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Importance of Ibd Biopsy Protocol In Clinical Practice: Analyses Comparing Two British Patients' Cohorts

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1. Abstract

1.1. Background & Aims: The correlation of histological features with clinical and endoscopic data is one of the crucial steps in the accurate diagnosis of inflammatory bowel disease (IBD). This study compares the diagnostic and clinical outcomes of two cohorts of patients undergoing colonoscopy before and after the introduction of a formal biopsy protocol.

1.2. Methods: The first dataset (n=88) was collected from June to December 2016. A putative "gold standard" IBD biopsy protocol was then implemented. A second dataset (n= 92) was collected from December 2018 to March 2019. All patients were followed up for a minimum of 2 years for confirmation of the diagnosis. Chi-squared test was used to compare variables. The exception was the patient age, where the unpaired t-test was used.

1.3. Results: Significantly more patients had a biopsy taken from four colonic sites after the biopsy protocol was implemented, the percentage increasing from 49% to 76%. In diagnosis-naïve patients, there was a statistically significant difference in the present diagnosis between the groups. Significantly fewer were diagnosed with IBD after implementation of the biopsy protocol (74%) than before (96%). Crucially, seven of 88 patients (8%) diagnosed with IBD in the first cohort were found not to have IBD at clinical and endoscopic follow up. No such diagnostic revisions were needed in the protocol-compliant cohort.

1.4. Conclusion: A standardised biopsy protocol is essential for IBD diagnosis and sub-classification.

2. Key summary

There are few or no data about the application of a standardised biopsy protocol in clinical practice. This study compared the characteristics of patients and diagnostic outcomes from two British cohorts before and after implementation of an IBD "gold standard" biopsy protocol. Significantly fewer patients were diagnosed as IBD after implementation of the biopsy protocol (74%) than before (96%). This study shows that correct use of a formal biopsy protocol results in a more comprehensive and correct clinical approach to the diagnosis of IBD and its mimics.

3. Introduction

Endoscopic examination is an essential part of the diagnostic pathway for all patients with suspected IBD. Ileocolonoscopy with biopsies is the standard method to confirm the diagnosis and allow an accurate assessment of disease extent and severity. Despite endoscopy providing high diagnostic accuracy, alongside support from histopathological examination, a minority of cases will remain undifferentiated. Moreover, some patients will be reclassified over time - i.e. from Crohn's disease (CD) to ulcerative colitis (UC) and (more often) conversely. Establishing the right diagnosis is of the utmost importance, not only because of the differences in the clinical and therapeutic approach between CD and UC, but also because both are long-term diagnoses. Many of the conditions, which mimic IBD, are, on the contrary, relatively benign and short-term, or require quite

different management.

Ileocolonoscopy has the best accuracy for distinguishing between UC and CD, and is considered still less fallible when supported by histological evidence. Routine ileocolonoscopic biopsy is therefore recommended by the European Crohn's and Colitis

Organisation (ECCO) to aid the diagnosis of inflammatory bowel disease (IBD). ECCO has proposed that ileocolonoscopic biopsies should be taken between the terminal ileum and the rectum at four distinct sites, with at least two samples from each site [1,2]. However, there are no published data to evaluate the adherence to and diagnostic outcome from such a standardized biopsy protocol. Moreover, there are limited data on which to challenge or expand the guideline recommendations in this particular area. Therefore, we performed a study to explore the importance of adhering to the IBD biopsy protocol with regards to clinical diagnosis of IBD, its sub-classification and the differential diagnosis of IBD-mimicking pathology. We analysed two datasets to determine the value and the application of the standardized biopsy protocol in clinical practice. One data set was analysed before any formal implementation of the ECCO biopsy protocol. The second dataset was collected after the biopsy protocol had been implemented as a unit standard with which all endoscopists were expected to comply. The aim of this study was to evaluate full adherence to standardized IBD biopsy protocol in clinical practice and to assess its impact on diagnostic accuracy in patients presenting with possible IBD.

4. Materials and Methods

Patients: The first analysis was performed retrospectively on data from June to December 2016. Demographic data such as age and sex were ascertained (data available on request). The study was reviewed and approved by the Research Ethics Committees of Princess Alexandra Hospital in Harlow, UK. Eligibility criteria included:

- Patients aged 16 and above with no known diagnosis (naïve) but with symptoms such as chronic diarrhoea, rectal bleeding, weight loss, or suggestive incidental findings on abnormal computed tomography (CT) scans performed for other reasons.
- Patients aged 16 and above with established diagnosis of IBD undergoing IBD assessment and/or surveillance

A second analysis was performed on data collected prospectively from December 2018 to March 2019 after implementation of the ECCO/BSG biopsy protocol. The inclusion criteria remained the same.

In both cohorts the clinical assessments, colonoscopies and biopsies were carried out at Princess Alexandra Hospital, Harlow, UK, by the regular gastroenterology and endoscopy staff.

Statistical methods: All data sets were categorical in nature, apart from patient age. Significance was assessed using chi squared tests and unpaired t-tests for the categorical data sets and patient age respectively.

A total of 182 patients were included in both study cohorts. A summary of the analysis results is reported in (Table 1-4). There were no significant differences in the presenting characteristics of the two cohorts. The two groups did not vary in terms of their age, gender, clinical presentation or diagnostic status (naïve vs. established).

Table 1: A table to compare quantitative differences in the variables between the audit and re-audit data sets, and to analyse for statistical significance between the data sets.

Variable	Category	First study (n=88)	Second study (n=94)	P-value
Age	-	46.3 ± 16.7	49.5 ± 17.4	0.21
Gender	Female Male	42 (48%) 46% (52%)	47 (50%) 47 (50%)	0.76
Clinical presentation (pre-endoscopy)	IBD assessment IBD surveillance naïve	51 (60%) 13 (15%) 24 (27%)	45 (48%) 11 (12%) 38 (40%)	0.17
Diagnosis status	Previous diag. naïve	65 (74%) 23 (26%)	59 (63%) 35 (37%)	0.11
Endoscopic diag. (post-endoscopy)	UC Crohn's Indet. Colitis Normal	33 (38%) 41 (46%) 9 (10%) 5 (6%)	42 (45%) 34 (36%) 7 (7%) 11 (12%)	0.26
Endoscopic diag. (categorised)	IBD Normal	83 (94%) 5 (6%)	83 (88%) 11 (12%)	0.15
Endoscopic diag. in naïve group only (*)	IBD	23 (96%)	28 (74%)	**0.03**

(categorised)	Normal	1 (4%)	10 (26%)	
TI Intubation	No	29 (33%)	32 (34%)	0.88
	Yes	59 (67%)	62 (66%)	
TI Biopsy	No	38 (43%)	40 (43%)	0.93
	Yes	50 (57%)	54 (57%)	
Biopsy in 4 colon Sites	No	45 (51%)	23 (24%)	**<0.001**
	Yes	43 (49%)	71 (76%)	
Rectal Biopsy	No	41 (47%)	9 (10%)	**<0.001**
	Yes	47 (53%)	85 (90%)	

Summary statistics are: mean ± standard deviation or number (percentage)

(*) Analysis performed for patients with a naïve clinical presentation (pre-endoscopy) only

Table 2: Biopsies of all four colonic sites pre and post implementation of standard biopsy protocol

	Pre implementation of protocol	**Post implementation of protocol**
Biopsy at all four colonic sites	N=43 (49%)	N=71 (76%)
Biopsy at fewer than four colonic sites	N=45 (51%)	N=23 (24%)

Table 3: Occurrence of rectal biopsy pre and post implementation of standard BSG protocol

	Pre implementation of protocol	**Post implementation of protocol**
Rectal biopsy	N=47 (53%)	N=85 (90%)
No rectal biopsy	N=41 (47%)	N=9 (10%)

Table 4: Diagnosis of IBD in naïve patients

Study Cohort	**Pre- implementation**	**Post- implementation**	**Pre-implementation group(5 yrs)**
Original diagnosis	IBD (n=23; 96%)	IBD N= 28 (74%)	IBD (n=16; 88%)
Final diagnosis	Non-IBD (n=1; 4%)	Non IBD (n= 10; 26%)	Non-IBD (n=7; 8%)
Rational for difference	Normal	Resolution of acute colitis	resolution of acute colitis and microscopic colitis

5. Results

There was no significant difference in endoscopic diagnosis between the two cohorts when all patients (that is, patients with both an existing IBD diagnosis and diagnosis naïve patients) were included in the analysis. Rates of TI intubation and TI biopsy also did not significantly vary between groups. However, significant differences were observed for whether biopsies were taken from four colonic sites. Following implementation of the biopsy protocol significantly more patients had biopsies at four colonic sites (; 76% in the second cohort in comparison to 46% in the first). The acquisition of rectal biopsies also dramatically improved, from just over half (53%) in the first data set, to 90% after the implementation of the biopsy protocol (Figure 1-4). The diagnosis was significantly different between the cohorts when only diagnostic naïve patients were considered. Significantly fewer patients were diagnosed with IBD following the implementation of the biopsy protocol; 96% of the naïve group received an IBD diagnosis in the first group, compared to 74% in the second group after implementation of the biopsy protocol had been implemented. Distant diagnostic check, with colonoscopy, standard protocol histology, and clinical review, to confirm the above data, was performed at 5 years in the first cohort and at 2 years in the more recent cohort. Seven patients of the eighty-eight in the first cohort with a diagnosis of IBD, had had their IBD diagnosis recanted after subsequent colonoscopy with standard protocol multiple biopsies. Four of the seven were from the naïve group (n= 23). These patients were also free of symptoms likely to have been caused by IBD. The later review provided a new diagnosis of microscopic colitis in two of them, but the other five patients, including three patients, from the existing IBD diagnosis group (before implementation of BSG biopsy protocol), initially had non-specific acute self-limiting colitis. The later review of the second cohort who underwent fully standardised IBD biopsy protocol, led to no changes in definitive diagnosis,.

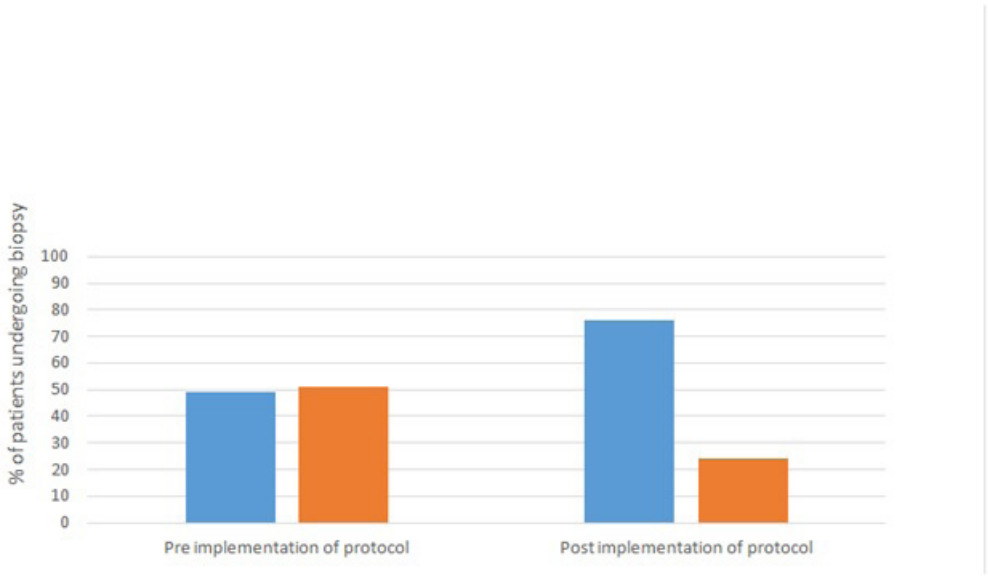

Figure 1: Graph comparing percentage of patients undergoing colonic biopsy at all four colonic sites pre-implementation and post implementation of the gold standard protocol

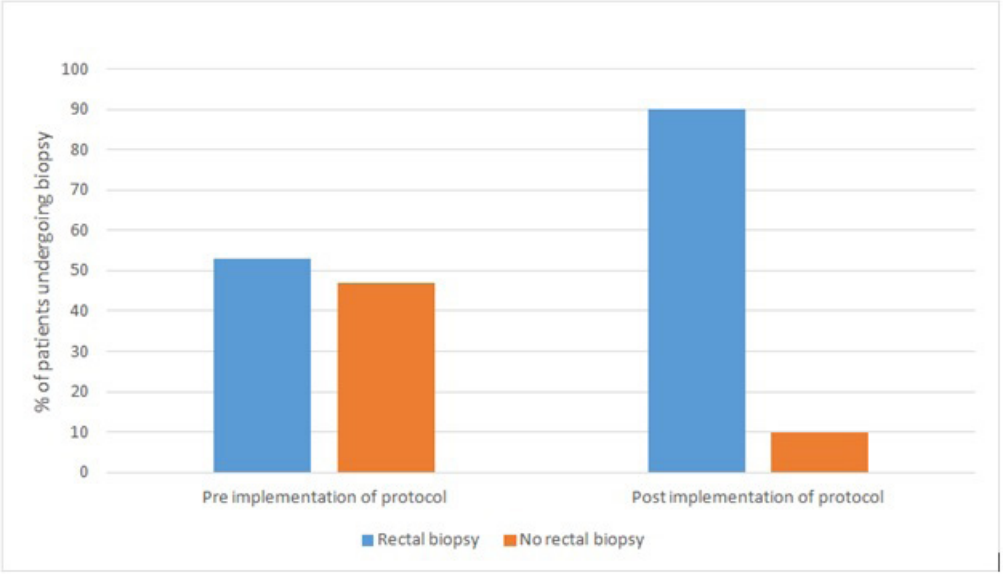

Figure 2: Graph to show the percentage of patients undergoing rectal biopsy pre and post implementation of the gold standard biopsy protocol

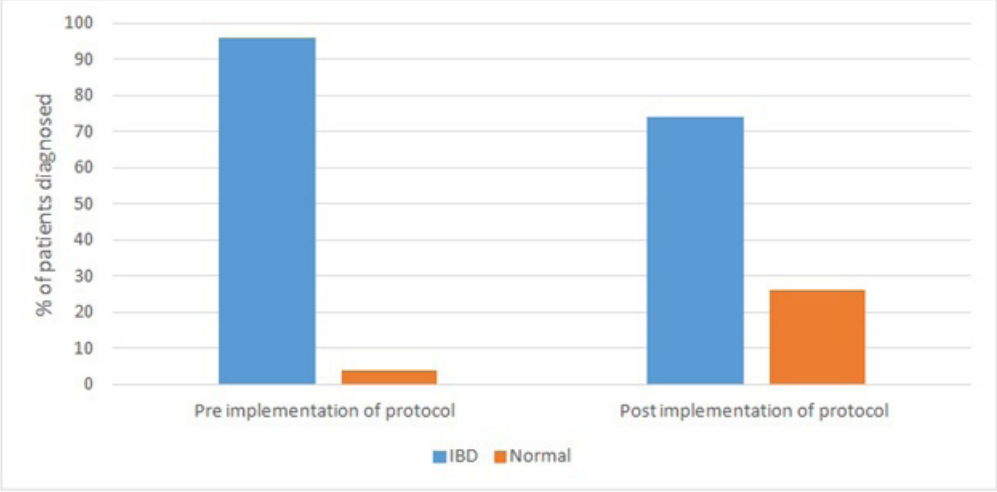

Figure 3: Shows the percentage of patients diagnosed with IBD or a normal colon in a population with a naive clinical presentation (pre-endoscopy)

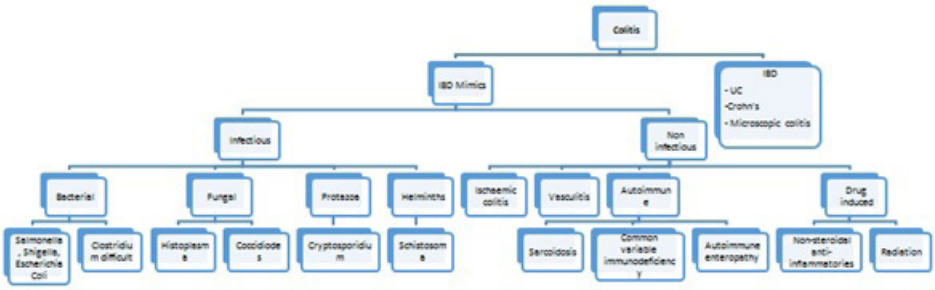

Figure 4: Classification of IBD and IBD mimicking pathology

6. Discussion

Chronic diarrhoea is a common presenting complaint in daily gastrointestinal practice. It may be of inflammatory or non-inflammatory cause; of the inflammatory causes IBD – including microscopic colitis - predominates in colonoscopic series [3-6]. There are however also many IBD-mimicking pathologies to be considered. The mimics include identifiable infections, a wide range of non-infectious causes including ischaemic colitis, vasculitis, diverticulitis, Behçet's disease, amyloidosis, immune-related, drug and radiation-induced colitis [7,8], Self-limiting non-specific colitis - a diagnosis made as much from time as from exclusion of other causes - is also seen and, almost by definition, clearly has an excellent prognosis. The importance of acquiring a thorough clinical history, including discerning the chronicity of the symptoms, and making an accurate physical examination, lie in their ability to refine a purely endoscopic diagnosis of "colitis". We must understand the nature of the complaint in order to deliver appropriate and targeted clinical care.

Whilst establishing the chronicity of the illness from symptoms is important, it is also important to seek histological support differentiating acute and chronic colitis. Features of acute colitis include inflammation of the crypts, crypt abscesses, ulceration and preservation of crypt architecture [7]. Conversely, chronic colitis often demonstrates features of increased lymphoplasmacytosis, Paneth cell metaplasia, and abnormal crypt architecture [7].

Frequently, the features of acute and chronic colitis may overlap, imposing challenges in discerning the causes of colitis and thus reaching an accurate diagnosis [9]. Misdiagnosis can be common. Odze et al. suggested that the main factors contributing to misdiagnosis are inadequate history taking, missing radiological information, and lack of endoscopic information, but also stressed the importance of incompleteness of histopathological information [10].

BSG and ECCO have recommended the acquisition biopsies from 4 random but topographically disperse colonic biopsy sites (with at least 2 biopsies at each site) as well as rectal biopsies to aid the diagnosis of IBD and confirm or exclude IBD-mimicking pathology [1,2] . Rectal biopsy is important for differential diagnosis between IBD and infective colitis as well as microscopic colitis, where mucosal abnormalities are mainly localized at the right colon. Our study compares the diagnostic outcomes in cohorts of patients undergoing colonoscopy for possible IBD before and after implementation of a standardised biopsy protocol. We found that the rate of diagnosis of IBD was significantly reduced (from 96% to 74%) after the standard biopsy protocol was implemented. We are clinically confident that this reduction represents an improvement in our collective diagnostic acumen. Indeed, at 5 years an initially confident diagnosis of IBD had been reversed in 8%, compared to none of the patients in the later cohort (although admittedly at 2 rather than 5 years). A limitation of our study was consistent with a quite suboptimal adherence to the standard biopsy protocol in the second cohort. This was especially notable with regards to ileum intubation and ileum biopsies. Another limitation of the study was the low number of IBD naïve patients. However our study replicates the application of the standard BSG biopsy protocol in the real world, as it was carried out in a busy Gastroenterology Department of a District General Hospital. Our study indeed supports the implementation of the guidelines recommended by BSG and ECCO, reducing the number of patients inadvertently exposed to unnecessary treatments and thus to the avoidable side effect profiles of IBD treatments. Moreover, an inaccurate diagnosis of IBD can also have major adverse impacts on cost effectiveness (e.g. cost of drugs, clinical follow-up and surveillance endoscopies, but also eventual later costs of reinvestigation in some patients

It is established that the accuracy of colitis diagnosis can be increased by involving two pathologists in difficult cases, and generally increasing the awareness of IBD-mimicking pathologies amongst these clinicians [11]. Chachu et al. also advocate re-evaluation of refractory IBD patients as unresponsiveness to treatment may reflect misdiagnosis [12]. From our own clinical experience, we can confirm this recommendation; once a misdiagnosis has been made, it is challenging to 'un-diagnose' its clinical pathology especially when subsequent IBD-mimicking pathology has been established [11].

Attention should also be given to bowel preparation preceding colonoscopy as sodium phosphate-based cleaning regimens can result in colonic mucosal distortions similar to those seen in IBD [13,14].In one study of 730 patients who had sodium phosphate bowel preparation, 24 developed mucosal lesions including erosions, aphthous lesions and ulcers. Histologically, 14 had localized active inflammation, 7 had mucosal distortion and erosion, 5 had oedematous lamina

propria, 5 had mucosal congestion or localized bleeding, 5 had lymphoid nodules and 1 had frank ulceration [15]. In another study all of the 42 patients who received sodium phosphate bowel preparations had histological findings of mild localizing oedema, and increased blood vessel congestion and bleeding [16]. Scattered mononuclear infiltrates were found in 26 patients, whereas neutrophil infiltration and crypt inflammation were found in 5 patients [16]. Two of them were found to have focal cryptitis and inflammatory pseudopolyps [16]. Thus, we agree with the recommendation of Bechtold et al [14] to avoid such cleansing regimens to reduce the chance of misdiagnosis.

Non-steroid anti-inflammatory drugs (NSAIDs) are also associated with drug-induced colitis which may mimic IBD colonoscopically, potentially causing strictures and frank ulcers as well as more diffuse inflammation [17-20]. In a study performed by Stolte et al, of 611 patients who had histological findings of localized erosions, ulcerations and strictures, 86.1% had received NSAIDs prior to colonoscopy [18]. The majority of the lesions were found in the right and transverse colon.[18] NSAIDs can also cause the distinctive histological feature of ischemic necrosis [17,18].The withdrawal of NSAIDs often helps to resolve colonic abnormalities and symptoms, even if stricture formation may require balloon dilatation or a surgical procedure [19]. Evaluation of the drug history, and correlation of clinical information with histopathological findings, as well as identifying the location of pathological abnormalities, are all needed in order to obtain an accurate diagnosis [20].

In addition, it is important to remember that medications such as steroids and novel therapies including anti-tumour necrosis factor as well as exclusive enteral nutrition can induce mucosal healing [21-25]. The performance of colonoscopy whilst on medical therapy can lead to partial or incomplete mucosal healing therefore altering the endoscopic and histological appearance of the colonic mucosa, which subsequently leads to an inaccurate diagnosis.

7. Conclusion

The use of a standard biopsy protocol is crucial to aid the diagnosis of IBD and exclude other IBD-mimicking pathology. It is important to correlate clinical information, radiological, endoscopic and histopathological findings to help diagnose the underlying cause of colitis. It is also important to increase the awareness of IBD-mimicking pathology to avoid misdiagnosis. We have demonstrated that adherence to a standard biopsy protocol improves the accuracy of a durable diagnosis of IBD, as well as helping to confirm or exclude IBD-mimicking pathologies.

8. Acknowledgement

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9. Author contributions

All authors contributed equally to the writing up of the paper. EA-CP MB –RF-LP performed and supervised the research study. RF-PB-CP-AF contributed to conceiving and implementing the research protocol.

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11. Conflict of interest

No conflicts of interest are declared.

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