Historical evolution of the management of severe ulcerative colitis

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1. Introduction

A patient with ulcerative colitis (UC) may present suddenly severe symptoms as bloody diarrhoea, fever, tachycardia and anaemia. Today such a patient risks to die only in rare and complicated cases, but no more than 60 years ago his mortality risk was expected to be up to 60%. This was the case of Miss Banks, the first patient described to have a "non infective dysentery" by Samuel Wilks of London, in 1859. The author defined this condition as a "simple ulcerative colitis" but it was not until the early 20th that UC became a well recognized clinical entity, due to the introduction of the electric sigmoidoscope and barium enema.

Miss Banks, like other patients with UC, died as the treatment at the early 20th century was empirical, anecdotal and inefficacious. Consequently, hemorrhage, peritonitis and sepsis were frequent complications of the disease and
ineluctable causes of death. Such outcome was the result of a medical treatment mainly consisting of in bed rest, high calory-protein, low residue diet, vitamin supplement and blood transfusion. Also topical treatment was tried to ameliorate prognosis, but rectal instillations of various substances such as hydrogen peroxide, silver nitrate, tannic acid, bis-muth didn’t modify the clinical course of the disease that was invariably dangerous and disabling.

The surgical approach to UC throughout the years has varied considerably with the operative procedure in the early 1900s being appendicostomy, caecostomy and ileostomy. These procedures were associated with many technical problems and complications and didn’t resolve patients’ problems. In the following years, the introduction of antibiotics and the modification in the ileostomy procedure by Brooke dramatically improved the results of the operation. Surgery became a curative procedure in the 1950s with the introduction of total proctocolectomy with end ileostomy. During these early years the reluctance to wear an uncomfortable bag led patients to be referred for surgery very late and in a severely debilitate state and prognosis was invariably poor. Therefore, until 1950 the mortality for UC continued to be high with reports of 75% in the Birmingham (UK) series in 1933 and 22% in the Oxford (UK) series in 1950.

The first drug really effective in the treatment of UC was sulphasalazine, introduced in the 1940s but the true revolution in the treatment of the severe disease was the advent of corticosteroids.

2. The cortisone period (1955–1990)

The cortisone period was characterized by the introduction of intravenous corticosteroids, the early surgery and the search for prognostic factors.

2.1. Intensive intravenous corticosteroid regimen

The introduction of steroid treatment dramatically improved the prognosis of patients with severe UC. In 1955, Truelove and Witts reported the results of the first controlled trial on the treatment of UC, in which, following steroids, the mortality of patients with severe UC, at the first attack, dropped to 7%, compared with 24% in the placebo group, although patients presenting with very severe attacks of UC were not included in this study. They also observed a significant improvement in the remission rate in the cortisone-treated group compared to the control group (42% vs 13%). In 1974, Truelove and Jewell reported the results of their uncontrolled experience in 49 patients submitted to a 5-day intensive regimen based on corticosteroids.

If no definite improvement was observed after 5 days of intensive treatment surgery was recommended (early surgery).

The Oxford method was found to be very useful not only because it was able to induce rapid remission, in many patients, but also because its failure proved to be a strong indication for urgent surgery.

2.2. Early surgery

Early surgery was an innovation of the cortisone period. To assess the validity of early surgery, Goligher from Leeds, in 1967, compared the outcome of a severe attack of UC in two consecutive groups of patients. In the first (observed between 1952 and 1963), the patients were treated with corticosteroids and late surgery, in the second (observed between 1964 and 1966) with corticosteroids and early surgery. The overall mortality rate in the two groups dropped from 11.3% to 1.3%. Surgery consisted of ileostomy with proctocolectomy or subtotal colectomy. These findings clearly suggested that early surgery might present considerable advantages in those patients presenting a severe attack of UC failing to respond rapidly to intensive medical treatment. The clear-cut reduction in mortality rate following the policy of an intensive corticosteroid regimen, associated with early surgery, was confirmed by several other European studies.

The surgical procedures performed during that period were proctocolectomy and ileostomy, subtotal colectomy and ileo-rectal anastomosis and, after 1980, proctocolectomy and ileo-anal pouch anastomosis.

Proctocolectomy combined with ileostomy (Brooke ileostomy, in particular), represented the standard operation for UC for many years. The advantages of this procedure were that it was simple to perform and removes all the diseased intestine. The disadvantages were stoma, and ensuing urinary or sexual dysfunction.

Subtotal colectomy with ileo-rectal anastomosis was rarely performed, primarily because a large area of diseased mucosa is left in situ. It was considered as an option in those patients refusing ileostomy and in whom the disease involved a minimal area of the rectum. Surveillance of the residual stump of the rectum was mandatory to monitor the risk of cancer.

After 1980, proctocolectomy, with ileo-anal pouch anastomosis, became the operation of choice for most patients with UC. The operation is attractive since it avoids a permanent ileostomy, cures the patient of the disease whilst preserving ano-rectal function.

The most commonly observed short-term complications are: small bowel obstruction, anastomotic stricture, pouch leak and pelvic abscess. Long-term complications include small bowel obstruction, pouch fistulae and pouchitis.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Prognostic factors in severe UC</th>
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<tr>
<td>Clinical-laboratory</td>
<td>Jalan, 1969</td>
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<tr>
<td>Altered consciousness</td>
<td>Pulse &gt; 120/min</td>
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<tr>
<td>Fever &gt; 38 °C</td>
<td>Intestinal sound &lt; 5/min</td>
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<tr>
<td>Albumin &lt; 3 g/100 ml</td>
<td>Lennard-Jones, 1975</td>
</tr>
<tr>
<td>Ca++ &lt; 4.0 mEq/l</td>
<td>Cl− &lt; 95</td>
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<tr>
<td>K+ &lt; 2.5</td>
<td>HCO3− &gt; 32</td>
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<tr>
<td>pH &gt; 7.50</td>
<td>CRP &gt; 45 mg/l</td>
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<td>Caprilli, 1976</td>
<td>Travis, 1996</td>
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2.3. Search for prognostic factors

The key prognostic factors most commonly used to predict the outcome of severe UC can be classified as clinical, laboratory, radiologic and endoscopic features. A C-reactive protein (CRP) concentration $>45$ mg/l on the third day of intensive medical treatment, in patients continuing to present diarrhoea (>3 bowel movements per day), was found to be associated with an 85% risk of colectomy. Evaluation of the full blood count, CRP concentration, serum electrolytes, acid–base balance, as well as serum albumin concentration should be performed every 24–48 h. Daily monitoring of stool frequency, consistency, amount of blood, pulse rate and temperature is also mandatory.

2.4. Clinical and laboratory features

In the very early studies, impaired consciousness and lethargy, related to toxicity, were considered to be signs of extremely severe disease (Table 1). Since treatment has meanwhile improved, these symptoms are now rarely found but, when present, are usually representative of an extremely severe condition, indicating the ongoing development of the so-called multiple organ dysfunction syndrome (MODs). In these patients mortality continues to be very high.

Tachycardia, high fever, reduced number of intestinal sounds, and hypoalbuminaemia were reported by Lennard-Jones to be factors indicative of poor prognosis. Patients with severe UC often present metabolic alkaloisis. It has been shown that arterial blood pH rises progressively with increased severity of UC and as the lesions become more widespread. High blood pH and high bicarbonate concentration, together with low serum potassium chloride and calcium levels, have been associated with fatal outcome in toxic megacolon complicating UC. A C-reactive protein (CRP) concentration $>45$ mg/l on the third day of intensive medical treatment, in patients continuing to present diarrhoea (>3 bowel movements per day), was found to be associated with an 85% risk of colectomy. Evaluation of the full blood count, CRP concentration, serum electrolytes, acid–base balance, as well as serum albumin concentration should be performed every 24–48 h. Daily monitoring of stool frequency, consistency, amount of blood, pulse rate and temperature is also mandatory.

2.5. Radiologic features

In patients with an acute attack of severe UC, daily abdominal X-rays, taken in the supine and erect position, provide very useful diagnostic features (Table 2). Increased small bowel gas, and occasional distension of the stomach, is a frequent finding on plain abdominal X-ray film, being present in approximately 50% of patients with severe colitis. The finding of persistent small bowel distension on plain abdominal X-ray film characterizes a subgroup of patients at high risk for the development of toxic megacolon, and indicates that they have a condition that we have called “impending megacolon” (Fig. 1). The early detection of impending megacolon is very important, in clinical practice, as it has been shown in a prospective study on patients with severe UC in which, mortality due to toxic megacolon was zero when megacolon was preceded by intestinal distension and intensive therapy was promptly started.

### Table 2  Plain abdominal X-ray

<table>
<thead>
<tr>
<th>Feature</th>
<th>Source</th>
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</thead>
<tbody>
<tr>
<td>Small bowel distension (“Impending megacolon”)</td>
<td>Caprilli, 1976</td>
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<tr>
<td>Mucosal islands</td>
<td>Caprilli, 1976</td>
</tr>
<tr>
<td>Colonic dilatation</td>
<td>Lennard-Jones, 1975</td>
</tr>
<tr>
<td>Colonic deep ulcerations</td>
<td>Lennard-Jones, 1975</td>
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![Figure 1](image1.png)  Impending megacolon evolving to toxic megacolon. Plain abdominal film of the abdomen in supine position in a patient with severe UC. On the left, gaseous distension of the small bowel (impending megacolon), with initial segmental distension of the transverse colon. On the right, two days later diffuse dilatation of the colon and the small bowel (overt toxic megacolon).
The pathogenesis of distension of the stomach and of the small bowel in patients with severe UC still remains to be fully elucidated. Pathophysiologic and experimental data suggest that distension results from the activation of extrinsic intestinal inhibitory reflexes, which induce paralytic ileus.27

Toxic megacolon is defined as total or segmental non-obstructive hypotonic dilatation of the colon, classically exceeding 5.5 cm in diameter, in the transverse colon, on plain abdominal X-ray film,28 with or without signs of systemic toxicity. Again, pathogenesis of toxic megacolon also remains to be fully elucidated. The most convincing explanation for colonic dilation appears to be the excessive local production of soluble inflammatory mediators with inhibitory effects on colonic muscle tone. Nitric oxide, which is considered to be the most important non adrenergic, noncholinergic neurotransmitter in the gut, might play a key role.29–31

Abdominal X-ray can also be used to detect deep colonic ulcerations (Fig. 2) and abnormalities of the colonic mucosa.32

2.6. Endoscopic features

Endoscopy is effective in revealing severe mucosal lesions which usually extend from the rectum to the caecum. Severe disease is characterized by ulcers and spontaneous bleeding.33

Deep colonic ulcerations, detected at endoscopy, are well correlated with the depth of ulcerations found in colectomy specimens, features predictive of complications, and associated with a higher rate of colectomy.22,32,33 Although sigmoidoscopy without air insufflations, is safe in experienced hands, several authors question the safety and usefulness of this examination in acute severe colitis.33 Total colonoscopy, such as double contrast enema, should be avoided due to the risk of complications (toxic megacolon, perforation and massive bleeding).

Rectal biopsy is important to confirm the diagnosis of UC and to exclude infective colitis.

In conclusion, the policy adopted in the cortisone period consisting of intensive intravenous corticosteroid regimen in association with early surgery and early detection of risk factors has proved to be successful in reverting the course of the disease towards fulminating colitis and in reducing the overall mortality to almost zero.

However, about 30–40% of patients with severe UC continue to need colectomy after failure of corticosteroid therapy, both in adults and children.34,35


Once reduced the mortality for severe UC near to zero, over the past 15 years, many attempts have been made to avoid surgery since colectomy has not only a negative effect on quality of life, but also a high peri-operative morbidity and mortality36 and, moreover, involves high costs.37 Treatment attempted to avoid surgery after failure of intravenous steroids is commonly defined as "rescue therapy". Two main "rescue therapy" strategies have so far been extensively studied (Cyclosporine and Infliximab) but others (Visilizumab, Tacrolimus, Leukocytapheresis) are also under investigation.

3.1. Cyclosporine

The use of intravenous (i.v.) Cyclosporine (CyC) in the management of severe UC resulted from a North American placebo-controlled randomised trial, published in 1994, that reported the efficacy of 4 mg/Kg of CyC i.v. administered to patients not responding to intravenous glucocorticosteroids.38 After some years a European double-blind controlled trial showed that CyC alone is at least as effective as corticosteroids in the treatment of patients with severe UC.39 The same group also performed a randomised, double-blind study comparing 4 mg/kg day with 2 mg/kg day i.v. CyC. The study showed that high-dose CyC has no additional clinical benefit over low-dose CyC in the treatment of severe attacks of UC. Although differences in adverse events were not observed in the short term, it was concluded that as most CyC-associated adverse events are dose dependent, the use of 2 mg/kg should improve the long-term toxicity profile of the agent.40

A frequency > 8 stools per day or CRP > 45 mg/l at day 3 has been demonstrated to predict the need for colectomy.22 If remission is achieved with CyC i.v., oral CyC is continued for 3–6 months.

The long-term outcome in a large series of patients treated with CyC for severe colitis refractory to intravenous steroids was recently reported. After 3 years, 90% of patients had relapsed; after 7 years 58% of patients had undergone colectomy. Long-term prognosis is reported to be improved by the introduction of azathioprine or mercaptopurine upon discharge from the hospital in association with oral CyC as bridge therapy.41

Following 12 years experience a Belgian group reported that CyC is an effective short- to medium-term treatment for patients with severe UC but at 7 years, 88% of patients will require colectomy.42

Figure 2 Deep colonic ulcerations. Plain abdominal film of the abdomen in supine position in a patient with severe UC. Diffuse intestinal distension. Presence of deep ulcerations in the sigmoid (arrows).
Very recently, CyC i.v. has been used as "top–down" monotherapy in severe UC. This strategy was found to be superior to the conventional "step-up" approach (CSA in patients who failed to respond to iv Steroids) in avoiding colectomy.43

A recent Cochrane review of the literature on severe UC including only randomised clinical trials comparing CyC with placebo or no intervention showed that the evidence indicating that CyC is more effective than standard corticosteroid therapy is weak and CyC does not avoid the overall need for colectomy.44 The drawback of this review is that only two randomised controlled trials have been included.

Concerns about toxicity have also prevented the widespread use of Cyc in many hospitals. Cyc can be associated with severe side-effects (e.g. hypertension, renal failure, neurotoxicity, hepatotoxicity, diabetes and hypertrichosis), which lead to death in a significant minority of patients, thus limiting its use. Adverse effects are less frequent with the lower 2 mg/kg/day dose. The benefits of avoiding colectomy should, therefore, always be balanced against the risk of inducing profound immunosuppression and severe side-effects. Furthermore, in many instances, administration of CyC only delays but does not prevent colectomy.

Very recently a Meta-Regression performed on 32 studies for a total of 1991 patients showed that the short-term colectomy rate, in severe UC, had remained stable over the last 30 years despite the introduction of CyC. In the pooled analysis, the mean colectomy rate was 27% and mortality of 1%.45

3.2. Infliximab

Monoclonal anti-tumour necrosis factor antibodies (i.e. Infliximab) have now been used to treat severe UC. However, most of the published studies are uncontrolled, include a small number of patients and show controversial results. The first randomised controlled trial on Infliximab for UC did not support its use in the management of moderately active glucocorticoid-resistant UC; however patients with severe disease were specifically excluded from the study.46

Since then, data from two randomised controlled clinical trials (ACT1 and ACT2), which included over 700 patients with moderate-to-severe UC, have been published in a single article.47 Infliximab, given i.v. at the dose of 5 mg/kg, at 0, 2 and 6 weeks, was effective at inducing clinical remission, healing the lesions and demonstrating a steroid-sparing effect. It was not clear, however, how many patients included in these trials had really severe UC requiring hospital admission with an intensive treatment regimen.

A Scandinavian placebo-controlled trial has recently shown that Infliximab given as a single 5 mg/kg infusion was significantly more effective than placebo in avoiding colectomy, at 3 months, in patients with severe UC refractory to corticosteroids.48 The results of this study at 2-year follow-up also showed a statistically lower colectomy rate in the Infliximab group (46% vs 76%; P<0.05).49 These results were confirmed by a pan-Scotland retrospective audit on 39 patients with severe UC showing that 66.6% of patients avoided urgent colectomy following Infliximab rescue therapy.50 Similar results were observed by a Spanish multicentre retrospective survey including 47 UC patients, either steroid resistant or dependent.51

In the Oxford experience, 85% of the patients receiving Infliximab as rescue therapy for severe UC, avoided early colectomy, but overall 57% of these patients ultimately underwent colectomy after a median period of 3 months since their last infusion.52

In the experience of the Leuven group, 19% of patients treated with Infliximab for moderate-severe UC, followed for a median time of 2.5 years needed colectomy.53

In summary, the use of Infliximab in the treatment for severe UC seems promising, even if its role still remains to be clearly defined. In a recent systematic review on Infliximab therapy in UC including 34 studies for a total of 896 patients, only 207 patients had severe disease.54 In particular, whether the early use of Infliximab will prevent colectomy is uncertain. Uncontrolled studies suggest that Infliximab used as rescue therapy, like CyC, is effective only in delaying the need of colectomy since >50% of treated patients require surgery over 5–7 years. The better safety profile and the simplicity of Infliximab versus CyC suggest that Infliximab is the best alternative to surgery in steroid-refractory severe UC.

4. Final considerations

The advent of corticosteroids in the 1950s with the application of the intensive regimen, early detection of risk factors, early surgery and strict collaboration between gastroenterologist and surgeon dramatically reduced the mortality rate in severe UC in the last decades.

Once mortality was reduced near to 0% gastroenterologists changed the primary outcome of treatment seeking to avoid colectomy and possibly heal the mucosal lesions. Currently, two drugs are used to avoid surgery in severe UC: Cyclosporine and Infliximab. However, despite high remission rates achieved with both Cyclosporine and Infliximab, about 50% of the treated patients ultimately will come to colectomy over the next few years. The need for new, safer and more effective drugs in the medical therapy of severe UC is therefore pressing.

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