



The pattern and outcome of acute severe colitis

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Abstract

Background: The prognosis of acute severe ulcerative colitis (ASC) influences therapeutic decisions, but data on prevalence or long-term outcome are few.

Methods: A systematic review of all patients with UC diagnosed in Oxford was performed to assess the prevalence of ASC defined by Truelove and Witts' (TW) criteria and determine whether outcome is related to disease activity on admission, likelihood of recurrence and long-term prognosis.

Results: 750 patients (median follow up 12.7 yr, range 0–648 mo) met inclusion criteria out of a total cohort of 1853 patients. 24.8% (186/750) had at least one admission for ASC (294 admissions in 186 patients). Overall, 12% (93/750) had a colectomy, compared to 39.8% (74/186) of patients with one or more episodes of ASC ($p < 0.0001$) and 3.4% (19/564) in those with no admission. The colectomy rate on first admission (37/186, 19.9%) was lower than on the second or subsequent admissions (OR 2.35, 95% CI 1.33–4.14, $p = 0.003$), being 29.0%, 36.6%, 38.2% after two, three, or subsequent episodes respectively. It was 8.5% (11/129) if patients had one TW criterion in addition to ≥ 6 bloody bowel motions/day, compared to 31% (29/94) if two additional criteria were present and 48% (34/71) if three or more additional criteria were present ($p = 1.4 \times 10^{-5}$; OR 4.35, 95% CI 2.20–8.56 one criterion vs two or more).

Conclusions: A quarter of all patients with ulcerative colitis experience at least one episode of ASC; 20% come to colectomy on first admission, but 40% after two admissions. The likelihood of colectomy is related to biological severity on admission.

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1. Introduction

Acute severe colitis (ASC) is potentially life-threatening. Furthermore, the colectomy rate has remained unchanged at 29% since 1974.¹ Yet the only data on the prevalence of ASC date back to 1963 when a study, also from Oxford, found an 18.8% chance of ASC as a presenting feature (47/250 cases) and a prevalence of 17.6% (109/619) for all cases of ulcerative colitis.² The likelihood of further admission and the long-term outcome with regard to colectomy remain unclear, although these are important measures of the burden of disease in patients most severely affected by ulcerative colitis.

The diagnosis of ASC is defined according to Truelove's original criteria as a bloody stool frequency ≥ 6 per day and at least one of the following: pulse >90 beats per minute, temperature >37.8 °C, haemoglobin <10.5 g/dL, or an ESR >30 mm/h.^{3–5} This is the definition used in Oxford since the 1950s. Nevertheless, it remains unclear whether the number of criteria in addition to a bloody stool frequency ≥ 6 /day on admission correlates with outcome.

Such data as there are indicate that the long term outcome after admission with ASC is not good, but data remain few. Long term follow up of a cohort of 49 patients admitted with 51 episodes of ASC in 1990–91 found that 32% complete responders came to colectomy compared to 77% incomplete responders (OR 7.2, 95% CI 1.4–36.2, $p=0.015$) over a 12 year period.⁶ It is remarkable that more than fifty years after the seminal paper that defined ASC, it remains unclear what might be the likelihood of a further episode of ASC, whether there are predictors other than pancolitis at diagnosis⁷ and whether subsequent episodes have a different prognosis. The aims of this study, therefore, were to define the prevalence of ASC for the first time since 1963, determine the outcome and likelihood of further attacks identify criteria on admission associated with a poor outcome (colectomy) and provide practical information to help clinicians advise patients when managing acute severe colitis.

2. Methods

2.1. Patients

A systematic, retrospective study of all patients with UC diagnosed in Oxford according to internationally agreed criteria³ from 1950–2007 was performed. Patients were selected from the records of all those with UC under follow up. Only those diagnosed and followed up in Oxford were included, to avoid tertiary-referral bias. Case and colectomy ascertainment were checked through colorectal surgical and pathology databases. Although 80% of those with UC under follow up at the John Radcliffe Hospital come from the local area, many were originally diagnosed elsewhere, with a minority being tertiary referrals. It was assumed that cases diagnosed within the Oxford area who moved away or were lost to follow up, would equally affect patients who did or did not need admission or colectomy, or disproportionately affect patients with mild disease and a good outcome. Although this assumption cannot be validated, it seems preferable to including all patients wherever diagnosed, for

whom records may be incomplete. To ensure data quality, all the case notes of both medical and surgical databases were reviewed by two of the authors (LD & AW).

2.2. Definitions

Acute severe colitis was defined as ≥ 6 bloody stools daily with evidence of systemic toxicity (fever, tachycardia, anaemia, or an elevated ESR, Table 1). The CRP is now more commonly used than ESR as a marker of inflammation, but no admission was based on the ESR or CRP criterion alone. However, where ESR data were lacking ($n=11$) a decision was made to include a CRP >30 mg/L as a surrogate for the criterion of an ESR >30 mm/h, in keeping with the arbitrary choice of the original criteria. The macroscopic extent of disease at diagnosis was defined by colonoscopy or barium enema. Extent of disease was defined according to the Montréal criteria⁸ as proctitis (confined to the rectum), left-sided (up to the splenic flexure), or extensive disease (proximal to the splenic flexure). For those with ASC, a first attack at presentation was defined as admission within a month of diagnosis.

2.3. Demographic and clinical characteristics

Demographic data included date of birth, gender, smoking habit at diagnosis (current, ex-, or never, but not quantified) and family history of UC or CD. Clinical characteristics included age at diagnosis, disease extent at diagnosis and maximal extent recorded during follow up, extra-intestinal manifestations (EIM) and previous appendectomy. Data on ASC included date of admission, number of Truelove and Witts' (TW) criteria in addition to a bloody stool frequency ≥ 6 /day on admission, medical treatment during admission (intravenous steroids, ciclosporin, infliximab) and ultimate outcome (medical management or colectomy).

2.4. Statistical analysis

All results are expressed as median and range, or proportions, since the data were not normally distributed. Statistical package SPSS version 16 was used for analysis. Data were classified as categorical, ordinal, or continuous as appropriate. Categorical and ordinal variables were compared using Chi-square and continuous, non-parametric data by Fisher's exact tests, together with an odds ratio (OR) and 95% confidence interval (95%CI) as appropriate. Odds ratios and 95% confidence intervals are derived from the exponential regression coefficient, including multiple regression analysis. Multivariate analysis was performed by binary

Table 1 Diagnostic criteria for acute severe ulcerative colitis.³

| Criterion | Severe |
|------------------------|------------------|
| Bloody stool frequency | ≥ 6 and |
| Pulse rate | >90 bpm, or |
| Temperature | >37.8 °C, or |
| Haemoglobin | <10.5 g/dl, or |
| ESR | >30 mm/h |

Table 2 Demographic and clinical characteristics of 750 patients with UC.

| Demographic data | ASC cohort (A) <i>n</i> =186 | Non-ASC cohort (N) <i>n</i> =564 | Total cohort (T) <i>n</i> =750 | <i>p</i> value (A vs N) |
|--|---------------------------------|-------------------------------------|-----------------------------------|-------------------------|
| No. of patients (<i>n</i> , %) | 186/750 (24.8) | 564/750 (75.2) | 750 ^a | |
| Female/male (%) | 46:54 | 52:48 | 50:50 | ns |
| Median age (range) at diagnosis, years | 35.8 (1–83) | 38.7 (1–86) | 38.7 (1–86) | ns |
| Median follow-up (range), months | 129 (0–648) | 129 (0–648) | 129 (0–648) | ns |
| Smoking (%) | | | | |
| Current smoker | 8.1 | 7.8 | 7.9 | ns |
| Ex smoker | 32.3 | 29.6 | 30.3 | ns |
| Never smoked | 57.5 | 59.8 | 59.2 | ns |
| Unknown | 2.2 | 2.8 | 2.7 | ns |
| Appendicectomy (<i>n</i> , %) | | | | |
| Yes | 6/186 (3) | 10/564 (2) | 16/750 (2) | ns |
| Family history of IBD (<i>n</i> , %) | | | | |
| Yes | 35/186 (19) | 86/564 (15) | 121/750 (16) | ns |
| Out of these FH of CD | 10/35 (29) | 19/86 (22) | 29/121 (24) | ns |
| Out of these FH of UC | 25/35 (71) | 67/86 (78) | 92/121 (76) | ns |

^a 750 Oxford-diagnosed patients out of a total 1853 patients with UC followed up in Oxford, but not necessarily diagnosed in Oxford. There were no significant differences in characteristics.

logistic regression using SPSS v10.0. The independent variables of sex, age at diagnosis, smoking status, family history, extent of disease, number of T&W criteria and number of extra intestinal manifestations were based on prior knowledge of factors potentially associated with colectomy. Extent of disease was coded as an ordinal variable (extensive>left-sided>proctitis). Statistical significance was corrected for multiple comparisons (Bonferroni).

3. Results

3.1. Demographic data

750 patients with UC diagnosed in Oxford between 1950–2007, with a median follow up 129 mo (range 0–648 mo), were evaluated out of a total cohort of 1853 patients with UC. Of these, 24.8% (186/750) were admitted at least once with ASC. There were 294 admissions in 186 patients. Patients with ASC were slightly younger (36 vs 39 yr) at diagnosis compared to the whole cohort ($p=0.049$, Table 2). There was no significant difference between ASC patients who were current ($n=15$), ex-smokers ($n=60$), or never smokers ($n=107$) and there was no correlation between

Table 3 Treatment during admission.

| Medication during admission for ASC | Admission 1 | Admission 2 | Admission ≥ 3 |
|-------------------------------------|------------------|----------------|--------------------|
| Steroids alone | 157/186 (84%) | 52/67 (78%) | 31/42 (74%) |
| Steroids and then CsA | 27/186 (15%) | 11/67 (16%) | 3/42 (7%) |
| Steroids and then IFX | 2/186 (1%) | 4/67 (6%) | 9/42 (19%) |

CsA: ciclosporin 2–4 mg/kg intravenously¹²; IFX: infliximab 5 mg/kg¹³.

smoking ($p=0.126$) and colectomy, although numbers are small (Table 2). Treatment of ASC was initially with intravenous steroids (Table 3). Rescue therapy with ciclosporin (CsA) or infliximab (IFX) was given to 56 patients admitted with ASC (see 'effect of different decades', below). Azathioprine, mercaptopurine or methotrexate were given at some time to 120/186 (65%) with ASC and 158/564 (28%) in the non-ASC cohort, but this includes treatment before or after admission, as well as intermittent therapy.

3.2. Pattern of ASC

Out of 186 patients admitted with ASC for intensive treatment, the first attack occurred at presentation in 34%, within 1 year of diagnosis in 24% (cumulative total 54%), and 18% within 1–5 years of diagnosis; 28% presented for the first time more than 5 years after diagnosis (Fig. 1). 119/186 (64%) were admitted once, 25/186 (13%) admitted twice and 30/186 (16%) three times, whereas only 12/186 (6.6%) had four or more

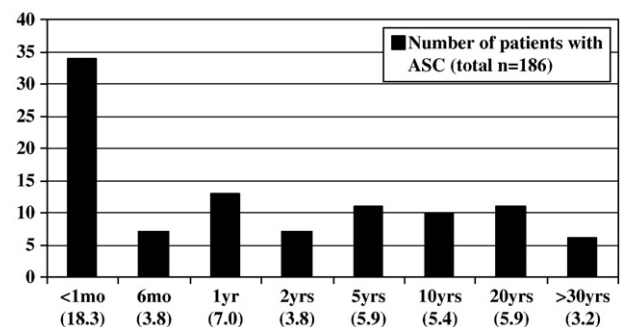


Figure 1 Time to first admission, Legend: The time to first admission in 186 patients admitted with acute severe colitis (y axis: total number; x axis: time from diagnosis and %).

Table 4 Interval to admission.

| Time (years) | Diagnosis to first admission | First to second admission | Second to third admission | Third to subsequent admissions |
|--------------|------------------------------|---------------------------|---------------------------|--------------------------------|
| < 1 year | 101/186 (54%) | 34/67 (51%) | 21/29 (73%) | 7/13 (54%) |
| 1–3 years | 12/186 (7%) | 11/67 (16%) | 5/29 (17%) | 3/13 (23%) |
| > 3 years | 73/186 (39%) | 22/67 (33%) | 3/29 (10%) | 3/13 (23%) |

admissions. The chance of a second or further admission was 36% (67/186). **Table 4** shows the interval to the first, second and subsequent admissions. Of those who had two or more admissions, 25% (17/67) had their initial admission at presentation and 16% (11/67) within 1 year, so 41% of patients appear to have had refractory UC in the year of diagnosis, based on an arbitrary criterion of refractoriness as two or more admissions in this context. It means that 59% subsequently developed refractory UC, with 25% (17/67) having their initial admission within 1–5 years and 30% (20/67) >5 years after diagnosis. The number of admissions influenced outcome.

3.3. Outcome

The colectomy rate in those admitted at least once with ASC was 39.8% (74/186), compared to 12.4% (93/750) in all patients with UC diagnosed in Oxford (OR 11.81, 95% CI 6.95–20.08 $p < 0.0001$). The mortality of patients admitted with ASC was 0%. For those 564 patients who never had an admission for ASC, just 19/564 (3.4%) came to colectomy. The principal reason for colectomy in the total cohort was acute severe disease in 66/93 (71%), persistently active disease in 20/93 (21.5%) and dysplasia or malignancy in 7/93 (7.5%). In the ASC cohort, 66/74 (89%) of colectomies were due to acute severe disease and the remainder due to persistently active disease in patients who had initially fulfilled the TW criteria on admission. There was one case of colonic perforation, from colonoscopy. Among the 564 patients who avoided admission for ASC, 19 came to colectomy and the indications were medically refractory symptoms in 63% (12/19), cancer or dysplasia in 37% (7/19). Multivariate analysis showed that six independent variables were associated with colectomy in patients admitted with ASC, principally disease severity (number of TW criteria on admission, OR 2.99, 95% CI 1.69–5.30), maximal extent of disease (OR 3.01, 95% CI 1.30–6.96) and the presence of an extraintestinal manifestation of UC (OR 11.59, 95% CI 4.73–28.41), but also marginal effects of gender (OR 0.36, 95% CI

0.01–0.99), age at diagnosis (OR 0.89, 95% CI 0.83–0.95) and age on admission (OR 1.08, 95% CI 1.10–1.11).

3.4. Disease severity on admission and colectomy

Disease severity on admission was associated with outcome (**Table 5**). Of all admissions for ASC (294 admissions in 186 patients) the colectomy rate was 8.5% (11/129) if patients had one additional TW criterion in addition to ≥ 6 bloody bowel motions per day, compared to 31% (29/94) if two additional TW criteria were present, 48% (29/60) if three additional and 45% (5/11) if four additional TW criteria were present. 61/165 patients who had ≥ 2 additional criteria came to colectomy, compared to 11/129 of those with one additional criterion ($p = 1.4 \times 10^{-5}$; OR 4.35, 95% CI 2.20–8.56). A p value < 0.0125 is significant, corrected for multiple comparisons). Nevertheless, 50% of patients with ASC and two additional TW criteria on admission and 19% of those with four additional TW criteria on admission escaped colectomy. It is not possible to say whether some criteria were more closely associated with colectomy than others, because numbers were small and there are 6 potential combinations of 2 of 4 criteria. A patient on a second or subsequent admission with at least two additional TW criteria was 4.8 times more likely to have a colectomy than a person on their first admission with one additional TW criterion.

3.5. Extent of disease and outcome

Patients with ASC had more extensive disease than the non-ASC cohort (**Table 6**). Of those who came to colectomy, 29/74 (39%) had extensive disease 35/74 (47%) had left-sided and 10/74 (14%) had proctitis at diagnosis. In those UC patients who never had an admission for ASC, 19/564 had a colectomy, of whom 14/19 (74%) had extensive disease 4/19 (21%) had left sided and 1/19 (5%) had proctitis at diagnosis. The maximal extent of disease was associated with

Table 5 Number of TW criteria for each admission.

| Admission | Bloody stool ≥ 6 /day | 1 additional criterion | 2 additional criteria | 3 additional criteria | 4 additional criteria |
|---------------------|----------------------------|------------------------|-----------------------|-----------------------|-----------------------|
| First | 186/186 (100%) | 81/186 (43%) | 59/186 (32%) | 39/186 (21%) | 7/186 (4%) |
| Second | 67/67 (100%) | 33/67 (49%) | 21/67 (31%) | 11/67 (17%) | 2/67 (3%) |
| Third or subsequent | 42/42 (100%) | 16/42 (38%) | 14/42 (33%) | 10/42 (24%) | 2/42 (5%) |

Table 6 Extent of ulcerative colitis.

| Extent of UC ^a | ASC cohort (A) n=186 | Non-ASC cohort (N) n=564 | p value |
|--|-------------------------|-----------------------------|---------|
| Extent of UC at diagnosis (n, %) | | | |
| E1 (Proctitis) | 40/186 (21) | 263/564 (47) | <0.0001 |
| E2 (Distal or left-sided) | 91/186 (49) | 238/564 (42) | ns |
| E3 (Extensive) | 55/186 (30) | 63/564 (11) | <0.0001 |
| Maximal extent of disease (n, %) | | | |
| E2 to E3 (Distal that became extensive) | 44/91 (48) | 44/238 (18) | <0.0001 |
| E1 to E2 (Proctitis that became distal) | 14/40 (35) | 16/263 (6) | ns |
| E1 to E3 (Proctitis that became extensive) | 13/40 (33) | 9/263 (3) | <0.0001 |

^a According to the Montréal classification.^b When corrected for multiple comparisons, a p value <0.008 can be considered significant.

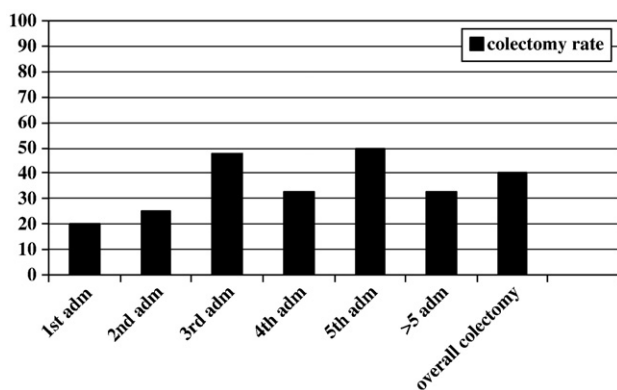
colectomy, with more extensive disease being associated with a greater risk of colectomy ($p=0.002$), but when advising patients it is the extent at diagnosis that is often more helpful. The risk of admission for ASC in all those with proctitis, left-sided, or extensive disease at diagnosis was 13% (40/303), 28% (91/329) and 47% (55/118) respectively. The overall risk of colectomy in relation to the extent of disease at diagnosis was 4% (11/303), 12% (39/329) and 36% (43/118) respectively.

3.6. Number of admissions and colectomy

The risk of colectomy during the first admission for ASC was 20% (37/186), but because most patients only had a single admission, then half of all the colectomies occurred on the first admission (37/74, OR 2.35 for colectomy on first admission out of all colectomies, 95%CI 1.33–4.14, $p=0.003$). Nevertheless, for individual patients, the risk of colectomy was lower on the first admission for ASC, because the cumulative risk increased with the number of admissions. There was a 50% risk of colectomy in the future if the patient escaped colectomy on the first admission (Fig. 2).

3.7. Effect of other factors on colectomy

The risk of colectomy was marginally lower for female patients with ASC (OR 0.37, 95%CI 0.013–0.99, $p=0.05$). The age of the patient at admission and the age at diagnosis both influenced the likelihood of colectomy, but while increasing age at admission increased the risk of colectomy (OR 1.09,

**Figure 2** Colectomy rate for each admission.

95%CI 1.01–1.16, $p=0.011$), increasing age at diagnosis marginally reduced it (OR 0.89, 95%CI 0.83–0.96, $p=0.001$). 31% of ASC patients had extraintestinal manifestations (EIMs); 10% had type 2 peripheral arthropathy, 3% primary sclerosing cholangitis and 2% sacroiliitis, but when all UC patients were compared with all ASC patients, there was no significant difference in the number with EIMs ($p=0.268$). Each extraintestinal manifestation, including erythema nodosum, increased the likelihood of colectomy by approximately 12% ($p<0.0001$, OR 1.6, 95%CI 4.8–28.4). Appendectomy was excluded from the analysis of colectomy risk because by chance it closely correlated with EIMs due to small numbers, not association.

3.8. Timing of admission and colectomy

The median time to first admission was 3.9 yr (0–35 yr) and median interval from diagnosis to colectomy 6.7 yr (0–20 yr). The colectomy rate was 36% (23/64) in those patients admitted at, or within 1 month of diagnosis, 30% (11/37) in those admitted within a year of diagnosis and 47% (40/85) in those admitted more than a year after diagnosis. The risk of colectomy was no higher for those admitted with ASC at diagnosis than at other times ($p=0.19$).

3.9. Effect of different decades

Out of the 294 admissions in 186 patients under follow up since diagnosis, there were 16 admissions in 14 patients in 1975–84, 96 admissions in 62 patients 1985–94, 134 admissions in 83 patients 1995–04 and 48 admissions in 27 patients since 2005. The colectomy rates per patient admitted per decade were 21%, 47%, 45% and 19% respectively. There was no significant trend either for colectomy ($p=0.53$) or admission rate ($p=0.78$) over the three decades. 9/62 (15%) admissions received CsA between 1985–1994 and 44/110 (40%) received CsA or IFX after 1995, but numbers are too small to interpret. Out of the whole cohort, 139/186 were only ever treated with steroids, of whom 61/139 (44%) had a colectomy. Another 38/186 also had CsA on one or more occasions, of whom 21/38 (55%) ultimately had a colectomy. Just 7/186 received IFX on one or more occasions, of whom 3/7 (43%) had a colectomy. 2 patients had both CsA and IFX on separate occasions and both later came to colectomy. No statistics were performed on these subgroups, because the

numbers are small and the decision to proceed to colectomy depended on many factors other than therapy.

4. Discussion

An episode of ASC is a marker for colectomy. This is illustrated by a colectomy rate in those admitted one or more times with ASC of almost 40% (74/186), compared to just 3% (19/564) in those who never had an admission for ASC (OR 11.81, 95%CI 6.95–20.08, $p < 0.0001$). The overall colectomy rate was 12% (93/750) in this Oxford-diagnosed UC cohort, which is similar to 10.4% reported in the most recent epidemiological study from Northern Europe⁹, but less than that reported from Olmsted County Minnesota, where a cumulative colectomy rate of 27% has been reported.¹⁷ This information matters to patients and their physicians. It is consistent with recent observations from Milwaukee, where a colectomy rate of 4% was reported in patients who had never been admitted for UC, compared to 11% overall and a surprisingly high 42% cumulative admission rate in 246 patients.¹⁰ Differences from our study are that the Milwaukee cohort included tertiary referrals and did not have the defined criteria for admission that have long been used in Oxford. The principal reason for colectomy in our patients was acute severe colitis in 66/93 (71%) and dysplasia or malignancy in only 7/93 (8%). This shows that any episode of ASC is a marker of treatment refractoriness and the driving factor for colectomy, not dysplasia or any other indication. Although our cohorts are not directly comparable, it is notable that the incidence of neoplasia in our group was similar to that reported from St Mark's Hospital, where a cumulative incidence of cancer of 7.6% at 30 years was found.¹¹

The severity of disease on admission was related to the outcome. This is intuitive, but it is the first time that this has been clearly demonstrated. Of all admissions for ASC the colectomy rate was 9% (11/129) if patients had one additional TW criterion in addition to ≥ 6 bloody bowel motions per day, compared to 31% (29/94) if two additional TW criteria were present and 48% (34/71) if three or more additional TW criteria were present. Put simply, the risk of colectomy is three-fold higher when there are two or more additional TW criteria on admission than when there is only one criterion. The factors associated with colectomy other than admission with ASC and biological severity on admission, included disease extent, the presence of extraintestinal manifestations and a marginal effect of gender or age of admission. Colectomy was more common in those with extensive disease either at diagnosis or follow-up, as might be anticipated.

Admission and colectomy rates increased for each decade of duration of disease. What was unexpected was that there was no striking change in admission or colectomy rates over time, despite the introduction of CsA in 1984 and IFX ten years later. The data should not be over-interpreted, because numbers are small even in this large cohort. There was, however, a substantial increase (from 15% to 40%) in those receiving 'rescue therapy' after failure to respond to intravenous steroids. It is at least consistent with the clinical impression that rescue therapy defers rather than prevents colectomy.^{12–14} On the other hand, the long term colectomy rate after IFX as rescue therapy for ASC has been reported to

be comparable to that in patients who initially respond to steroids (18% vs 11% respectively; OR 1.9, 95%CI 0.26–14.5).¹⁵ The timing of colectomy for those admitted with UC is important, since a 13% mortality has been reported in the 3 years after admission for UC, compared to 4% in the 3 yr after elective colectomy for UC in England.¹⁶ These latter data are consistent with a US study of over 7000 patients who had a colectomy for UC.¹⁷ This showed that in-hospital mortality was increased five-fold in patients admitted as an emergency (adjusted OR 5.40; 95%CI 3.48–8.40) and doubled for patients whose surgery was performed 6 days after their admission (OR 2.12; 95%CI 1.13–3.97). Whether avoidance of colectomy is the ultimate marker of success in treating UC has been questioned¹⁸: the aphorism about saving lives rather than colons remains true today.

The chance of a second or further admission with ASC was 36%. This is useful clinical information. Patients can be advised on their first admission with ASC that a third will have a further attack. It is also helpful to know whether people have refractory UC from the outset, or whether some acquire refractory UC for reasons unknown. Only 41% of those who had two or more admissions had their initial admission within a year of diagnosis and the median time to first admission was 3.9 yr. It is not possible to infer whether this reflects genetic or environmental factors.

Clinically relevant messages include a 20% risk of colectomy during the first admission for ASC, but 50% if the patient escapes colectomy on the first admission and has to be re-admitted. On the other hand, the colectomy rate among patients who have any admission for ASC is 40%, compared to 12% for all patients and just 3% for those with no admission with ASC. These are data that both the patient and physician can understand, which should inform practice. When it is considered that half of all presentations with ASC occur within the first year and only 30% after 5 years, it encourages early introduction of immunomodulators.

Do these data have any messages for the diagnostic definition of ASC? The outcome that matters to patients (apart from survival) is colectomy. We suggest that the threshold for diagnosis is best based on biological activity associated with $> 10\%$ risk of colectomy. This means a single criterion (tachycardia, temperature, anaemia, or raised inflammatory markers) in addition to a bloody stool frequency $\geq 6/\text{day}$. Others may set the bar higher (such as $> 25\%$ chance of colectomy, meaning that two or more criteria are needed for diagnosis) before patients are admitted for intensive therapy. Other markers of biological severity (including metabolic alkalosis and an ileus on plain abdominal radiography) have also been described.⁵ Either way, a distinction needs to be drawn between disease that is biologically severe, and disease that is treatment-refractory, which is often referred to as 'severe'. Our belief is that the term severe UC should be preserved for those with biologically severe disease. A further distinction is necessary for patients with severe UC who need rescue therapy after early failure to respond to intensive treatment.⁵

This is the largest cohort study on the natural history of ASC and the clinically relevant messages are clear. A quarter of all patients with UC experience at least one episode of ASC. A third have a second or subsequent episode and this doubles the likelihood of colectomy from 20% to 40%. In contrast, only a tiny minority (3%) of patients with UC who do not have an

admission for ASC, come to colectomy. The risk of colectomy is related to the biological severity on admission. When there are two or more TW criteria in addition to a bloody stool frequency ≥ 6 /day, the risk of colectomy is 31%, and three-fold higher than when there is only one additional criterion on admission. These simple data can inform discussion with patients admitted with ASC to help them better to understand their disease and potential outcome.

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