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Alimentary Tract

Short term colectomy rate and mortality for severe ulcerative colitis in the last 40 years. Has something changed?

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ABSTRACT

Background: About 20% of ulcerative colitis patients will experience a severe attack during the course of the disease. Intensive treatment, early surgery and, more recently, "rescue therapies" improved prognosis.
Aims: To evaluate in-hospital colectomy and mortality rates for severe ulcerative colitis over 40 years in two referral centres.
Methods: All in-patients with severe ulcerative colitis from 1976 to 2010 were considered. 159 patients were assigned to 4 cohorts: cohort 1 $n = 34$ (1976–1980); cohort 2 $n = 29$ (1986–1990); cohort 3 $n = 45$ (1996–2000); cohort 4 $n = 51$ (2006–2010).
Results: The colectomy rate was 64.7%, 62.0%, 44.4% and 9.8%, respectively, in the four cohorts ($p < 0.0001$). The mortality rate decreased from 8.8% in cohort 1, to 0 in cohort 4 ($p = 0.04$). Infliximab was used only in cohort 4 (17 patients).
Conclusions: A significant reduction of colectomy and mortality rates in severe ulcerative colitis was observed in the last 40 years. Better management of patients, reduced attitude to operate severe ulcerative colitis, as well as the use of Infliximab in the last cohort, all could have contributed to the improved outcome.

1. Introduction

Approximately 15–20% of ulcerative colitis (UC) patients will experience a severe attack during the course of the disease [1]. Severe UC is a potentially life-threatening condition, that must be promptly recognized and managed in hospital. Early recognition of negative prognostic factors, intensive medical therapy, and early surgery for non-responders all contributed to the improved outcome in the last decades [2] and mortality for UC is at present minimal [2]. In the pre-steroid era mortality was 22% in the first year after diagnosis [3], but decreased to 7% after the introduction of steroids [4]. In the seventies, the introduction of the so called "Oxford regimen", led to a further decrease of mortality to less than 2%, with a colectomy rate of approximately 30% [5–12]. Mortality is largely dependent upon severe acute complications, such as toxic megacolon (TMC), massive rectal bleeding, multiple organ dysfunction syndrome (MODS) or to surgical complications [13] and is particularly relevant in elderly patients with multiple comorbidities [14]. In non-referral centres, mortality after urgent colectomy is still a problem. Recent population-based nationwide studies carried out in United Kingdom, USA and Denmark, report a 30-day mortality rate after urgent colectomy of approximately 5% [13–16].

In spite of intensive intravenous glucocorticoid treatment, the short term colectomy rate remained stable over the last 30 years [17], as approximately 20–30% of patients fail to respond and require surgery. Moreover, one third of those patients, who escape early colectomy, will eventually require surgery, due to further severe attacks or relapsing disease [18].

Surgery is considered curative in UC, but the quality of life after restorative proctocolectomy is generally poorer than that of patients responding to medical therapy [19]. Thus, different rescue strategies were proposed to avoid surgery in non-responders, without affecting the mortality rate. In the nineties intravenous (iv) cyclosporine (CyA) has been proposed as "rescue therapy" for these patients [20]. This led to high short term remission rates, but colectomy was delayed more than prevented. Indeed approximately 50% of patients treated with CyA will eventually require colectomy [21]. Moreover, CyA is burdened by the risk of severe side-effects, including death. More recently, infliximab (IFX), a chimeric

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Table 1
Demographics, clinical characteristics and baseline laboratory data in the 4 cohorts of patients. Data have been expressed as median values and range.

	Cohort 1 1976–1980	Cohort 2 1986–1990	Cohort 3 1996–2000	Cohort 4 2006–2010	*p*
Age (years)	30 (14–64)	26 (17–53)	32 (17–68)	37.1 (18–82)	***0.0486***
Gender (F/M)	22/12	9/20	23/22	26/25	0.06
Disease extension (left sided/extensive)	13/21	7/22	18/27	16/35	0.49
Disease duration (mo)	31.5 (1–148)	12 (1–96)	30 (7–90)	36.1 (0–246)	0.157
Bowel movements	5 (1–20)	7 (3–20)	8 (1–16)	7 (5–12)	***0.01***
Hb (g/dl)	10.3 (7.1–14.5)	11 (5.3–15)	11 (6.8–15)	10.8 (6–14.2)	0.82
WBC $\times 10^3$ mL	9.8 (4.6–23.4)	9.2 (4.5–17.3)	9.5 (2.5–20)	10.7 (4.5–29)	0.3
ESR 1ªh	60 (10–121)	42 (5–96)	54 (8–130)	60 (8–120)	0.25
Albumin (g/dl)	2.4 (1.6–4.3)	2.8 (2.2–5)	3.1 (1.4–5.8)	2.7 (1.8–4)	0.18
Arterial pH	7.49 (7.41–7.61)	7.46 (7.41–7.64)	7.5 (7.4–7.7)	7.45 (7.4–7.52)	0.07

monoclonal antibody anti-tumour necrosis factor-α (TNF-α), has been used as "rescue therapy" in severe steroid-refractory UC. A single 5 mg/kg infusion of IFX reduced the colectomy rate by 40% within 3 months in a Scandinavian randomized placebo-controlled trial [18]. Although the benefits of the "rescue therapy" with IFX remain in the subsequent 3-year follow-up [22], few data are available about long-term benefits. Open label series with different length follow-up and different IFX doses report an overall colectomy rate ranging from 18% to 75% [23–28].

The aim of our study was to evaluate the early colectomy rate and in-hospital mortality for acute severe UC over the last 40 years in two referral centres, and to explore the impact of "rescue therapies" on surgery and mortality rates.

2. Materials and methods

Four phases, from 1976 to 2010, were considered representative of pivotal changes in the management of acute severe colitis, from the introduction of the "Oxford regimen", to the institution of "rescue therapies" with biologics.

The records of all the 159 patients admitted to the hospital for a severe attack of UC in two referral Gastrointestinal Units in Rome (Department of Internal Medicine and Medical Specialties of "Sapienza" University and "San Filippo Neri" Hospital) in four 5-year cohorts were reviewed. Patients were stratified, according to the calendar period of hospital admission: cohort 1 (1976–1980); cohort 2 (1986–1990); cohort 3 (1996–2000); cohort 4 (2006–2010). The diagnosis of UC was established according to standard criteria [29]. A severe attack was defined according to Truelove and Witts, modified by Chapman, as the passage of >6 bloody stools daily with at least one of the following criteria: temperature >37.8 °C, pulse rate >90/min, haemoglobin <10.5 g/dl or erythrocyte sedimentation rate (ESR) >30 mm/h [30].

Clinical and demographic characteristics of all patients were recorded upon admission, including age, gender, disease duration, disease extension and bowel movements. Laboratory data included haemoglobin (Hb), erythrocyte sedimentation rate (ESR), white blood cells, serum albumin and arterial pH. The occurrence of local or systemic complications at admission or during the hospital stay was also recorded: toxic megacolon, "impending megacolon", massive rectal bleeding and multiple organ dysfunction syndrome. Gastrointestinal gas distension was evaluated on plain abdominal X-rays. Toxic megacolon was defined as dilatation of the transverse colon exceeding 6 cm in diameter [31] and "impending megacolon" as an increased colonic gas content (<6 cm) and/or persistent gas distention of small bowel loops [32].

All patients in the four cohorts were treated according to a standard regimen: intravenous (iv) steroids (hydrocortisone 100 mg qid or 6-methylprednisolone 60 mg/day), rectal steroids, fluid-electrolytes and albumin replacement, when needed. Total parenteral nutrition and blood transfusions were used if appropriate, and antibiotics were administered according to clinical judgement. Colectomy was performed in patients who failed to respond to iv steroids and in patients who deteriorated or developed complications during the steroid treatment. Infliximab was used as "rescue therapy" for patients who failed to respond to iv steroids only in the cohort 4.

The co-primary end points were early colectomy rate, defined as surgery performed within two months from hospital admission, and in-hospital mortality.

2.1. Statistical analysis

Kruskal–Wallis test was used to compare median values between groups. Chi-square test was used when appropriate. A p value <0.05 was considered statistically significant. Stats Direct statistical tools (Copyright © 1990–2001) was used for all calculations.

3. Results

All the 159 patients admitted in the two Institutions for acute severe UC were enrolled and stratified in four cohorts, according to the calendar period of hospital admission: cohort 1 (1976–1980) $n = 34$; cohort 2 (1986–1990) $n = 29$; cohort 3 (1996–2000) $n = 45$; cohort 4 (2006–2010) $n = 51$. The clinical and demographic characteristics of patients are shown in Table 1.

The characteristics of patients were slightly different across the 4 cohorts: an older age at admission was observed in cohort 4, compared to other cohorts ($p = 0.048$) and a lower number of bowel movements in cohort 1 ($p = 0.01$) (Table 1). Overall, the disease was less severe in more recent cohorts, as suggested by a lower occurrence of local or systemic complications (toxic megacolon, massive rectal bleeding and multiple organ dysfunction syndrome), 38%, 24%, 17.7% and 15.6% in cohorts 1, 2, 3 and 4, respectively ($p < 0.0001$). Toxic megacolon occurred in 32%, 17.2%, 17.7%, 9.8% of patients in cohorts 1, 2, 3 and 4, respectively ($p = 0.0003$).

In cohort 4, 17 patients received infliximab as "rescue therapy". Infliximab was administered after a mean of 8.8 + 4.1 days, after iv steroid regimen. All infliximab treated patients achieved clinical response and none required colectomy during hospitalization.

The early colectomy rate was 64.7% (22/34), 62.0% (18/29), 44.4% (20/45) and 9.8% (5/51) in cohort 1, 2, 3 and 4, respectively ($p < 0.0001$) (Fig. 1), showing a significant reduction in early need for surgery in more recent years. However when considering the subgroup of patients with complicated disease at admission or who developed local or systemic complications during the hospital stay (36/159), the early colectomy rate was similar across the 4 cohorts: 84.6% (11/13), 71.4% (5/7), 87.5% (7/8) and 50% (4/8) in cohort 1, 2, 3 and 4 respectively ($p = 0.25$) (Fig. 2). Conversely, the early colectomy rate is significantly reduced across cohorts in the subgroup of patients with severe, but uncomplicated disease: 47.8% (11/21) in cohort 1 and 2.3% (1/43) in the cohort 4 ($p < 0.0001$) (Fig. 2).