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 Sauar, I Lygren, T Schulz, N Stray, O Fausa

Department of
Internal Medicine,
Østfold Central
Hospital, Fredrikstad,
Norway
B Moum

Department of
Medicine A, the
National Hospital,
Oslo, Norway
M H Vatn
O Fausa

Department of
Internal Medicine,
Aker University
Hospital,
Oslo, Norway
E Aadland

Department of
Internal Medicine,
Ullevål University
Hospital, Oslo, Norway
I Lygren

Department of
Internal Medicine,
Telemark Central
Hospital, Skien,
Norway
J Sauar

Department of
Internal Medicine
Aust-Agder Central
Hospital, Arendal,
Norway
T Schulz

Department of
Internal Medicine,
Norwegian Lutheran
Hospital, Oslo, Norway
N Stray

Cancer Epidemiology
Unit, University
Hospital, Uppsala,
Sweden
A Ekbom

Correspondence to:
Dr Bjørn Moum,
Med Dept ØSS, Fredrikstad,
N-1603 Fredrikstad,
Norway.

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 10^5 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 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.
(*Gut* 1997; **40**: 328–332)

Keywords: Crohn's disease, diagnosis assurance, epidemiology, incidence, indeterminate colitis, ulcerative colitis.

Descriptive epidemiological studies of inflammatory bowel disease (IBD) have disclosed a high annual incidence, especially in the northern hemisphere and Scandinavia.[1–10] The time trends are difficult to interpret, and the reported incidence shows considerable geographical variation. This may be due to differences in the diagnostic methods and classification criteria. Moreover, there is an inherent difference between retrospective and prospective studies.

In retrospective studies, the diagnosis is automatically re-evaluated because in most instances the clinical course has been followed up for years after the patients have been included in the study. In most prospective studies, on the other hand, there is no validation of the diagnosis as mostly the information about a patient is confined to what was current at the time of inclusion. This could well lead to the point estimate of the incidence being too high if the criteria are not stringent enough or too low if the criteria are too stringent.[1–17] The classification indeterminate colitis (IND) – which was initially applied by Price in 1978 to patients in whom it was impossible to distinguish ulcerative colitis (UC) from Crohn's disease (CD)[18 19] – and the classification possible IBD also constitute a problem. In most other studies patients classified as having IND or possible IBD are not included in the initial incidence, and there are only two studies of the incidence of IBD, one of which was prospective, in which the classification IND has been used as a separate entity.[20–22]

Moreover, in up to 40% of patients with a clinical picture of acute colitis usually no definite aetiology can be found; they probably have an acute reversible infection in which the organisms cannot be identified by routine culture.[23] Although endoscopy with biopsy can help to distinguish infectious colitis from a first attack of IBD, there will always be some patients for whom the primary diagnosis will remain uncertain. This uncertainty can be minimised by a re-evaluation of the diagnosis over a follow up of 12 months or more, utilising all the data available for each individual patient.[16 24–26]

In a previously presented prospective study of the incidence of IBD between 1990 and 1993 in south eastern Norway we identified 527 cases of UC, 228 cases of CD, 36 cases of IND, and 55 cases of possible IBD, which yielded an annual incidence of 13·6, 5·9, 0·9, and 1·4 per 10^5 respectively.[20 21 27]

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.[28] 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 aphtous 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 I). 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 classified as 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

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

Cases at first diagnosis (n)	Cases at follow up* (n(%))					Lost to follow up
	UC	CD	IND	pIBD	non-IBD	
UC (527)	464 (88)	15 (3)	4	23 (4)	9 (2)	12 (2)
CD (228)	6 (3)	208 (91)	1	9 (4)	3 (1)	1
IND (36)	12 (33)	6 (17)	2 (6)	10 (29)	5 (14)	1 (3)
pIBD (55)	14 (25)	3 (5)	3 (5)	23 (42)	10 (18)	2 (4)
All (846)	496 (59)	232 (27)	10 (1)	65 (8)	27 (3)	16 (2)
Adjusted incidence**	12·8	6·0	0·25	1·7	0·7	0·4

UC=Ulcerative colitis; CD=Crohn's disease; IND=cases of either UC or CD; pIBD=possible IBD.
Figures <1% are not given.
*Follow up investigation n=772, telephone interview or information from medical records 42, deaths 16, lost to follow up 16.
**Incidence 100 000 people/year.

TABLE II   *Reclassification at follow up distribution of disease*

Cases at first diagnosis (n)	Cases at follow up (n(%))					Lost to follow up
	UC	CD	IND	pIBD	non-IBD	
UC proctitis (168)	147 (91)	1	2	7	4	7
UC left sided colitis (176)	154 (90)	4	2	9	3	4
UC extensive colitis (183)	163 (90)	10	–	7	2	1
CD large bowel disease (103)	5	87 (85)	1	6	3	1
CD colonic and small bowel disease (65)	1	64 (98)	–	–	–	–
CD small bowel disease (60)	–	57 (95)	–	3	–	–

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

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 at 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 10^5 in UC and 6·0 per 10^5 in CD (Table I) compared with 13·6 and 5·8 respectively. The reclassification at follow up with respect to the initial distribution 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 830 (93%) 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 revaluating the diagnosis were 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 an 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

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 were deemed to have IBD at follow up.[26] 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 (n=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.[21 27] 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 rediagnosed 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 as 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.

1 Whelan G. Epidemiology of inflammatory bowel disease. *Med Clin North Am* 1990; **71:** 1–11.
2 Haug K, Schrumpf E, Barstad S, Fluge J, Halvorsen JF. Epidemiology of ulcerative colitis in western Norway. *Scand J Gastroenterol* 1988; **23:** 517–22.
3 Kildeo S, Breckan R, Norgaard K, Burhol PG, Jorde R. The incidence of Crohn's disease in northern Norway from 1983 to 1986. *Scand J Gastroenterol* 1989; **24:** 1265–70.
4 Langholz E, Munkholm P, Nielsen OH, Kreiner S, Binder V. Incidence and prevalence of ulcerative colitis in Copenhagen county from 1962 to 1987. *Scand J Gastroenterol* 1991; **26:** 1247–56.
5 Ekbom A, Helmick C, Zack M, Adami HO. The epidemiology of inflammatory bowel disease: a large, population-based study in Sweden. *Gastroenterology* 1991; **100:** 350–8.
6 Lindberg E, Jarnerot G. The incidence of Crohn's disease is not decreasing in Sweden. *Scand J Gastroenterol* 1991; **26:** 495–500.
7 Roin F, Roin J. Inflammatory bowel disease of the Faroe Islands 1981–8. *Scand J Gastroenterol* 1989; **24** (suppl 170): 44–6.
8 Fellows IW, Freeman JG, Holmes GKT. Crohn's disease in the city of Derby, 1951–85. *Gut* 1990; **31:** 1262–5.
9 Srivastava E, Mayberry JM, Morris T, Smith P, Williams G, Roberts G, *et al.* Incidence of ulcerative colitis in Cardiff over 20 years: 1968–87. *Gut* 1992; **33:** 256–8.
10 Stonnington CM, Phillips SF, Melton LJ, Zinsmeister AR. Chronic ulcerative colitis; incidence and prevalence in a community. *Gut* 1987; **28:** 402–9.
11 Mayberry JF, Rhodes J. Epidemiological aspects of Crohn's disease: a review of the literature. *Gut* 1984; **25:** 886–99.
12 Brostrom O. Prognosis in ulcerative colitis. *Med Clin North Am* 1990; **71:** 201–17.
13 Farmer RG, Easly KA, Rankin GB. Clinical patterns, natural history, and progression of ulcerative colitis. A long-term follow up of 1116 patients. *Dig Dis Sci* 1993; **38:** 1137–46.
14 Munkholm P, Langholz E, Haagen Nielsen O, Kreiner S, Binder V. Incidence and prevalence of Crohn's disease in the county of Copenhagen, 1962–87: a sixfold increase in incidence. *Scand J Gastroenterol* 1992; **27:** 609–14.
15 Shivananda S, Hordijk ML, Pena AS, Mayberry JF, van Blankenstein M. Summary of discussion relating to disease definition and diagnostic verification procedure to confirm the presence or absence of inflammatory bowel disease. *Scand J Gastroenterol* 1989; **24** (suppl 170): 16–9.

16 Myhren J, Bouchier AD, Watkinson G, Softley A, Clamp SE, De Dombal FT. The OMGE multinational inflammatory bowel disease survey 1976–86. A further report on 3175 cases. *Scand J Gastroenterol* 1988; **23** (suppl 144): 11–9.

17 Lind E, Fausa O, Elgjo K, Gjone E. Crohn's disease. Diagnostic procedures and problems. *Scand J Gastroenterol* 1985; **20**: 660–4.

18 Price AB. Overlap in the spectrum of non-specific inflammatory bowel disease – "colitis indeterminate". *J Clin Pathol* 1978; **31**: 567–77.

19 Wells AD, McMillan I, Price AB, Ritchie JK, Nicholls RJ. Natural history of indeterminate colitis. *Br J Surg* 1991; **34**: 685–9.

20 Moum B, Vatn M, Ekbom A, Fausa O, Aadland E, Sauar J, Schulz T. Incidence of inflammatory bowel disease in southeastern Norway. Evaluation of methods after one year of registration. *Digestion* 1995; **56**: 377–81.

21 Moum B, Vatn M, Ekbom A, Aadland E, Fausa O, Lygren I, et al. Incidence of ulcerative colitis and indeterminate colitis in four counties in southeastern Norway 1990–3. A large prospective population-based study. *Scand J Gastroenterol* 1996; **31**: 356–60.

22 Stewenius J, Adnerhill I, Ekelund G, Floren C-H, Fork F-T, Janzon L, et al. Ulcerative colitis and indeterminate colitis in the city of Malmø, Sweden. *Scand J Gastroenterol* 1995; **30**: 38–43.

23 Goldman H. Interpretation of large intestinal mucosal biopsy specimens. *Hum Pathol* 1994; **25**: 1150–9.

24 Schumacher G, Kollberg B, Sandstedt B. A prospective study of first attacks of inflammatory bowel disease and infectious colitis. *Scand J Gastroenterol* 1994; **29**: 318–32.

25 Surawicz CM, Belic L. Rectal biopsy helps to distinguish acute self-limited colitis from idiopathic inflammatory bowel disease. *Gastroenterology* 1984; **86**: 104–13.

26 Schumacher G, Kollberg B, Sandstedt B. A prospective study of first attacks of inflammatory bowel disease and infectious colitis. Clinical findings and early diagnosis. *Scand J Gastroenterol* 1994; **29**: 265–74.

27 Moum B, Vatn M, Ekbom A, Aadland E, Fausa O, Lygren I, et al. Incidence of Crohn's disease in four counties in southeastern Norway 1990–3. A large prospective population-based study. *Scand J Gastroenterol* 1996; **31**: 349–55.

28 *Statistics Norway*, Oslo: Kongsvinger, Population Statistics, 1992: I–II.

29 Lennard-Jones JE. Classification of inflammatory bowel disease. *Scand J Gastroenterol* 1989; **24** (suppl 170): 2–6.

30 Munkholm P, Langholz E, Davidsen M, Binder V. Disease activity in a regional cohort of Crohn's disease patients. *Scand J Gastroenterol* 1995; **30**: 699–706.