Risk of Relapse in New Cases of Ulcerative Colitis and Indeterminate Colitis

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PURPOSE: Changes in morbidity pattern of ulcerative colitis have created a need to update understanding of the course of the disease. METHOD: A follow-up study was done of relapse rates and progression of inflammation in 571 nonselected patients with ulcerative and indeterminate colitis. RESULTS: Relapse rate ten years after diagnosis was 70 percent in definite ulcerative colitis, 22 percent in probable ulcerative colitis, and 77 percent in indeterminate colitis. During the study period, there was no change in the relapse rate. In relapsing proctitis, 52 percent developed more extensive inflammation. Fifty-four percent of patients with only one attack of colitis had persistent signs of inflammatory bowel disease. CONCLUSIONS: Shift in morbidity pattern to a greater proportion of patients with proctitis at diagnosis and a shorter time from onset of symptoms to diagnosis had no influence on the relapse rate. Indeterminate colitis has a worse prognosis than definite ulcerative colitis. Considering the documented efficacy of sulfasalazine, the high relapse rate calls for studies of the effectiveness of such treatment in everyday practice. [Key words: Extent; Indeterminate colitis; Inflammation; Relapse; Ulcerative colitis]

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Prognosis for new cases with inflammatory bowel disease ranges from complete recovery following a single, fairly benign episode to need of colectomy because of severe inflammation or colorectal cancer.[1] We have in previous studies reported an increasing incidence of proctitis from 1958 to 1982.[2] We have also reported that patients with indeterminate colitis have a worse prognosis compared with those with definite ulcerative colitis concerning risk of colectomy and risk of colorectal cancer.[3, 4] Our study has also shown data indicating that time between onset of symptoms and diagnosis of colitis has been shortened during the studied period 1958 to 1982.[2] There has hence been a change in the morbidity pattern and in giving new patients appropriate advice with regard to prognosis and choice of treatment; there is a need for new studies dealing with the natural course of disease.

The aim of this study was to analyze relapse and progression of inflammation in nonselected patients with ulcerative colitis and indeterminate colitis who were diagnosed in the city of Malmö, Sweden, during a time period when there has been a shift of the morbidity pattern.

MATERIAL AND METHODS

Study Cohort

The study cohort consists of 354 patients with definite ulcerative colitis, 117 with probable ulcerative colitis, and 100 with indeterminate colitis. These are all of the patients with colitis diagnosed between 1958 to 1982 in the city of Malmö, Sweden[2] (Table 1).

Definite or probable ulcerative colitis has been defined according to Evans and Acheson.[5] These criteria are in summary. For *definite ulcerative colitis*, there was a history of diarrhea or rectal bleeding for six weeks or more, with characteristic signs of inflammation at sigmoidoscopy, barium enema, surgical specimen, or autopsy. However, a history shorter than six weeks was accepted for a definite diagnosis if the patient had been prescribed proper treatment or undergone colectomy within these weeks. For *probable ulcerative colitis*, criteria are as above but with either a history or diagnostic findings inadequate for a definite diagnosis. Patients with a diagnosis of inflamma-

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Table 1.
Sex, Age, and Extent of Inflammation at Diagnosis and During Follow-Up in Patients with Ulcerative Colitis and Indeterminate Colitis

	Definite Ulcerative Colitis (n = 354)	Probable Ulcerative (n = 117)	Indeterminate Colitis (n = 100)
Sex (n)			
Men	209 (59)	61 (52)	49 (49)
Women	145 (41)	56 (48)	51 (51)
Age at diagnosis (yr)			
Mean	37.2	41.7	32.6
Range	6–87	4–88	5–77
Time from onset of symptoms to diagnosis (mo)			
Mean	12.3	10.0	21.4
Median	2.0	1.0	2.0
Extent of (n) inflammation at diagnosis			
Proctitis	208 (59)	64 (55)	29 (29)
Left-sided colitis	82 (23)	33 (28)	19 (19)
Total colitis	64 (18)	20 (17)	52 (52)
Severity of first attack (n)			
Severe	16 (5)	1 (1)	14 (16)
Moderate	158 (47)	43 (42)	44 (49)
Mild	165 (49)	59 (57)	32 (36)
Maximum extent of inflammation during follow-up (n)			
Proctitis	131 (37)	50 (43)	2 (2)
Left-sided colitis	118 (33)	38 (32)	11 (11)
Total colitis	105 (30)	29 (25)	87 (87)

Percents are within parentheses.

tory bowel disease but with insufficient diagnostic criteria for ulcerative colitis and for Crohn's disease were classified as suffering from *indeterminate colitis.*

Excluded from the study of ulcerative colitis were those with an initial diagnosis of definite or probable ulcerative colitis but who during the follow-up were found to suffer from indeterminate colitis. These patients were said to have had an incorrect diagnosis and were instead included in the study of indeterminate colitis with a date of diagnosis from the date of diagnosis of colitis. Patients with an initial diagnosis of ulcerative colitis or indeterminate colitis who during the follow-up period were found to suffer from Crohn's disease were also excluded.

Extent of Disease at Diagnosis. Extent of disease at diagnosis included *proctitis* with mucosal disease in whole or part of the rectum at sigmoidoscopy and no evidence of disease in the colon, *left-sided colitis* (including the transverse colon), or *total colitis* (Table 1). In 292 of 301 cases classified as proctitis, double-contrast barium enema (DCBE) was performed and did not show any inflammation above the rectum.

Severity of First Attack. Severity of first attack was defined as severe, moderate, or mild in accordance with Truelove and Witts[6] (Table 1).

Time, in Months, from Onset of Symptoms to Diagnosis. Time, in months, from onset of symptoms to diagnosis of colitis was extracted from the medical records (Table 1).

Remission. Remission in the present study means that there is an explicit statement in the medical record that the patient has recovered from the episode of bowel inflammation. This was not always confirmed with endoscopy or radiography. There were no standardized rules with regard to follow-up clinically or radiologically. Clinical remission after the first attack was documented in 331 patients (94 percent) with definite ulcerative colitis, in 110 (94 percent) with probable ulcerative colitis, and in 80 (80 percent) with indeterminate colitis.

Treatment Policy. Treatment policy included sulfasalazine in patients with ulcerative colitis. Patients have been offered treatment on an individual basis. It has, however, not been possible to evaluate length or dosage of sulfasalazine treatment from the medical records. Patients with proctitis were routinely treated with corticosteroid enemas.

Follow-Up

Incidence of relapse is based on an up-date of the status of all but ten patients on January 1, 1990. Seven of these ten patients had emigrated and three did not reply to repeated letters. These three patients were, according to public registers, all alive. Patients in remission, were followed to date of death, date of colectomy, or date of a first relapse. Mean follow-up time from diagnosis of colitis to first relapse for the 522 patients in remission was 6.9 (range, 0–30) years. Registration of the extent of inflammation included all examinations performed to January 1, 1990.

Relapse. Relapse is defined as a clinically diagnosed relapse verified either by endoscopy or radiology in patients in remission and based on information in the medical records. Of 180 patients without relapse, 85 had left-sided or total colitis at diagnosis. These 85 patients were offered endoscopy and radiology to

determine if signs of colitis persisted for more than one year after diagnosis of colitis. Thirteen of these 85 had no follow-up examination.

Progression of Extent of Inflammation in Patients with Proctitis. Two hundred eight patients had definite ulcerative proctitis. All but six of these patients had at least one DCBE. Of these 208 patients, 158 had a second DCBE or colonoscopy. In the 64 patients with probable ulcerative proctitis, all but three had at least one DCBE and 40 had a second DCBE or colonoscopy during follow-up. All 29 patients with indeterminate proctitis had at least one DCBE, and 25 of them had further examinations.

Maximum Extent. Maximum extent is defined as the most inflammation documented at any examination during the entire follow-up period.

Statistical Methods. Survival analyses, using the Kaplan-Meier method with generalized Wilcoxon test[7] and Cox's proportional hazards model for multivariate analyses,[8] were used to study relapse-free survival in relation to type of colitis. Ninety-five percent confidence intervals were calculated around risk estimates. Risk of relapse associated with gender, age at diagnosis, time interval from onset of symptoms to diagnosis of colitis, extent of disease at diagnosis, and severity of the first attack of colitis were estimated similarly. In the analyses of risks associated with age at diagnosis and with time interval from onset to diagnosis, patients were grouped by tertiles.

RESULTS

Relapse

Relapse in patients in remission after the first attack was confirmed in 249 of 331 patients with definite ulcerative colitis, in 23 of 110 with probable ulcerative colitis, and in 66 of 80 with indeterminate colitis, which corresponds to a relapse rate of 128, 19, and 149/1,000 person years, respectively (Table 2). Relapse risk in patients with indeterminate colitis was twice as high (relative risk, 1.9; 95 percent confidence interval, 1.6–2.4) as in patients with definite ulcerative colitis, whereas in patients with probable ulcerative colitis the risk was lower (relative risk, 0.3; 95 percent confidence interval, 0.2–0.4; Table 2). Risk estimates were unchanged after adjustment for age at diagnosis and for time from onset to diagnosis. After a follow-up time of ten years, patients with definite ulcerative colitis, probable ulcerative colitis, and indeterminate colitis had had a relapse of 70, 22, and 77 percent, respectively (Fig. 1).

Relapse rate did not differ among patients diagnosed in any of the three time periods, 1958 to 1966, 1967 to 1974, and 1975 to 1982 (Fig. 2). To make this comparison feasible, the follow-up period was limited to seven years. Of the 72 patients with left-sided or total colitis in remission after the first attack without clinical relapse, 41 (54 percent) were found to have persistent signs of colitis at follow-up one year or more after diagnosis of colitis.

Risk Factors for Relapse

Patients who at diagnosis had presented with proctitis or left-sided colitis had higher relapse rates than those who had total colitis. Associated risk remained when adjusting for type of colitis (Table 3). No similar associations were found between relapse rate and gender, age at diagnosis, time from onset of symptoms to diagnosis, or severity of first attack (Table 3).

Progression of Extent of Inflammation from Proctitis in Patients with Relapse

Of the 188 patients with proctitis who were in remission after the first attack, 91 (48 percent) had at least one further episode of proctitis and 97 (52 percent) had relapsing disease with more extended inflammation (Table 4). Forty-five percent of patients

Table 2.
Relapse-Free Survival in Patients in Remission After the First Attack and Relapse Risk in Relation to Type of Colitis

	No. of Patients	No. of Patients with Relapse	Total Follow-Up Time (Yr)	Relapse Incidence/1,000 Person Years	Relative Risk (95% Confidence Interval)
Definite UC	332	249	1,944	128	1.0*
Probable UC	110	23	1,204	19	0.3 (0.2–0.4)
Indeterminate colitis	80	66	442	149	1.9 (1.6–2.4)
All	522	338	3,589	94	

UC = ulcerative colitis.
* Reference group.

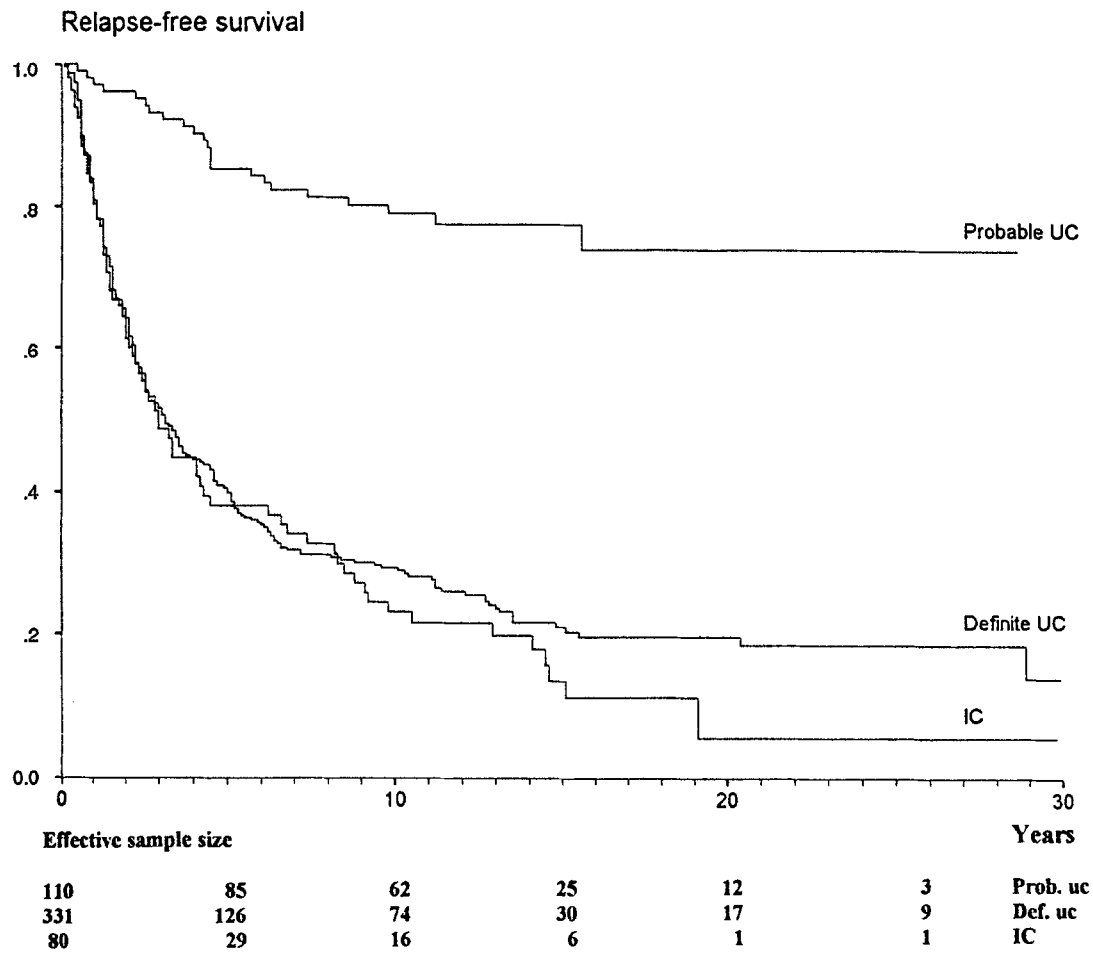

Figure 1. Relapse-free survival after diagnosis of colitis in patients with definite ulcerative colitis (UC), probable ulcerative colitis, and indeterminate colitis (IC).

with initial definite ulcerative colitis had relapse with more extended inflammation. Corresponding figures for patients with probable ulcerative colitis and indeterminate colitis were 57 and 96 percent, respectively.

DISCUSSION

In a previous study from the city of Malmö in southern Sweden, we found that during the time period between 1958 to 1982 there was a shift toward a greater proportion of patients with proctitis and a shorter time lag from debut of symptoms to diagnosis and treatment in patients with inflammatory bowel disease.[2]

The present study does not indicate that this shift in the morbidity pattern has had any influence on the course of the disease with regard to relapse rate. The unchanged relapse rate observed in our study is contrary to what was reported in the Organisation Mondiale de Gastro-Enterologie study in which patients diagnosed in the 1980s were found to have a more favorable prognosis than patients diagnosed 20 years earlier.[9] As we have had no standardized follow-up, with only 69 percent of patients with initial proctitis being followed with DCBE or colonoscopy, the relapse rate in our study may be underestimated; it is likely that at least some patients with benign symptoms abstain from seeking medical advice.

Ten years after diagnosis of colitis, seven of ten patients had at least one further episode of inflammation. This rate is similar but somewhat lower than reported from northeastern Scotland, Denmark, and from other areas in Sweden.[10-13] For more than one-half of patients in remission after an initial attack of proctitis, relapse is associated with more extended inflammation. The lower rate of progressive inflammation of about 30 percent, reported in other studies may depend on differences in definition of the population at risk.[10, 12, 14, 15] In our study, we have computed patients at risk as those with a relapse, whereas in other studies patients without relapse or patients

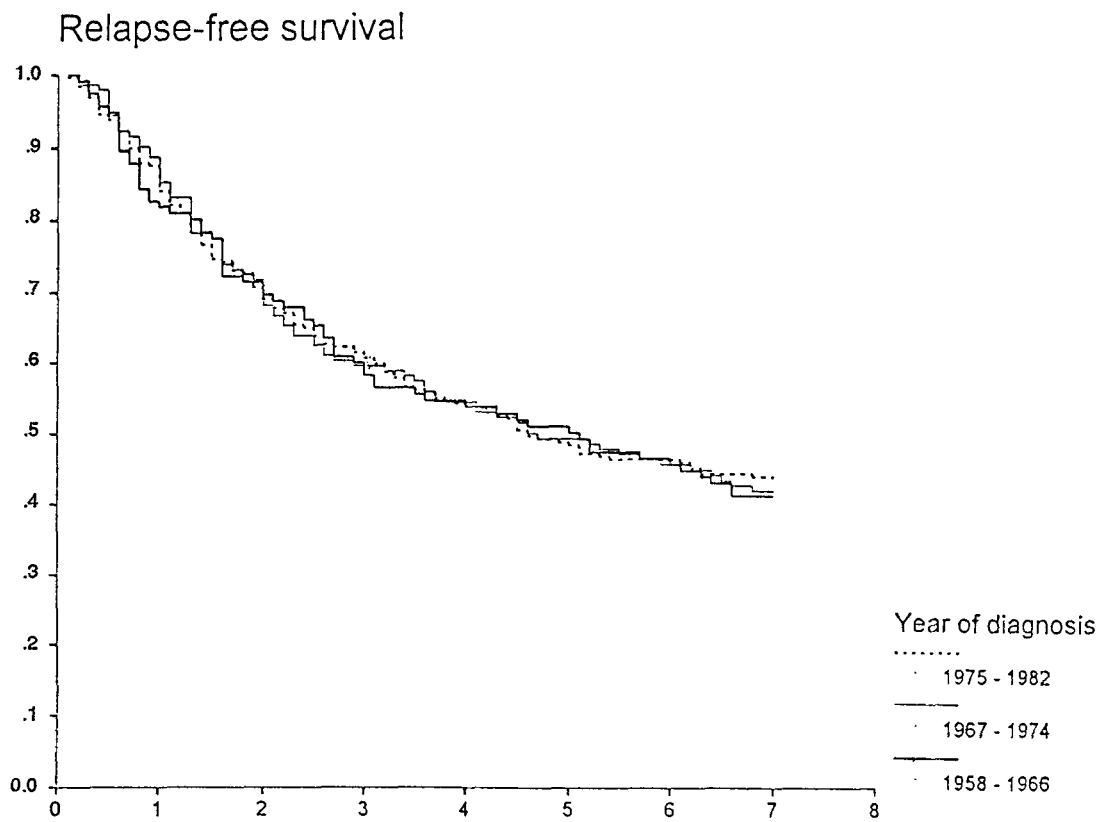

Figure 2. Relapse-free survival after diagnosis of colitis in relation to time periods of diagnosis.

not in remission might have been included in the denominator. Another contributing factor is the mode of follow-up. In the present study, only macroscopic extent of inflammation has been reported.

Patients with indeterminate colitis have a worse prognosis compared with those with definite ulcerative colitis, both with regard to risk of relapse and risk of progressive inflammation. This is in line with our previous observation of an increased colectomy rate and an increased incidence of colorectal cancer in patients with indeterminate colitis.[3, 4] The higher colectomy rate in patients with indeterminate colitis compared with that found in patients with definite ulcerative colitis was also seen in subgroups such as patients with total colitis at diagnosis, in patients in remission after the first attack, and in patients with a severe attack.[4]

Considering the high early relapse rate and the high prevalence of documented inflammatory lesions in asymptomatic patients, it seems appropriate to question if remission in fact means complete recovery. Our results concerning patients without relapse indicate that the misclassification may be as high as 50 percent. This figure is estimated from the fact that 41 patients of 72 in remission after the first attack without clinical relapse were found to have persistent signs of inflammation. For this reason, it is difficult to assess significance of factors that seem to be associated with relapse and progression of inflammation.

When patients with only one attack of colitis are included in studies of inflammatory bowel disease, it is important to discuss the possibility of self-limited colitis and infectious colitis. An indirect sign that the frequency of such patients is low in the present study is that the figure for persistent signs of inflammation is high, *i.e.*, 41 of 72 patients.

Treatment with sulfasalazine is known to reduce the relapse rate.[16, 17] Treatment recommendation during the study period has been to put patients with ulcerative colitis on lifelong treatment with sulfasalazine. However, because there has been no standardized rules for treatment or follow-up, it is likely that a certain number of patients with proctitis have been treated only with corticosteroid enemas and, that in a certain number of sulfasalazine-treated cases, treatment has been withdrawn because of cessation of symptoms. This may explain why the relapse risk was higher for patients with proctitis and left-sided colitis

Table 3.
Relapse-Free Survival in Relation to Sex, Age at Diagnosis of Colitis, Time from Onset of Symptoms to Diagnosis of Colitis, Extent of Disease at Diagnosis, and Severity of First Attack; Multivariate Risk Analysis of Each Factor in Relation to Type of Colitis

Risk Factor		No. of Patients	No. of Patients with Relapse (%)	Total Follow-Up Time (yr)	Incidence of Relapse/1,000 Person Years	Relative Risk (95% Confidence Interval)
Sex	Male	296	193 (65)	1,939	100	1.1 (0.9–1.3)*
	Female	225	145 (64)	1,650	88	1.0†
Age at diagnosis (yr)	0 –25	172	123 (72)	1,186	104	1.1 (0.9–1.3)*
	26–43	175	112 (64)	1,296	86	0.9 (0.8–1ÿ1)*
	44–	174	103 (59)	1,108	93	1.0*†
Time from onset to diagnosis (mo)	0–1	171	99 (58)	1,315	75	0.9 (0.8–1.1)*
	1–4	173	121 (70)	980	123	1.2 (1.0–1.4)*
	4–	177	118 (67)	1,294	91	1.0*†
Extent of disease at diagnosis	Proctitis	284	188 (66)	1,711	110	1.6 (1.2–2.2)*
	Left-sided	125	80 (64)	955	84	1.4 (1.1–2.0)*
	Total	112	70 (63)	923	76	1.0†
Severity of first attack	Severe	22	15 (68)	147	102	1.0 (0.8–1.2)*
	Moderate	218	138 (63)	1,505	92	1.0 (0.8–1.2)*
	Mild	248	162 (65)	1,699	95	1.0*†

* After adjustment for type of colitis.
† Reference group.

Table 4.
Progression of Extent of Inflammation in Patients with Ulcerative Colitis or Indeterminate Colitis in Remission and With at Least One Relapse

Extent of Inflammation at Diagnosis	No. of Patients	Maximum Extent of Inflammation During Follow-Up		
		Proctitis	Left-Sided Colitis	Total Colitis
Proctitis	188	91 (48)	55 (29)	42 (22)
Left-sided colitis	80	—	52 (65)	28 (35)
Total colitis	70	—	—	70
Total	338	91	107	140

Percents are within parentheses.

at diagnosis compared with those with total colitis. This may also explain why one-half of patients without relapse have persistent signs of inflammation and, perhaps also in part, the high relapse rate.

Considering the documented effect of sulfasalazine treatment, it is our view that there is a need for further follow-up studies of patients with inflammatory bowel disease to improve our understanding of factors that influence the effectiveness of pharmacologic treatment, *i.e.*, besides dosage and side-effects also patient compliance and physicians' adherence to recommended guidelines for treatment.

CONCLUSION

The present study does not indicate that shift in the morbidity pattern to less extensive disease at diagnosis and a shorter time lag from onset of symptoms to diagnosis and treatment has had any influence on course of the disease with regard to relapse rate. Patients with indeterminate colitis have a worse prognosis in these respects than patients with definite ulcerative colitis. Considering the documented efficacy of sulfasalazine treatment, this high relapse rate calls for studies of the effectiveness of such treatment in everyday practice.

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