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Alimentary Tract

# Improved outcome of acute severe ulcerative colitis while using early predictors of corticosteroid failure and rescue therapies

Jordina Llaó[a], Juan E. Naves[b], Alexandra Ruiz-Cerulla[c], Jordi Gordillo[a], Míriam Mañosa[b], Sandra Maisterra[c], Eduard Cabré[b], Esther Garcia-Planella[a], Jordi Guardiola[c], Eugeni Domènech[b,*]

[a] Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain
[b] Hospital Universitari Germans Trias i Pujol, Centro de Investigaciones Biomédicas en Red de Enfermedades Hepáticas y Digestivas, Badalona, Spain
[c] Hospital Universitari de Bellvitge, IDIBELL, L'Hospitalet de Llobregat, Spain

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ABSTRACT

*Background and aim:* Intravenous corticosteroids remain the first line therapy for severe attacks of ulcerative colitis although up to 30–40% of patients do not respond to treatment. The availability of alternative therapies to colectomy and the knowledge of early predictors of response to corticosteroids should have improved the clinical outcomes of patients with severe refractory ulcerative colitis. The aim of the study is to describe the current need, way of use, and efficacy of rescue therapies, as well as colectomy rates in patients with severe ulcerative colitis flares.
*Methods:* Between January 2005 and December 2011, all patients admitted in three referral centres for a severe ulcerative colitis flare who received intravenous corticosteroids were identified and clinical and biological data were accurately collected. Patients were followed-up until colectomy, death, or date of data collection.
*Results:* Sixty-two flares were included. Initial efficacy of intravenous corticosteroids (mild activity or inactive disease without rescue treatment, at day 7 after starting intravenous corticosteroids) was achieved in 50% of flares, and rescue therapies were used in 27 episodes (43%). After a median follow-up of 18 months, the colectomy rate was 6.5%. Failed oral corticosteroids for the index flare were the only baseline feature that predicted the need for rescue therapy and colectomy.
*Conclusions:* There is a marked reduction in the colectomy rate and an increased use of medical rescue therapies as compared to historical series. Patients worsening while on oral corticosteroids for a moderate flare are at high risk of rescue therapy and colectomy and, therefore, should be directly treated with rescue therapies instead of attempting intravenous corticosteroids.


## 1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory condition of the colon characterized by a relapsing-remitting course. Up to 25% of UC patients will require hospital admission in their lifetime for intensive intravenous treatment because of severe flares [1]. Intravenous corticosteroids (IV-CS) remain the treatment of choice for severe attacks of UC [2] though it has been repeatedly reported that up to 30–40% of patients do not respond to treatment [3], a clinical situation known as steroid-refractory UC. Although a universally accepted definition of steroid-refractoriness is still unavailable, the most accepted criterion is the lack of clinical improvement after 7–10 days of intravenous prednisolone at a dose of 1 mg/kg/day [4] or persistent active disease after treatment with oral prednisolone 0.75 mg/kg/day for 4 weeks [2]. However, waiting for 1–4 weeks to define treatment refractoriness seems too long for patients with severe inflammatory activity because it may lead to clinical deterioration and the development of disease-related complications such as toxic megacolon, malnutrition, sepsis, or thromboembolic events.

Clinicians' main concern in the management of severe attacks of UC is to identify those patients who are unlikely to respond to IV-CS therapy. Great efforts have been made to discern early predictors of CS failure in order to allow the identification of candidates for rescue therapies. Travis et al. [5] found that patients with more

* Corresponding author at: Hospital Universitari Germans Trias i Pujol, Gastroenterology Department, Carretera del Canyet s/n, 08916 Badalona, Catalonia, Spain.
*E-mail address:* eugenidomenech@gmail.com (E. Domènech).

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than 8 bowel movements per day or with 3–8 stool passages and serum C-reactive protein levels higher than 45 mg/L, on the third day of intensive intravenous treatment, had a 85% risk of colectomy. Similar results were subsequently reported [6–8]. In addition to clinical variables, the presence of severe endoscopic lesions has also been associated with a worse prognosis [9].

For many decades, the only treatment option in this clinical setting was colectomy. Twenty years ago, cyclosporine A (CsA) became the first alternative to colectomy for steroid-refractory UC [10], avoiding colectomy in up to 70% of patients as reported in a systematic review [11]. A decade later, infliximab (IFX) became a new medical alternative for steroid-refractory UC, as shown in the first controlled study by Järnerot et al. [12]. Both drugs were compared recently, reporting similar short-term [13] and long-term [14] efficacy.

The availability of both rescue therapies and predictors of poor response to CS should have improved the prognosis of patients with steroid-refractory UC, mainly in terms of the colectomy rate. Nevertheless, large series reporting the long-term outcomes of patients with severe UC flares in the era of biological agents are scarce. Therefore, the aims of the present study were to describe the need, type, the way of use, and efficacy of rescue therapies in this clinical setting, as well as the short and long-term colectomy rate in patients admitted for an acute severe UC flare.

## 2. Patients and methods

Between January 2005 and December 2011, all patients admitted for UC flares who received IV-CS were identified from the electronic records of three referral University hospitals in the Barcelona area. Patients were only included in the study if they had severe activity at the time treatment with IV-CS was started, according to the Montreal classification of UC severity (6 or more bloody stools per day together with at least one symptom or sign of severity – tachycardia, fever, anaemia, or raised ESR or CRP-) [15]. Patients whose disease extent was limited to the rectum were excluded.

All patients were treated with intravenous methyl-prednisolone at a dose of 1 mg/kg/day. Rescue therapies (CsA or IFX) were prescribed at the discretion of treating physician. Patients receiving CsA were treated intravenously at a dose of 2–4 mg/kg/day (with dose adjustment according to therapeutic range of drug serum trough levels measured every 48–72 h). Patients achieving clinical remission with CsA were thereafter maintained on oral azathioprine 2.5 mg/kg/day. Patients receiving IFX were treated with 5 mg/kg infusions at weeks 0, 2 and 6; in case of clinical response, IFX 5 mg/kg every 8 weeks, azathioprine 2.5 mg/kg/day, or both, were prescribed maintenance therapy at the discretion of their treating physician. In cases of gastrointestinal intolerance to azathioprine, mercaptopurine was prescribed.

Collected data included epidemiological data (gender, age, smoking habit, family history of IBD), clinical (UC duration, previous CS courses, UC extent, failed oral CS for the index flare, extraintestinal manifestations, disease severity at day 3 and 7 of intravenous CS, steroid-dependency criteria and/or colectomy during follow-up), biological data (C-reactive protein at baseline – CRP-, 3, and 7 days), and treatment data (previous maintenance therapy, need for rescue therapy during the index flare, colectomy during admission) parameters. Finally, Truelove's severity criteria, in addition to the number of the daily bloody motions at the time CS treatment was started, was also recorded and converted into dichotomous variables (CRP > 35 mg/L, haemoglobin concentration < 10 g/L, presence of any systemic symptom – heart rate > 90 bpm, arterial hypotension, temperature > 37.5 °C, or extraintestinal manifestations).

For the purposes of the study, and in line with previous studies [8], we defined *initial efficacy* as mild activity or inactive disease, according to the Montreal severity score for UC [15], together with the lack of the need for rescue treatment, at day 7 after starting IV-CS. *Steroid-dependency* was defined as either the impossibility of reducing the corticosteroid dose to less than 10 mg/day after 3 months of treatment, or disease relapse within 3 months after steroid discontinuation [16]. Patients were followed-up until colectomy, death, or date of data collection. The development of steroid-dependency or the need for colectomy during follow-up was also recorded.

The study was approved by the Institutional Review Board of the coordinating centre (Hospital Universitari Germans Trias i Pujol).

All statistical analyses were carried out in SPSS12.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are expressed as median and interquartile range (IQR) or absolute and relative frequencies. Chi-square analysis and Student's *t*-test were performed for the between-group comparison of qualitative and quantitative variables, respectively. Variables reaching statistical significance (*P*-value ≤0.05) upon univariate analysis were included in the binary logistic regression analysis to identify predictors of the need for rescue therapy and colectomy. The cumulative probability of colectomy was calculated by the Kaplan–Meier method.

## 3. Results

A total of 62 acute severe UC flares were included and their main clinical features are summarized in Table 1. As expected, most patients had extensive disease, were not current smokers, and had high CRP levels at the time of hospital admission. Interestingly, up to 23% of the index flares were treated with oral CS for an initially moderate flare but required hospital admission due to clinical worsening (failed oral CS). Finally, 33% of patients had been previously exposed to thiopurines at the time of the index flare.

### 3.1. Early outcome

As shown in Table 2, 77% of episodes showed clinical improvement after 3 days of intravenous CS therapy, with only mild to moderate activity according to the Montreal's classification. CRP levels at baseline and after 3 days of intravenous CS were available in 79% of flares. There was a decrease in CRP levels in 96% of cases, with 67% of flares showing CRP levels ≤45 mg/L at day 3. Nevertheless, only 50% of episodes met initial efficacy criteria as defined in the study.

In all, rescue therapies were used in 27 episodes (43%), twelve of which were initially treated with CsA and 15 with IFX, with 3 episodes receiving sequential rescue therapies (1 CsA after IFX and 2 IFX after CsA). Median time from intravenous CS to rescue

**Table 1**
Baseline characteristics of severe flares. Expressed as absolute numbers (frequency) or median (IQR).

| | |
|---|---|
| Female gender | 30/62 (48) |
| Age (years) | 37 (29–47) |
| Ulcerative colitis duration (months) | 46 (0–96) |
| Ulcerative colitis extent | |
| Distal | 19 (31) |
| Extensive | 43 (69) |
| Smoking status | |
| Never | 36 (58) |
| Current | 11 (17) |
| Former | 15 (24) |
| Prior corticosteroid courses | 28/62 (45) |
| Failed oral corticosteroids for the index flare | 14/62 (23) |
| Maintenance treatment with thiopurines | 18/62 (33) |
| Baseline C-reactive protein (mg/L) | 99 (55–163) |