Inflammatory bowel disease: re-evaluation of the diagnosis in a prospective population based study in south eastern Norway

B Moum, A Ekbom, M H Vatn, E Aadland, J Saur, I Lygren, T Schulz, N Stray, O Fausa

Abstract

Background—The incidence figures for ulcerative colitis (UC) and Crohn’s disease (CD) have been difficult to interpret, and geographical variations may be due to differences in classification criteria and study design. Few studies have based the incidence on prospective systematic follow up to confirm the initial diagnosis.

Methods—Between 1990 and 1993, in a prospective incidence study of inflammatory bowel disease (IBD) in south eastern Norway, 527 cases of UC, 228 cases of CD, 36 cases of indeterminate colitis (IND), and 55 cases of possible IBD were identified, yielding an annual incidence of 13.6, 5.9, 0.9, and 1.4 per 10⁵ respectively. The diagnosis and all clinical data were reviewed by two gastroenterologists independently of each other. One to two years after diagnosis, all patients were offered a clinical follow up in which the initial diagnosis was assessed.

Results—Between the time of diagnosis and the follow up, 16 patients had died, four of complications related to IBD. Of the remaining 830 patients, 98% (814/830) were available for follow up, 93% (772/830) attended a clinical examination which included a colonoscopy in 77% (637/830), and the remainder had a telephone interview, or reassessment based on hospital records, or both. Twenty seven patients were reclassified as not having IBD (3%), and 65 patients were characterised as possible IBD (8%). Of the patients initially classified as UC, 88% had their diagnosis confirmed, compared with 91% with an initial diagnosis of CD. In patients with indeterminate colitis, 33% were classified as definite UC and 17% as CD. This reclassification of patients yielded a corrected annual incidence of 12.8 for UC and 6.0 for CD.

Conclusion—At follow up one to two years after the diagnosis of IBD, the initial incidence was only marginally altered. This is probably due to uniform inclusion criteria and careful diagnostic methods. The study also illustrates the importance of the re-evaluation of the initial diagnosis as close to 10%, both among patients with UC and CD, were reclassified at follow up.

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Keywords: Crohn’s disease, diagnosis assurance, epidemiology, incidence, indeterminate colitis, ulcerative colitis.
The aim of the present study was to re-evaluate the initial diagnosis in these patients 12 months later to assess the extent to which such a re-evaluation affects the original incidence figures.21 27

Methods
The study covered four geographically well-defined areas in south eastern Norway with a total population on 1 January 1992 of 966 427 inhabitants, all of whom had uniform access to well organised healthcare services.20 The administration and organisation of the study as a whole, with a senior gastroenterologist responsible for the clinical examination and collection of patient data in all four counties, has been described in previous publications.20 21 27

The extent and localisation of colonic disease were based on endoscopical findings and were verified by characteristic histological signs of inflammation in the same parts of the colon.20

The basis for inclusion in the study was that the patient had had symptoms consistent with IBD for more than four weeks, excluding infections and other acute or chronic non-IBD. The diagnosis of UC was based on the presence of at least three of the following criteria: (1) a history of diarrhoea and/or blood or pus in the stools; (2) macroscopic appearance on endoscopy of continuous mucosal inflammation affecting the rectum in continuity with some or all of the colon; (3) microscopic features on biopsy compatible with UC; and (4) no suspicion of CD on small bowel radiography, ileocolonoscopy, or biopsy. The diagnosis of CD was based on the presence of two or more of the following criteria: (1) typical clinical features including abdominal pain, diarrhoea, and weight loss; (2) macroscopic appearance at operation or endoscopy: segmental, discontinuous, or patchy lesions with or without rectal involvement, discrete or aphthous ulcerations, fissuring and penetrating lesions, cobblestone or strictures; (3) radiological evidence of stenosis in the small bowel, segmental colitis, or fistulae; and (4) histological evidence of transmural inflammation or epithelial granulomas with giant cells.29

The diagnostic criterion for the classification of IND was that both endoscopy and histopathology were conclusive for a diagnosis of IBD but divergent or inconclusive for a diagnosis of definite UC or CD. For example, in one and the same patient, features typical of one disease might be evident at endoscopy while histopathology showed signs of the other or the endoscopical distribution indicated one disease whereas the appearance of the macroscopic or microscopical changes were more typical of the other. Thus characteristics of both diseases could be present either at endoscopy, histopathology, or both. If the patient had symptoms and signs of IBD at the initial stage of the investigation but did not fulfil the criteria for definite IBD, if the quality of the diagnostic examination was not satisfactory, or the findings were uncertain, the classification of possible IBD was used.

All initial slides were reviewed by the same pathologist at follow up. Moreover, cases classified as IND and possible IBD were discussed and reviewed by the diagnosing gastroenterologists and one of the gastroenterologists at the university hospital.

Patients were followed up for a period of at least 12 months and were then asked to return to the local hospital for a re-examination, if possible by the doctor who had performed the initial examination. The main purpose of this was to review the primary diagnosis by an interview, a clinical examination, laboratory tests, and if necessary and if agreed to by the patient, colonoscopy with biopsies and small bowel enema. The time lag from the first examination and this follow up was on average 14 months (interquartile range 12–18). In some cases the follow up examination had to be replaced by a telephone interview, sometimes supplemented by hospital notes. For patients who could not be reached by telephone, hospital records were used.

As a further test of the validity of our classification, we broke down the figures for each diagnosis according to the disease distribution.

Ethics
The study was approved by the regional ethics committee and the Norwegian Data Inspectorate. The patients’ identity and records were treated as confidential on the basis of the guidelines laid down by the Ministry of Health and Social Affairs.

Statistics
Population data for the region by age and sex were obtained from Statistics Norway,28 and the annual incidence was directly standardised to the 1992 study population in south eastern Norway. The median time interval between the time of diagnosis and follow up was calculated with an interquartile range (25th and 75th percentiles).

Results
Between diagnosis and follow up 11 patients with UC (2.2%) and five patients with CD (2.2%) had died, four of complications related to IBD (two cases of spontaneous colon perforation (one UC and one CD), one of cholangiocarcinoma related to primary sclerosing cholangitis (UC), one of septicaemia (CD)). Of the remaining 830 patients, 98% (814/830) were available for follow up (Table 1). Of these 93% (772/830) underwent a clinical examination which included a colonoscopy in 77% of them (637/830). After the clinical examination, or a telephone interview, or information gathered from patient notes, 27 patients (3%) were reclassified as not having IBD, and 65 patients (8%) were characterised as having possible IBD. Of the patients initially diagnosed having UC, 88% (464/527) had their diagnosis confirmed, compared with 91% (208/228) of patients initially classified as having CD. In patients with indeterminate
colitis, 33% (12/36) were classified as definite UC and 17% (6/36) as CD. After follow up, half of the patients initially classified as IND, had a definitive classification compared with 31% (17/55) of the patients with an initial diagnosis of possible IBD (Table I).

Of the 27 cases classified as non-IBD, 56% (15/27) were initially classified as IND or possible IBD, – that is, of the UC and CD cases only 2% and 1% respectively were later reclassified as having non-IBD. The initial classification shows that the main reason why these 27 patients were reclassified as non-IBD was an uncertain diagnosis from the beginning. Furthermore, they had no relapses or disease activity during the follow up period and as follow up there were no endoscopical findings, histological signs of inflammation, or pathological findings on small bowel radiography.

In 47% of the patients with UC and in 50% of the patients with CD there had been no symptoms between the patients’ first attack and the follow up, compared with 50% (5/10) in IND and 89% (58/65) in cases of possible IBD. In 29% (120/410) of the cases of UC and 23% (37/164) of the cases of CD, there was endoscopical remission and in 23% (92/408) of the cases of UC and 22% (36/164) of the cases of CD there was no histological evidence of continuing IBD. Correspondingly, the figures for IND and possible IBD were 20% (2/8) and 86% (36/42) in endoscopical remission and 0% and 76% (32/42) without any histopathological changes respectively. Of the 36% (84/232) of patients with CD who had radiography of the small bowel at follow up, 55% (46/232) had pathological findings.

There were significant differences in the incidence of UC and CD between the counties, but there were no differences between the counties as regards the proportion of cases classified as UC, CD, IND, or possible IBD.21 27

The reclassification of the diagnoses yielded a corrected annual incidence of 12.8 per 105 in UC and 6.0 per 105 in CD (Table I) compared with 13.6 and 5.8 respectively. The reclassification at follow up with respect to the initial distribution of patients of disease did not show any significant differences between proctitis, left sided colitis, and extensive colitis (proximal to the splenic flexure) in UC. In CD the frequency of reclassification in Crohn’s colitis differed from that of CD with regard to combined small and large bowel disease (p=0.013; Table II).

**Discussion**

The results of the present study are reassuring as regards the accuracy of the initial diagnosis. The estimated incidence was only marginally altered and in as many as about 90% of the patients initially classified as UC or CD the initial diagnosis remained unaltered.

We managed to reach a high compliance at follow up, and as many as 772 of 777 (99%) of the patients who were still alive attended a clinical examination. Furthermore the great majority of the remaining patients were interviewed by telephone, or had their hospital records reviewed, or both. Because of the high frequency of patient follow up, the clinical data used as a basis for re-evaluating the diagnosis was of high quality. The fact that as many as 83% (637/772) of the patients attending the clinical examination at follow up had a colonoscopy performed, further improved the quality of the data used for assessing the diagnosis.

The high frequency of colonoscopies performed at follow up increases the diagnostic accuracy of the present study compared with other studies with less rigorous standards for re-evaluation. It is therefore surprising that as many as 8% (n=65) of the patients in our study still had no definite diagnosis after follow up, even though most cases of IND were classified as either UC, CD or non-IBD. Of cases classified as UC or CD at diagnosis, most of these had a clinical course with symptomatic relapse or endoscopical or histological evidence of continuing and chronic IBD at follow up. Even so, only about half of the cases of UC and CD had a symptomatic relapse, and altogether 73% (417/574) had endoscopical findings confirming a chronic course of their disease. In most of the cases classified as non-IBD and possible IBD no symptomatic relapse occurred; nor was there endoscopical or histological evidence of continuing IBD. In addition, the diagnosis of IBD must be treated with caution, as in a substantial number of cases the line between UC and CD in remission and non-IBD is unclear. The diagnosis at follow up in this study was made on the basis of an overall evaluation of clinical symptoms, course of disease, and endoscopical and histological examinations. In the 23% of patients with UC and CD with no histological evidence of IBD at follow up, the patients were kept in the original diagnostic groups because of the presence of one or more criteria other than histology. By contrast with this, in the

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**Table I** Re-evaluation of the diagnosis at follow up

<table>
<thead>
<tr>
<th>Cases at first diagnosis (n)</th>
<th>Cases as follow up* (n(%))</th>
<th>UC</th>
<th>CD</th>
<th>IND</th>
<th>pIBD</th>
<th>non-IBD</th>
<th>Lost to follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>UC (527)</td>
<td></td>
<td>153</td>
<td>4</td>
<td>21</td>
<td>23(4)</td>
<td>9(2)</td>
<td>12(2)</td>
</tr>
<tr>
<td>CD (228)</td>
<td></td>
<td>208(93)</td>
<td>3</td>
<td>9</td>
<td>4(1)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>IND (36)</td>
<td></td>
<td>6(17)</td>
<td>2</td>
<td>6(10)</td>
<td>27(42)</td>
<td>5(14)</td>
<td>1(3)</td>
</tr>
<tr>
<td>pIBD (35)</td>
<td></td>
<td>14(25)</td>
<td>3</td>
<td>5(15)</td>
<td>23(42)</td>
<td>10(18)</td>
<td>2(4)</td>
</tr>
<tr>
<td>All (946)</td>
<td></td>
<td>496(27)</td>
<td>10</td>
<td>1(5)</td>
<td>65(58)</td>
<td>27(33)</td>
<td>16(2)</td>
</tr>
<tr>
<td>Adjusted incidence**</td>
<td></td>
<td>12-8</td>
<td>6-0</td>
<td>0-25</td>
<td>1-7</td>
<td>0-7</td>
<td>0-04</td>
</tr>
</tbody>
</table>

UC=Ulcerative colitis; CD=Crohn’s disease; IND=cases of either UC or CD; pIBD=possible IBD.

**Table II** Reclassification at follow up distribution of disease

<table>
<thead>
<tr>
<th>Cases at first diagnosis (n)</th>
<th>Cases as follow up (n(%))</th>
<th>UC</th>
<th>CD</th>
<th>IND</th>
<th>pIBD</th>
<th>non-IBD</th>
<th>Lost to follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>UC proctitis (168)</td>
<td></td>
<td>147</td>
<td>91</td>
<td>2</td>
<td>7(4)</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>UC left sided colitis (176)</td>
<td></td>
<td>154</td>
<td>90</td>
<td>2</td>
<td>3(4)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>UC extensive colitis (183)</td>
<td></td>
<td>163</td>
<td>90</td>
<td>10</td>
<td>7</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CD large bowel disease (103)</td>
<td></td>
<td>5</td>
<td>87(85)</td>
<td>1</td>
<td>6(5)</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>CD colonic and small bowel disease (65)</td>
<td></td>
<td>1</td>
<td>64(98)</td>
<td>3</td>
<td>5(8)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>CD small bowel disease (60)</td>
<td></td>
<td>57</td>
<td>95(95)</td>
<td>3</td>
<td>5(8)</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

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27 cases reclassified as not having IBD, and the 65 classified as possible IBD, signs of the chronicity of the disease were either lacking or uncertain.

Altogether, very few patients (3%) (27/846) were classified as non-IBD, by contrast with another prospective study, in which only 52 of 105 patients with symptoms were deemed to have IBD at follow up. The basis for the initial classification as definite or possible IBD in this study was that the patient had had symptoms consistent with IBD for more than four weeks, which, together with the more stringent diagnostic criteria, could be one reason for the low rate of exclusion from the classification of IBD after one year.

Of the cases initially classified as UC, 15 diagnoses (3%) were changed to CD, and in those initially classified as CD, six diagnoses (3%) were changed to UC. These figures are in accordance with other reported findings, even though the time of follow up in these studies was considerably longer than in the present one.4 14 16 17

Despite meticulous diagnostic efforts, in as many as 9% of the patients (10/75) with IND or possible IBD definitive UC or CD could not be confirmed after the follow up period, which raises problems in the further diagnostic characterisation of these patients. However, the numbers are so low they would have little influence on the incidence.

There was a small but not significant reduction in the incidence of UC, whereas the incidence of CD remained more or less unaltered, which means that the overall incidence of IBD is still consistent with the high incidence reported in other studies in Norway and Scandinavia in the 1970s and 1980s.2 7–14

There were some differences in the mean annual incidence of UC and CD between the four counties at the time of diagnosis.12 22

The re-evaluation of the diagnosis had no effect on these differences in incidence, as there were no differences in the proportion of patients excluded as not having IBD. The high annual incidence of UC and CD in this study, and the higher incidence in mixed rural-urban than in urban areas, therefore seem to be real.

Most of the cases of UC reclassified as CD had extensive colitis initially, but in the other patients with UC no difference was found between subgroups with respect to distribution and reclassification of disease. As expected, nearly all the patients initially classified as CD who received a new diagnosis had colonic disease only. One third of these patients were re-diagnosed as having UC. There was a very high diagnostic accuracy initially compared with follow up diagnosis in patients with small bowel disease (Table II).

In a small group of patients the distinction between UC and CD may be difficult and must, at least temporarily, be left unresolved. The term "indeterminate colitis" ought thus to be used until more definitive information is collected, and it should be regarded as a provisional, descriptive term rather than a specific diagnostic entity.22

The importance of an accurate diagnosis must be emphasised if we are to discover more about these diseases and their pathogenic factors. Furthermore, a precise diagnosis is necessary if clinicians and researchers are to be able to communicate with each other internationally.

In conclusion, this prospective study, which was designed to ensure a high validity of the diagnosis of UC and CD by means of a re-evaluation after one year resulted in only marginal alterations in the initial incidence for the two diseases. This is probably due to the uniform, stringent inclusion criteria and to the diagnostic methods used. Despite the high correlation between the initial diagnosis and the diagnosis at follow up, the study illustrates the importance for the individual patients of re-evaluating the initial diagnosis, as close to 10% of patients with UC and with CD were reclassified at the time of follow up.

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