 (IQR 9.1, 12.45) with 215/224 (96%) being anaemic using age related reference values. 110/215 (51%) were not previously known to be anaemic but 105/215 (49%) had been shown to be anaemic previously of which just under half had been identified as being anaemic > 3months prior to admission (figure 3). Though 51% of those identified as being iron deficient prior to admission had received iron therapy, half parenterally and half enterally, in 49% their iron deficiency had not been treated. In those treated, both parental and enteral iron was assessed as being 100% effective by the child's clinical team.

Surgery

For the first time in this audit, all medical and surgical admissions were captured for this IBD cohort over a year, and surgical data such as ileal pouch surgery were captured systematically to monitor both frequency (table 3) and outcome (tables 4+5).

53 children had 58 operations during their admissions, 35 admitted electively for surgery and 23 children non-electively. All children had one surgical procedure except one child who had 3 and another who had 4 different surgeries, respectively. The indications for surgery

performed are shown in Table 4 and the type of procedures in Table 5. Most of the children requiring surgery in both the elective and non-elective admission had a colectomy, 21/35 and 19/23 respectively, (p=0.38). Comparison of the audits rounds illustrates an increasing number of patients receiving anti-TNFalpha for rescue and maintenance therapy, but a similar proportion of children with UC requiring colectomy (table 3).

Pouch surgery continues to be uncommon in the paediatric population with only seven elective procedures recorded in this 1 year period. Laparoscopic or laparoscopically assisted surgery was used in 12/30 (40%) of all resecting procedures and there was no statistical difference in the use of laparoscopic techniques in the elective or non-elective surgical groups (p=0.49).
Broad categories of surgical complications were recorded in the audit with 19/58 (35%) of all operations. Infections were prominent in emergency procedures (5/35) whereas stoma and motility problems in elective operations (6/23). Complications appear different per urgency of the procedure (Figure 4). Intrabodominal sepsis and anastomotic leakage was described in 4/55 (7%) children undergoing elective or non elective surgery. The proportion of children who had surgery for toxic megacolon was 2/55 (4%); the overall rate of toxic megacolon being 2/224 patients admitted with UC (table 3).

National consistency

To analyse why 2/32 centres (Liverpool and Newcastle) had disproportionately large numbers of children admitted with UC, subanalysis of their data was undertaken. Newcastle and Liverpool jointly had 86 (median 43.5 (IQR 36, 50)) admissions during the study period compared to 212 in the other 30 sites (median 6 (IQR 3, 9)) (Mann-Whitney U test p=0.004); with the next largest centre entering 17 children. When compared to all other sites Newcastle

and Liverpool had a significantly larger overall IBD population, median 283.5 (IQR 252, 315) versus median 165 (IQR 84,264) (Mann-Whitney test, p=0.004) but the proportion of children with UC or IBD-U was no different in Liverpool and Newcastle (43%) to national figures (41%). PUCAI scores were more consistently recorded in Liverpool and Newcastle in 78%, (67, 86) versus 55% other sites (117, 212; p=0.004) and were similar on admission (median PUCAI 65 versus 65) and on discharge (median PUCAI 10 versus 15)(n.s.).

The mode of admission (elective versus emergency) was higher electively in Liverpool/Newcastle (20/86, 23%) versus others (23/212, 11%)(p=0.004) and respectively Liverpool/Newcastle had a lower rate of emergency admissions (30/86, 35%) versus other centres (102/212, 48%) (p=0.037). A slightly higher rate of readmissions of children with UC in Liverpool/Newcastle in the previous two years (54/86, 63%) versus others (112/212, 53%) was statistically not significant (p=0.12), and if patients had to be admitted for surgery or had surgery performed their proportion was similar in Liverpool/Newcastle to the other centres.

Although not formally asked in the audit questionnaire, we further interviewed participating centres if there was a treatment difference regarding steroid application, steroid sparing, 2nd line therapy, or use of biologics. In their region, children requiring inpatient treatment for UC were always admitted in Liverpool and Newcastle, while it was practice in some other tertiary centres to arrange admission and treatment for less severe UC in secondary hospitals from their network. In acute severe colitis (PUCAI score 65-85) , the Liverpool centre administered i.v. steroids as high dose bolus (20mg/kg), but applied similar second line treatment and steroid reduction scheme as other units.

Discussion:

Our national audit programme over six years was conducted to improve clinical standards in order to reduce morbidity of children with UC, implement steroid sparing strategies, optimise escalation treatment, assess surgical outcomes, identify and resolve geographical differences.

Quality indicator rescue therapy in ASC

Second-line therapy in the steroid failure group has changed over the audit rounds and now the majority of children requiring second-line therapy receive anti-TNFα rather than Cyclosporine; with clinicians more comfortable with its use as maintenance therapy due to national licence. All 13 children receiving Cyclosporine as second line therapy avoided colectomy, whereas three of the 16 (18.8%) receiving anti-TNFα required colectomy as failed to respond to anti-TNFα therapy. This is comparable to a single centre experience from Italy (n= 32) for children with ASC, of which 20% treated with infliximab required urgent colectomy and further 50% required colectomy in a 2 year follow-up (19). According to a meta-analysis from 2011, Infliximab was considered as effective with a pooled 1-year response of 64% as cyclosporine (75% n = 126, six studies) (20). Our national paediatric audit data and the paediatric meta-analysis are in contrast to data from the previous UK audit (203 sites, n=1836 admissions) on adults with ASC, in which second-line therapy response was more frequently observed with anti-TNFa (80%) than with Cyclosporin (58%), indicating the necessity to conduct paediatric studies and the pitfalls of extrapolating adult data to paediatric conditions (21). Our data appear to contrast paediatric head to head RCTs which showed not difference between the two treatments, but it is a limitation of our data that it relates only to inpatient admissions and does not describe the long-term outcome of the overall cohort (20).

Quality indicator: steroid sparing in refractory UC

Steroid dependency is a major problem in children with UC as in addition to the common side effects of long-term steroids it can affect their growth and pubertal development (5).

Historically, using mainly 5-ASA and azathioprine/6-mercaptopurine , the North American IBD network reported steroid dependency as 45% (22). More recently, an USA-network reported steroid dependency from their whole cohort (including stable outpatients and inpatients) as 15%, based on optimised Azathioprine/6-mercaptopurine levels, special training and coaching of doctors and nurses, audit and self-report on performance (23), however the proportion of patients on anti-TNFalpha was not reported. We escalated treatment to thiopurines, infliximab, or cyclosporine in 76% of inpatients. To our knowledge there is no published data about children admitted for treatment of UC, but our rate of steroid dependency of 26% (45/170) over one year indicates substantial improvement to previous audits, and appears comparable to recent reports from USA (14,22,23).

Notably, an alternative treatment for successful treatment of ASC published recently by the Liverpool centre, was applied in 5% (15/298) of children admitted in this audit (24). Based on a short-term course of high dose (20mg/kg) iv methylprednisolone, with this protocol the steroid dependency rate had been reported before as 21% after 6 months and 0% after 1 year (24).

Quality indicator: iron treatment in iron deficiency anaemia:

In our previous audit, iron deficiency anaemia had been recognised as a major shortfall of quality indicators. One of the audit action plans had been to recognise and treat iron deficiency orally or intravenously (14). In this audit 61% of patients seen in clinic prior to

admission had iron deficiency anaemia. This is the first confirmation that paediatric gastroenterologists in the UK prescribe intravenous iron for iron deficiency anaemia in paediatric IBD. In a single-centre study from the USA, 24 children with IBD scheduled for infliximab treatment were iron deficient, which was corrected by administering i.v.-iron in 63% and anaemia corrected in 79% (25). Our cohort is the largest number of children with paediatric UC (n=55) reported to benefit (100% efficacy) from the use of i.v. treatment. To address the deficit in all children with IBD, the BSPGHAN IBD working group produced a diagnostic and therapeutic algorithm available online (26).

Quality indicator: colectomy rate

In our series, the colectomy rate for children admitted for UC electively or urgently was 15%. This compares to a North American study of children admitted for ASC with a colectomy rate of 9% by discharge and 19% at 1 year follow-up (15). In another study from Italy, children with non-response to steroids had a 50% colectomy rate over 2 years despite escalating treatment with infliximab (19).

The rate of toxic megacolon appears to decline over 3 audit rounds from 6% to 3% (p=0.29). As a sign of quality control over our audit rounds, restorative proctocolectomy (ileal pouch surgery) is offered and increasingly registered (4% to 56%), allowing for the first time monitoring of surgical outcomes and a benchmark for individual centres.

Quality indicator: surgical complications

In our series, 1 in 4 children admitted with UC required surgical management, highlighting the requirement for provision for medical and psychosocial consequences of colectomy or stoma.

Our data indicate the complications of surgery in paediatric UC are significant at 33%. This rate is comparable to other published series with 25-33% (27, 28). Notably, postoperative complications in the UK in this audit were substantially better for urgent colectomies with 52% versus 90% in the USA, which may be a combination of timing, experience, immunosuppression, or other hospital characteristics and pathways. Elective colectomy, which us reported to have a better outcome of morbidity and mortality than urgent colectomy, was performed in higher proportion in the UK with 44% versus 37% in the USA, which may reflect the combined quality efforts to monitor disease activity early and to implement guidelines for ASC in all participating paediatric hospitals.

Surgical complications not only affect morbidity for the individual child but adversely affect length and cost of the admission (27-29), highlighting the importance of optimising medical care and interdisciplinary teamwork.

Addressing geographical differences

Over six years, we demonstrated an increase in the application of guidelines for acute severe colitis from 43% to 77%, similar to reports from our adult gastroenterologists from 47% to 84% in the same time (30).

As a measure to monitor outcome of ileal pouch surgery in children with UC, a registry was established and promoted, leading to an increase of patient data entry from 4% to 56%, and illustrating the surgical actions to analyse and improve patient outcomes. Although it did not reach statistical significance in all variables, the three rounds of our national audit indicated reduction of the incidence of toxic megacolon, in agreement with the national adult IBD audit (14, 30, 31).

Along with an increasing number of patients treated with anti-TNFalpha, fewer children required colectomy, although this did not reach statistical significance. For future studies, it would be valuable to examine how patients perceived the preparation and timing of colectomy with regard to their quality of life, impact on growth, puberty, and psychosocial development.

In contrast to other published national reports, which were limited to tertiary centres (14, 32, 33), our audit was truly representative for the national practice including 9% of patients with severe UC managed in non-specialised sites. We observed a wide range in the catchment area, size of the IBD population, and referral pattern within regional networks over the audit period. The audit illustrated variation in areas of service provision (e.g. risk assessment by a nutritional screen) or compliance to quality standards (e.g. prescription of bone protection), which enables each individual hospital to benchmark against the national median and IQR (7, 17).

Our audit and action plan programme compares to an initiative for quality improvement in Northern America, that showed that early identification of children with sub-optimally managed disease and, where appropriate, early treatment escalation, has improved outcome (15). Another group from the USA has shown that adherence to agreed management targets can improve the proportion of children in remission of UC from 61% to 72%. The fact that only 19% of our patients with active disease had a change of treatment or were admitted in 27% indicates room for improvement in our system and action plans (23).

Conclusions:

Over 6 years, progress has been made that nearly all centres providing secondary and tertiary gastroenterology contributed to the national audit rounds, applying agreed quality standards of

PUCAI score, guidelines for acute severe colitis, and ileal pouch surgery registration. Nearly all children admitted had iron deficiency anaemia and half of them were prescribed oral or intravenous iron therapy, both considered as effective. More than half of inpatients with UC required iv steroids and of those one third were not responding and requiring second line therapy or surgery.

More than half children with rescue therapy received anti-TNFalpha, and nearly 20% of those failed to respond and required colectomy. Although prescription of rescue therapy (50%) and proportion of anti-TNFalpha (50% of those) had significantly increased, over a period of 6 years the reduction of colectomy rate (15%) had not reached statistical significance. Subtotal colectomy was required in 13.7% of patients admitted, nearly half of them admitted non-electively, and complications occurred in one third of surgical patients with UC.

Our national audit programme has proven effective to reduce steroid side-effects and iron deficiency anaemia in children with UC. Although over 6 years in the era of biologics there was a trend of decreasing colectomy rates, nearly half of children requiring colectomy had to be operated non-electively, indicating the importance of early recognition, optimising treatment, and collaborative gastro-surgical assessment.

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References:

1. Van LJ, Russell K, Drummond E, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology* 2008;135(4):1114.

2. Turner D, Otley R, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology* 2007;133(2):423.

3. Turner D, Hyams J, Markowitz J, et al. Appraisal of the pediatric ulcerative colitis activity index (PUCAI). *Inflamm Bowel Dis.* 2009;15(8):1218.

4. Turner D, Travis PL, Griffiths M, et al. Consensus for managing acute severe ulcerative colitis in children: a systematic review and joint statement from ECCO, ESPGHAN, and the Porto IBD Working Group of ESPGHAN. *Am J Gastroenterol.* 2011;106(4):574.

5. Turner D, Levine A, Escher C, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr*. 2012;55(3):340.

6. NICE National Institute for Health and Care Excellence. Ulcerative colitis: management. Clinical guideline [CG 166]. Published date: June 2013. Available at: https://www.nice.org.uk/guidance/cg166. Accessed June 25, 2016.

7. The IBD Standards Group. Standards for the healthcare of people who have Inflammatory Bowel Disease (IBD Standards). 2013 update. Available at: www.ibdstandards.org.uk. Accessed June 25, 2016.

8. Benchimol I, Fortinsky J, Gozdyra P, et al. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis*. 2011;17(1):423.

9. Molodecky A, Soon IS, Rabi M, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012;142(1):46.

10. Henderson P, Hansen R, Cameron L, et al. Rising incidence of pediatric inflammatory bowel disease in Scotland. *Inflamm Bowel Dis*. 2012;18(6):999.

11. Varni JW, Bendo CB, Nurko S, et al. Health-related quality of life in pediatric patients with functional and organic gastrointestinal diseases. *J Pediatr.* 2015;166(1):85.

12. Gibson R, Vaizey C, Black M, et al. Relationship between disease severity and quality of life and assessment of health care utilization and cost for ulcerative colitis in Australia: a cross-sectional, observational study. *J Crohns Colitis* 2014;8(7):598.

13. Cohen RD, Yu AP, Wu EQ, et al. Systematic review: the costs of ulcerative colitis in Western countries. *Aliment Pharmacol Ther*. 2010;31(7):693.

14. Russell K, Protheroe A, Roughton M, et al. Contemporary outcomes for ulcerative colitis inpatients admitted to pediatric hospitals in the United Kingdom. *Inflamm Bowel Dis.* 2013;19(7):1434.

15. Turner D, Mack D, Leleiko N, et al. Severe pediatric ulcerative colitis: a prospective multicenter study of outcomes and predictors of response. *Gastroenterology* 2010;138(7):2282.

16. Dayan B, Turner D. Role of surgery in severe ulcerative colitis in the era of medical rescue therapy. *World J Gastroenterol.* 2012;18(29):3833-8.

17. Arnott I, Glynn M. National clinical audit of inpatient care for young people with ulcerative colitis. UK inflammatory bowel disease (IBD) audit. National report, June 2014. Royal College of Physicians, London, UK. www.rcplondon.ac.uk. ISBN 978-1-86016-536-8. eISBN 978-1-86016- 539-9. Accessed June 25, 2016.

18. 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(6):1314.

19. Aloi M , D'Arcangelo G , Capponi M , Managing paediatric acute severe ulcerative colitis according to the 2011 ECCO-ESPGHAN guidelines: Efficacy of infliximab as a rescue therapy. *Dig Liver Dis*. 2015 Jun;47(6):455-9.

20. Turner D, Griffiths M. Acute severe ulcerative colitis in children: a systematic review. *Inflamm Bowel Dis*. 2011;17(1):440.

21. Alrubaiy L, Arnott I, Protheroe A, et al. Inflammatory bowel disease in the UK: is quality of care improving? *Frontline Gastroenterol.* 2013;4:296–301.

22. Hyams J, Markowitz J, Lerer T, et al. The natural history of corticosteroid therapy for ulcerative colitis in children. *Clin Gastroenterol Hepatol*. 2006;4:1118–23.

23. Crandall WV, Margolis A, Kappelman D, et al. Improved outcomes in a quality improvement collaborative for pediatric inflammatory bowel disease. *Pediatrics* 2012;129(4).

24. Vora R, Finnamore HE, Crook K, et al. Clinical Experience of Use of High-dose Intravenous Methylprednisolone in Children With Acute Moderate to Severe Colitis. *J Pediatr Gastroenterol Nutr.* 2016 Jul;63(1):51-7.

25. Danko I , Weidkamp M. Correction of Iron Deficiency Anemia With Intravenous Iron Sucrose in Children With Inflammatory Bowel Disease. *J Pediatr Gastroenterol Nutr.* 2016 Nov;63(5):e107-e111.

26. Fell JM, Muhammed R, Spray C, et al. Management of ulcerative colitis. *Arch Dis Child.* 2015;0:1-6.

27. Soon IS, deBruyn JC, Hubbard J, et al. Rising post-colectomy complications in children with ulcerative colitis despite stable colectomy rates in United States. *J Crohns Colitis* 2014;8(11):1417-26.

28. Soon IS, Wrobel I, deBruyn JC, et al. Postoperative complications following colectomy for ulcerative colitis in children. *J Pediatr Gastroenterol Nutr.* 2012;54(6):763-8.

29. Lindsay JO, Bergman A, Patel AS, et al. Systematic review: the financial burden of surgical complications in patients with ulcerative colitis. *Aliment Pharmacol Ther.* 2015;41(11):1066.

30. St Clair Jones A, Murray S. Multidisciplinary working when developing the UK inflammatory bowel disease standards and IBD audit. *ECCO Abstracts* 2016, P458. Available at:

https://www.ecco-ibd.eu/index.php/publications/congress-abstract-s/abstracts-2016/item/p458-multidisciplinary-working-when-developing-the-uk-inflammatory-bowel-disease-standards-and-ibdx00a0audit.html. Accessed June 25, 2017.

31. Lynch RW, Churchhouse AM, Protheroe A, et al. UK IBD Audit Steering Group. Predicting outcome in acute severe ulcerative colitis: comparison of the Travis and Ho scores using UK IBD audit data. *Aliment Pharmacol Ther*. 2016 Jun;43(11):1132-41.

32. Nguyen, GC, Murthy SK, Bressler B, et al. Quality of Care and Outcomes Among Hospitalized Inflammatory Bowel Disease Patients: A Multicenter Retrospective Study. *Inflamm Bowel Dis*. 2017; 23(5): 695-701.

33. Poojary, P, Saha, A, Chauhan K. Predictors of Hospital Readmissions for Ulcerative Colitis in the United States: A National Database Study. *Inflamm Bowel Dis.* 2017; 23(3):347-56.

Figure legends:

Figures 1-4:

[No legends required, information is contained in Figure titles]

Figure 1:

Treatment and progress of all admissions, excluding elective surgical admissions.

Figure 2:

Steroid sparing management in 45 children who received steroids for > 3 months in 12 month prior to admission. Fifty steroid sparing agents were tried in 34 children, but no steroid sparing agents or only 5-aminocylic acid (5-ASA) was used in 11 children.

Figure 3:

Length of time n=105 children known to be anaemic prior to admission.

Figure 4:

Surgical complications in 35 elective and 23 non-elective surgical procedures

Tables:

Table 1:

Patient demographics and characteristics

		Median (IQR) **% (numerical)**
Age	**Total n=224 children**	14 (11, 15) years
Age distribution	**< 3**	0.9% (2/224)
	< 6 years	3.6% (8/224)
	6 -18 years	95.5% (214/224)
Gender	**Female 50.4% (113/224)**	Male 49.6% (111/224)
Paris classification	**Proctitis (E1)**	3% (8/298)
	Left sided (E2)	18% (54/298)
	Extensive (E3)	17% (52/298)
	Pan colitis (E4)	51% (151/298)
	Unknown	11% (33/298)
Medication of patients not admitted from clinic	**5-ASA**	52% (53/103)
	Steroids	52% (53/103)
	Topical	52% (53/103)
	Thiopurine	52% (53/103)
Ambulatory disease management	**Days prior to admission**	26 (7, 61) days

Previous admissions	**Admitted for UC in previous 2 years**	41% (92/212)
PUCAI	**On admission**	60 (50, 70)
	On discharge	15 (7.5, 25)
Length of stay		6 (3, 10) days
Type of admission	**Newly diagnosed severe UC**	18% (55/298)
	Emergency admissions for established UC	44% (131/298)
	Elective medical or surgical admissions for known UC	27% (52/298)
	Transfer from other sites	11% (36/298)
Comorbidity	**None**	82% (245/298)
	Cardiovascular	0.3% (1/298)
	Respiratory	4% (11/298)
	Diabetes	1% (4/298)
	IBD related liver disease	7% (20/298)
	Active cancer	0.7% (2/298)
	Other	6% (17/298)
Admissions	**n=298 admissions**	**13 (11, 14) years)**

Table 2:

National recruitment of children with UC admitted over 1 year

Centre	**City**	**Admissions**
Alder Hey Children's Hospital	Liverpool	16.8% (50/298)
Great North Children's Hospital	Newcastle upon Tyne	12.1% (36/298)
Chelsea and Westminster Hospital, Children's Services	London	5.7% (17/298)
Birmingham Children's Hospital	Birmingham	5.4% (16/298)
Royal Hospital for Children Glasgow	Glasgow	5.4% (16/298)
Royal London Children's Hospital, Barts Health	London	5.0% (15/298)
Southampton Children's Hospital	Southampton	4.7% (14/298)
Leicester Royal Infirmary Children's Hospital	Leicester	4.0% (12/298)
Royal Bristol Hospital for Sick Children	Bristol	3.7% (11/298)
King's College Hospital	London	3.7% (11/298)
Children's Hospital, John Radcliffe	Oxford	3.4% (10/298)
Leeds General Infirmary	Leeds	2.7% (8/298)

University Hospitals of North Midlands	Stoke	2.7% (8/298)
Royal Hospital for Sick Children Edinburgh	Edinburgh	2.0% (6/298)
Nottingham Children's Hospital	Nottingham	2.0% (6/298)
Royal Free Hospital	London	2.0% (6/298)
Queen Mary's Hospital for Children	St Epsom and Helier	2.0% (6/298)
St George's Hospital	London	2.0% (6/298)
Morriston Hospital	Swansea	1.7% (5/298)
Addenbrooke's Hospital	Cambridge	1.7% (5/298)
Tunbridge Wells Hospital	Maidstone	1.7% (5/298)
Royal Aberdeen Children's Hospital	Aberdeen	1.3% (4/298)
Royal Belfast Hospital for Sick Children	Belfast	1.3% (4/298)
Royal Devon and Exeter Hospital	Exeter	1.3% (4/298)
Great Ormond Street Hospital	London	1.3% (4/298)
Luton and Dunstable University Hospital	Luton	1% (3/298)
Sheffield Children's Hospital	Sheffield	1% (3/298)
Noah's Ark Children's Hospital	Cardiff	0.7% (2/298)
Jenny Lind Children's Hospital	Norwich	0.7% (2/298)
University Hospital of North Tees	Hartlepool	0.03% (1/298)

The Children's Hospital Lewisham	Lewisham	0.03% (1/298)
Royal Manchester Children's Hospital	Manchester	0.03% (1/298)
Queen's Hospital Burton	Burton	0% (0/298)

There are 25 specialist paediatric gastroenterology centres in the UK, of these 24 (96%) participated. Specific centres admitting smaller numbers of paediatric patients with UC were also invited to participate; of the additional 10 sites invited, eight participated giving a total of 32/35 (94%) of all sites. The median number of children entered per site was 6 (IQR 3,9).

Table 3:

Comparison of the paediatric data in 3 rounds of the national UK inflammatory bowel disease (IBD) audits

Variables examined	**Round 2** **2008-10**	**Round 3** **2010-12**	**Round 4** **2012-14**	χ^2 test, p-value
Participating centres	N=23	N=24	N=32	NA
Clinical nurse specialist for IBD	61% (14/23)	83% (20/24)	81% (25/31)	0.14
Guidelines for Acute Severe Colitis	43% (10/23)	63% (15/24)	77% (24/31)	0.04
Recording of PUCAI score on Day 1 in emergency admissions	Not asked	23% (24/104)	55% (77/139)	<0.001
Transitional care in place	Not asked	Not asked	90% (28/31)	NA
Relapsing patients seen within 7 days	87% (20/23)	91% (21/23)	94% (29/31)	0.71
Database or registry for IBD patients	48% (11/23)	78% (18/23)	68% (21/31)	0.09
Ileal pouch surgery entered on registry	Not asked	4% (1/23)	56% (9/16)	<0.001
Stool samples sent for *Clostridium difficile*	35% (44/124)	45% (57/126)	60% (74/123)	<0.001
Prescribed rescue therapy	26% (10/38)	52% (17/33)	49% (30/61)	0.04
Proportion = Cyclosporin A	80% (8/10)	70% (12/17)	43% (13/30)	0.051
Proportion = anti-TNFalpha	20% (2/10)	18% (3/17)	53% (16/30)	0.03
Presence of toxic megacolon	6% (3/50)	4% (2/45)	3% (3/86)	0.79
Plans for maintenance anti-TNFalpha	Not asked	5% (11/173)	14% (24/177)	0.02

Colectomy rate in steroid failures	23.7% (9/38)	15.2% (5/33)	15% (9/61)	0.50

χ^2 test was applied to compare rounds 2,3 and 4, where available. If round 2 were not available, p-values illustrate the comparison between rounds 3 and 4.

Table 4:

Indication for surgery in 58 children admitted with UC

	Elective surgical admission (n=35)	Non-elective surgical admission (n=23)	χ^2 test, * Fisher's exact test, p-value
Failure of medical therapy	22 (62.9%)	17 (73.9%)	0.38*
Toxic megacolon	0	2	0.15
Bleeding	2	1	1.0
Obstruction	2	2	1.0
Perforation	0	1	0.40
Abscess	0	1	0.40
Closure of stoma	9	0	0.008
Pouch	1	0	1.0
Other	1	0	1.0

Children were admitted electively or non-electively for surgery of ulcerative colitis in round 4 of the national audit.

Table 5:

Surgical procedure performed on 58 children admitted with UC

	Elective surgical admission (n=35)	Non-elective surgical admission (n=23)	Fisher's exact test, p-value
Subtotal colectomy	21 (60.0%)	19 (82.6%)	0.09
Proctocolectomy	1 (2.9%)	0 (0%)	1.0
Ileoanal pouch with stoma	2 (5.7%)	0 (0%)	0.51
Ileoanal pouch without stoma	5 (14.3%)	0 (0%)	0.15
Formation of ileostomy	17 (48.9%)	11 (47.8%)	1.0
Other	6 (17.1%)	4 (17.4%)	1.0

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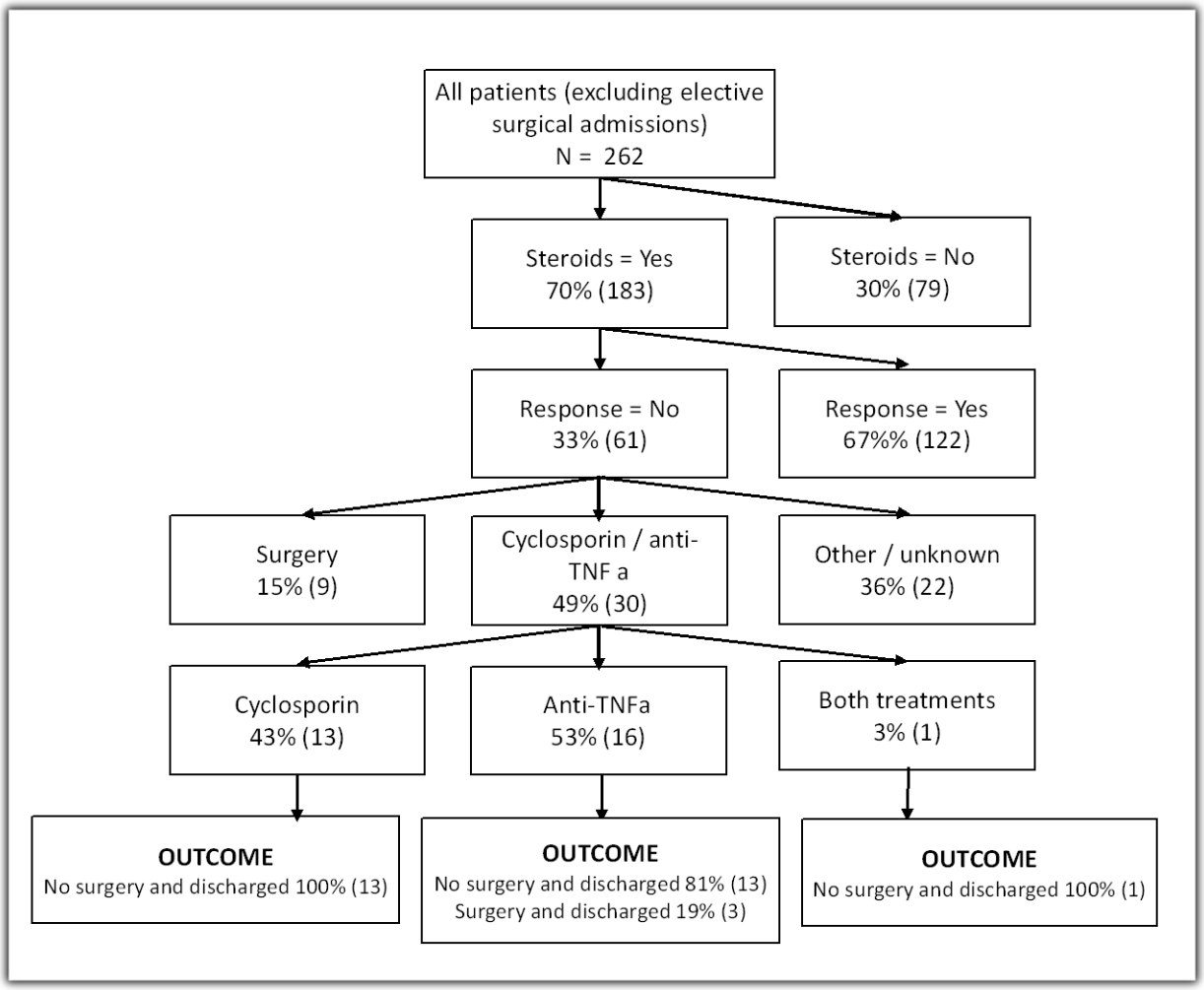
FIGURES

Figure 1:

Treatment and progress of all admissions, excluding elective surgical admissions.



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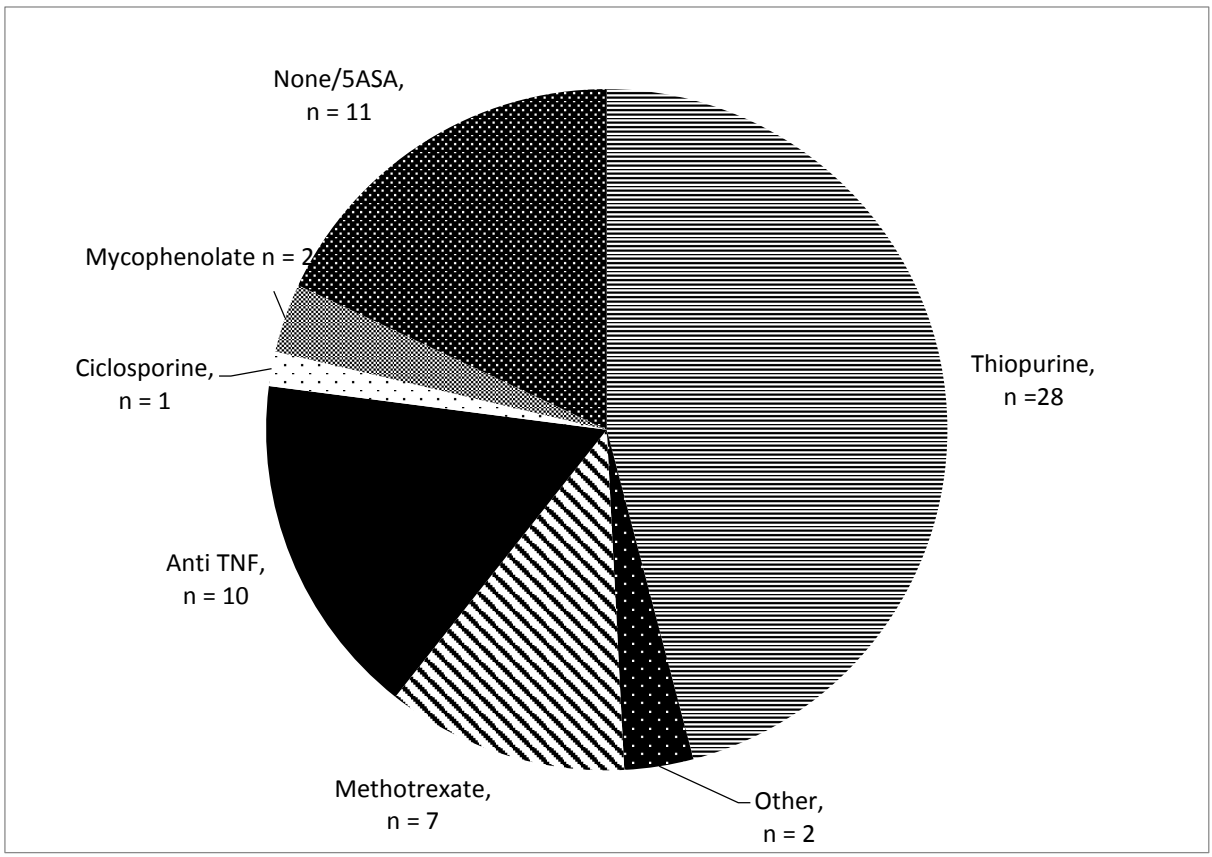

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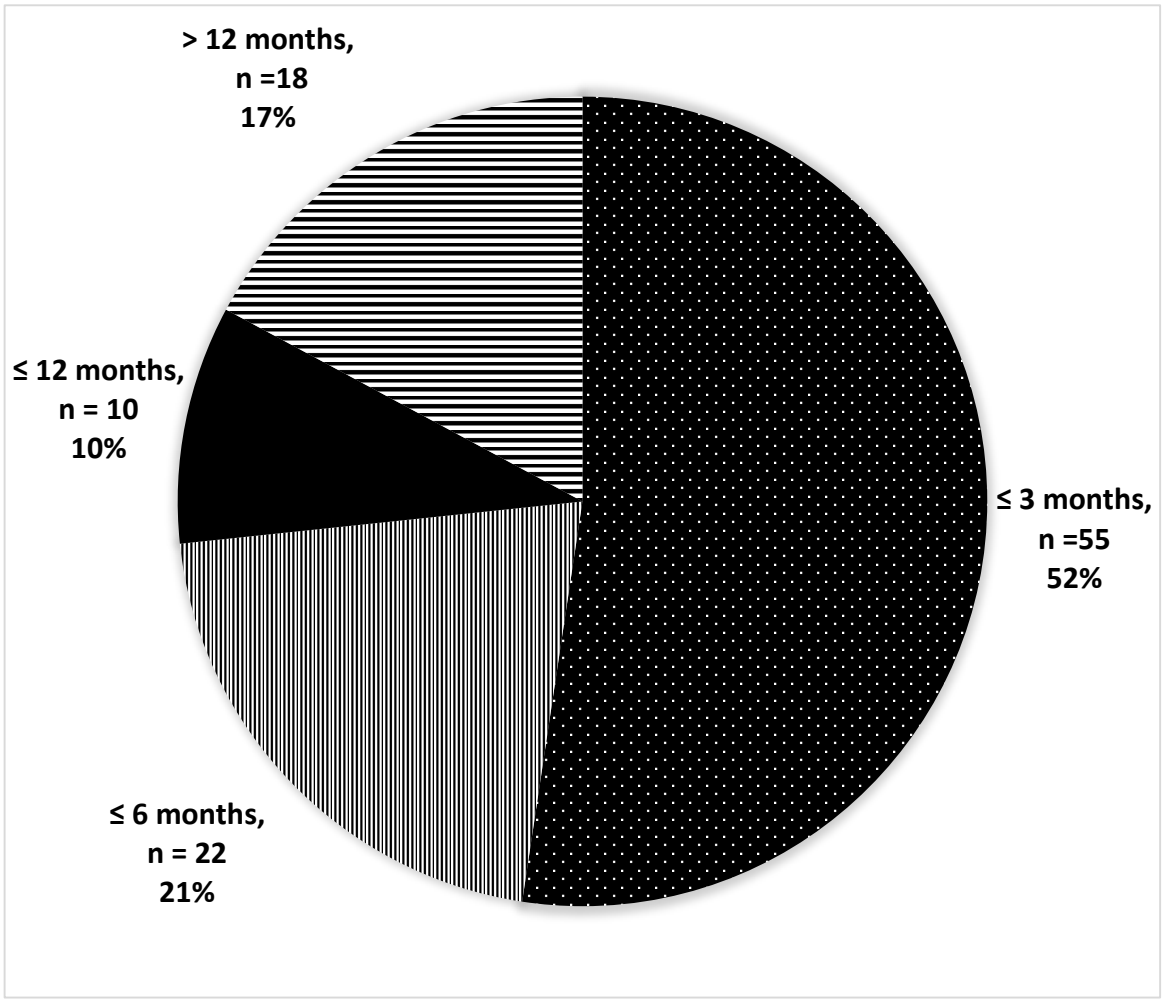

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