

Evolutionary Profile of Severe Acute Ulcerative Colitis in Chronic Inflammatory Bowel Diseases

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Abstract

Background: Severe acute colitis is a common complication of inflammatory bowel disease (IBD). Their diagnosis is based on clinical, laboratory, endoscopic and radiological. The severe acute colitis is a medical and surgical emergency; its mortality is 1% to 3%. The management should be swift and coordinated, upon admission, between medical and surgical teams. **Methods:** This is a retrospective study in Gastroenterology Service at the University Hospital HASSAN II Fez, over a period of 10 years (2005-2015). We included all patients admitted for severe acute colitis; all the epidemiological, clinical, endoscopic, histological, and therapeutic monitoring of patients were collected. **Results:** We collected 123 patients. Their average age was 35 years (16 - 70). It was a female predominance (sex ratio F/M = 1.19). 54 patients were admitted for an inaugural severe acute colitis (43%), while 69 patients were known carriers of IBD (56%). All patients were admitted to an array of severe acute colitis according to the criteria of Truelove and Witts modified. 9 patients were operated urgently because there was the presence of complications (5 cases of perforation, 3 cases of massive rectal bleeding, and one patient with an abscess in the right iliac fossa). Corticosteroids intravenously was administered to 114 patients, 74 patients (64%) had remission. Patients who have not responded to corticosteroids IV (N = 40): 1) 12 patients received treatment with oral cyclosporine: the remission rate was 66%. 2) 8 patients were put under Infliximab: The response rate was 75%. 3) Patients who have not responded to a second-line treatment underwent subtotal colectomy with a dual stoma. 4) The surgery was indicated as a second-line treatment in 20 patients who all received a subtotal colectomy with double stoma; totalizing colectomy and ileoanale anastomosis were made in 4 patients. The mortality rate is higher in our series (12%) mainly postoperatively; it is due to the delayed admission of patients, which promotes the development of complications. **Conclusion:** Acute Severe Ulcerative Colitis is a medical and surgical emergency

that requires a multidisciplinary approach; medical treatment is the basis of initial treatment; but surgery must always be indicated at the right time avoiding increasing the death rate, this rate is important in our series.

Keywords

Acute Severe Ulcerative Colitis, Infliximab, Cyclosporine, Colectomy

1. Introduction

Severe acute colitis (SAC) is a classic complication of ulcerative colitis (UC) that can be life-threatening in the short term. This anatomico-clinical entity can also be observed during Crohn's disease (CD) or infectious colitis. The diagnosis is based on the association of clinical and biological criteria and can be supported by morphological criteria (endoscopy, imaging). SAC is a medical and surgical emergency whose mortality according to the literature is 1% to 3% [1] [2] [3]. Its management must be fast and coordinated, from the admission of the patient, between medical and surgical teams.

2. Materials and Methods

We carried out a retrospective study of 123 patients admitted for severe acute colitis in gastro-enterology department of Hassan II University Hospital of Fez over a period of 10 years (2005-2015). We included in this study all cases of severe acute colitis retained on the clinical-biological criteria of Truelove and Witts modified.

All epidemiological, clinical, endoscopic, histological and therapeutic data as well as patient follow-up were collected.

3. Results

During the study period, we collected 123 patients with an average age of 35 [16 - 70], with a slight female predominance (sex ratio F/M = 1.19). Fifty four patients were admitted for an inaugural severe acute colitis (43%), while 69 patients were already known to have IBD (56%): 56 patients with UC (45%), 10 patients with Crohn's disease (8%) while 3 patients (2%) with IBD not yet determined.

For previous treatments in known patients with IBD: 20 patients were on mesalamine, 12 patients on Salazopurine, 7 patients on Azathioprine, 3 patients on 6-Mercaptopurine, 20 patients on oral corticosteroids, 5 patients on mesalamine enema, and 2 patients under corticosteroid enema.

The mean duration of disease progression before the flare was 30 months [4 - 240 months]. All patients were admitted to SAC (Truelove and Modified Wittz score) with average score of Lichtiger at 12 (11 - 14). The average onset of symptomatology was 15 days earlier in our patients (10 - 20). On admission, a

radiograph of the Abdomen without preparation (ASP) was performed in all patients: No case of colectasia was found, but the presence of pneumoperitoneum was objectified in 3 patients who carried out a CT scan confirming the presence of colonic perforation in these 3 patients. Biologically, the average level of CRP was 84 (23 - 370), the mean hemoglobin level was 7.4 g/dl (2.7 - 14) with an average albumin level of 19 g/l (13 - 38). Stool coproparasitology was requested for all patients. It found pathogenic forms of amoebiasis in 8 patients, Shiguella infection in 2 patients, while it was negative for the rest of the patients. Initial rectosigmoidoscopy was performed in all patients except for the 3 patients with perforation; it objectified the presence of signs of endoscopic gravity in 47 patients (38%) while 73 patients hadn't endoscopic signs of severe disease activity.

Systematic biopsies were made for the pathological study and for the search for certain pathogenic germs whose CMV was positive in 2 patients. Surgery was indicated immediately (before any drug treatment) in 9 patients presenting a complication upon admission:

- Peritonitis with perforation in 5 patients.
- massive rectal bleeding in 3 patients.
- Abscess of the right iliac fossa with a luminal disease flare in one single patient.

All these patients underwent subtotal colectomy with double stoma; the post-operative history in these patients was marked:

- By mortality of 6 patients:
 - 5 were admitted for colonic peritonitis by colonic perforation and who have set up a septic shock in the immediate postoperative history.
 - One patient admitted for massive rectal bleeding with hemodynamic instability and hemorrhagic shock)
- By a good evolution in the 3 remaining patients.

Regarding first-line medical treatment, 114 patients were first treated with intravenous corticosteroid at a dose of 0.8 - 1 mg/kg/day; heparin therapy was routinely administered in all patients because of the risk of thromboembolism in severe acute colitis, metronidazole was also administered systematically in all patients since Morocco is an endemic country with amoebiasis. The daily clinical-biological monitoring, based on the evaluation of the Lichtiger score, showed a good evolution under intravenous corticosteroid in the seventh day in 74 patients (64%) hence the use of oral corticosteroid, a gradual decline in corticosteroid was started in these patients after clinical remission.

For patients who failed to respond to intravenous corticosteroid (N = 40), the use of second-line treatment was indicated:

- Oral ciclosporin was used in 12 patients: The oral form was administered at a dose of 4 mg/kg/day (Injectable ciclosporin not available in Morocco) with the aim of achieving ciclosporinemia of 150 to 250 ng/ml, Lipid and magnesium supplementation has been done with strict biologic monitoring to watch for side effects that are well known for this treatment. A favorable

clinical response was observed in 8 patients (66%) while 4 patients (34%) had failed oral ciclosporin, hence surgery with subtotal colectomy with double stoma. For patients with a good response to oral ciclosporin, an immunosuppressive therapy based on thiopurines was started (knowing that 7 patients were naive to thiopurines) with good clinical and biological evolution. After approximately 2 years of evolution, only one patient (8%) presented a second episode with failed medical treatment, hence the use of subtotal colectomy.

- Infliximab was used in 8 patients with an induction regimen (5 mg/kg/day at w0, w2 and w6) followed by maintenance treatment (5 mg/kg/day every 8 weeks) for patients having responded to induction therapy. A clinical response was observed in 6 patients (75%) whereas a failure in Infliximab was observed in one patient. In one patient, we noted the onset of a severe systemic infection obliging to stop the continuation of Infliximab. For these last 2 patients, a subtotal colectomy with double stoma was performed. Only one patient died from septic shock secondary to febrile pancytopenia after treatment with Infliximab.
- Surgery was indicated as second-line treatment in 20 patients because of the unavailability of second-line medical treatment.
 - A preparation for surgery was done first in intensive care unit.
 - Subtotal colectomy by laparotomy was performed for all these patients with double stoma within an average of 12 days (5 -21 days) ; The sigmoidostomy allowed to clean the remaining colon post-operatively;
 - Postoperative follow-up was marked by:
 - The appearance of peritonitis in 5 patients with 100% mortality due to septic shock despite surgical revision;
 - One case of mortality of massive pulmonary embolism.
 - Simple post operative follow-up in 14 patients.
 - Nearly 80% of histologic examinations of the colectomy specimens concluded to ulcerative colitis, while it was non-specific acute colitis in 20% (n = 4).
 - Only 4 of our patients benefited from a secondary intervention with proctectomy and ileoanal anastomosis on J reservoir, of whom 3 patients presented stenosis of the colo-anal anastomosis afterwards (after about 3 months of anastomosis). These patients have benefited from several anal dilation sessions with good evolution.
 - The subsequent evolution after an initial remission of 4 patients (after approximately 1 year) was marked by the installation of luminal flare revealing their Crohn's disease which was initially considered as an ulcerative colitis UC.

In total, we have a high mortality rate of 12% (15 patients):

- 12 patients who died post-operatively,
- 2 patients who died of complications during their hospitalizations despite a clinical remission of their flare (pulmonary embolism and septic shock),

- 1 patient died from septic shock secondary to pancytopenia after treatment by Infliximab.

The evolutionary profile of our patients is summarized in **Figure 1**.

Statistical analysis of our study showed that hemoglobin levels less than 10 g/dl, severe hypo albuminemia and the presence of signs of endoscopic severity are predictive factors for failure of intravenous corticosteroid and recourse to a second-line treatment (**Table 1**).

4. Discussion

Severe acute colitis (SAC) is a complication of chronic inflammatory bowel disease that can complicate RCH or Crohn's disease as well as other forms of colitis (infectious, ischemic or medicated) [1]. A CAG can initiate the disease in about 1/3 of the cases, or it can complicate an already known IBD; In our series the severe flare was inaugural in 43% of patients. The introduction of corticosteroids in the 1950s significantly reduced the mortality rate for acute severe colitis from 30% - 60% to less than 1%, and since then, corticosteroids have been considered the first-line treatment for severe flare of IBD [2]. However, the rate of response

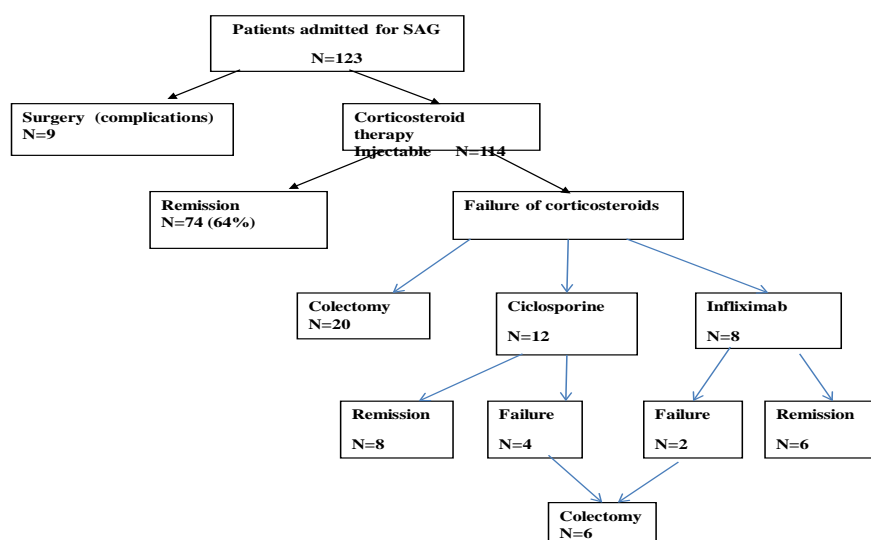


Figure 1. Evolutionary profile of severe acute colitis in our series.

Table 1. Risk factors for failure of injectable corticosteroid therapy in our series.

The variables	Response to corticosteroid therapy	second ligne therapy	<i>P</i>
middle age (years)	35	34	0.9
Sex			
- man	63%	36,7%	0.61
- woman	69%	31%	
Anemia < 10 g/dl	32%	48%	0.048
severe Hypoalbuminemie	8,6%	40%	0.001
endoscopic gravity signs	36,2%	64%	0.019

to intravenous corticosteroids has not changed over the years, with up to 30% - 40% of patients presenting with an inadequate response to treatment [3]. The first prognostic studies [4] [5] looked for the parameters associated with the need for a colectomy and they led to the implementation of the clinical and biological parameters for this decision. Thus, a high stool number, the persistence of high levels of CRP, the persistence of rectal bleeding after three days of intravenous corticosteroids have become simple criteria for the introduction of rescue therapies such as ciclosporin or Infliximab. Using similar criteria for clinical response, two prospective studies [4] [6] and two retrospective studies [5] [7] reported an initial efficacy of intravenous corticosteroids of 40% - 57%. In the long-term follow-up of patients with severe acute colitis, Bojic *et al.* reported that patients who had a partial response after 7 days of intravenous corticosteroid had a significantly higher cumulative probability of colectomy in follow-up than those who achieved early clinical remission [8]. Colectomy should not be considered as the last recourse in case of failure of drug treatments, but also as a therapeutic option discussed at each stage of the management of a SAC. This is a treatment that has reduced SAC mortality, provided it is not proposed too late. Colectomy is indicated as an emergency in cases of perforation, toxic megacolon, massive rectal bleeding or multi-visceral failure [9]. These complications have become less common since the early management of severe inflammatory colitis. They concern 7% of our series. A UK Oxford study in 2009 by Dinesen *et al.* about 750 patients reported a colectomy rate in patients who were admitted once or more for severe acute colitis as much as 40% (74/186) compared to only 3% (19/564) among those who have never been admitted for severe flare. The overall colectomy rate was 12% [10]; In this British cohort, these results are similar to 10.4% reported in study in Northern Europe in 2007 [11], but lower than that reported in a US study by Kaplan *et al.* where a colectomy rate cumulative 27% has been reported [12]. A study by Kumar *et al.* in 2015 looked at the effect of early colectomy (in the first 7 days) in case of failure of the intravenous corticosteroid on the postoperative mortality rate; the results showed that the postoperative mortality was 1.1%, significantly lower than the mortality observed in cases of colectomy beyond 7 days (15.6%, $p = 0.006$) [13]. Although intravenous corticosteroids are the basis of medical treatment, approximately 30% to 40% of patients are resistant to steroid treatment. In the past, when other drug treatments were unavailable for corticosteroid-refractory SACs, the only option was emergency colectomy, which resulted in about 10% of the mortality rate 3 months after surgery. Recently, ciclosporin and Infliximab have shown both their ability to have certain benefits for patients with severe acute colitis resistant to intravenous corticosteroid therapy. However, since 2005, several placebo-controlled randomized clinical trials have demonstrated that Infliximab is safe and effective in SAC refractory to intravenous corticosteroid with 60% to 80% remission in the short term by avoiding colectomy rates [14]. A meta-analysis of 34 studies on Infliximab found a mean short-term response and

remission of 68% and 40%, respectively, and an average long-term response and remission of 53% and 39%, respectively [15]. A Belgian study done in 2014 grouped 285 patients with acute severe corticosteroid colitis who were put on infliximab; 61% of patients had a relapse and 20% had a colectomy. Clinical response and mucosal healing are independent predictors of short-term relapse-free survival; while independent predictors of survival without colectomy were mucosal healing, clinical remission, and albumin above 35 g/l. Infliximab serum levels greater than 2.5 mg/ml at week 14 of treatment predicted survival without recurrence ($P < 0.001$) and survival without colectomy ($P = 0.034$) [16]. Monterubbianesi *et al.* reported in a study involving 113 patients admitted to 11 Italian centers treated with Infliximab (induction therapy: S0, S2, S6) that colectomy rates at 3 and 12 months were 18.6%. (95% CI 11.8% - 26.9%) and 25.6% (95% CI 17.9% - 34.7%) respectively. High CRP values and severe endoscopic lesions were associated with the risk of colectomy at 12, 24, 36 by 91%, 85%, 81% respectively, whereas signs of endoscopic severity were the only predictor of long-term colectomy (RR = 7.0, 95% CI 1.09 to 44.7) [17]. Since 1994, through several controlled and uncontrolled clinical trials, intravenous ciclosporin has been shown to be effective in severe acute colitis with a response rate who can reach 64% to 82%. However, ciclosporin has been associated with a high risk of long-term colectomy (88% colectomy rate at 7 years). In addition, a significant risk of toxicity and side effects as well as monitoring have limited its use in clinical practice [18]; Conventionally, ciclosporin is administered by continuous intravenous infusion at the dose of 2 mg/kg per day, with the objective of ciclosporinemia effective between 150 and 250 ng/ml. In case of response to intravenous treatment, a relay by oral ciclosporin is then undertaken. Some teams proposed out of hand oral micro-emulsion treatment with ciclosporin (Neoral®), at an initial dose of 2 mg/kg per 12 hours and the objective of a circulating residual rate around 100 ng/ml and a peak (2 hours after taking the drug) close to 600 ng/ml [19] [20]. In our study ciclosporin was administered orally given the unavailability of the intravenous form in Morocco with an initial response rate of 66% which is concord with the results of the literature. Currently, some guidelines recommend intravenous ciclosporin or Infliximab as rescue therapy for patients with severe acute colitis resistant to intravenous corticosteroid therapy.

A recent meta-analysis of six retrospective cohort-type studies comparing the clinical result of patients with SAC corticoreistant receiving Infliximab or ciclosporin as a rescue therapy showed no significant difference in colectomy rate at 3 months and 12 months, in the adverse effects, and in postoperative complications between the two groups [21].

In addition, the first prospective randomized controlled trial comparing the efficacy of ciclosporin versus Infliximab, recently published in Europe, demonstrated that there is no significant difference in treatment result between the two groups [22].

Although there has been several data comparing the efficacy of intravenous ciclosporin with Infliximab, there is still debate about which drug is more effective in severe acute colitis refractory to corticosteroids [23] [24].

A study by Kim *et al.* compared the efficiency of ciclosporin and infliximab in corticoreistant CAG: No difference between infliximab and ciclosporin compared to colectomy prevention was noted. However, infliximab with azathioprine may be more effective than ciclosporin alone to avoid colectomy [25].

Table 2 compares the results of our study with those of a recent Spanish study done in 2016 involving 62 patients with severe acute colitis [26]; it shows a high rate of colectomy in our series compared to the Spanish series, and this is due to the unsatisfactory availability of second-line medical treatment which impose us to recourse to colectomy frequently (**Table 2**).

A recent study conducted in 2016 assessed the short-term colectomy rate and mortality for severe acute colitis over the last 40 years (1976 to 2010) in 159 patients in 4 cohorts; cohort 1: (1976-1980); cohort 2 (1986-1990); cohort 3 (1996-2000); cohort 4 (2006-2010). The colectomy rate was 64.7%, 62.0%, 44.4% and 9.8%, respectively, in the four cohorts ($p < 0.0001$) and the mortality rate decreased by 8.8 % in cohort 1, at 0 in cohort 4 ($p = 0.04$) [27].

The operative mortality of subtotal colectomy is null or close to 1% in the absence of complication, but it increases considerably, especially if there is colonic perforation, Thus, in one series, the operative mortality was less than 1%, whereas 25% of the patients had complicated forms (hemorrhage, perforation, colectasia) [28]. Preoperative mortality for patients operated on peritonitis was 100% in our series. On the other hand the mortality remains very high in our series even in the absence of peritonitis since it is 12%. We impute this abnormally high rate of mortality to late arrival of patients within our hospital.

Table 2. Comparison of the results of our study with the results of a recent Spanish study.

	Spanish study [26] N = 62	Our study N = 123
Response to corticotherapy	31 (50%)	74 (60%)
Reponse to second line medical treatment	27 (43%)	12 (9%)
- Infliximab	14	6
- Ciclosporine	10	8
- both	03	
Surgery:	5 (6.5%)	35 (28%)
Immediatly	1	9
After failure of medical treatment	4	26

5. Conclusion

SAC is a medical and surgical emergency requiring multidisciplinary approach. The initial treatment is based on intravenous corticosteroid, followed in case of failure by ciclosporin or Infliximab. However, colectomy should still be considered a standard treatment for SAC and not a last recourse solution in case of failure of drug treatments given the risk of mortality which is 1% to 3% but which is even higher in our series (12%), therefore it is essential to confide the patient to the surgeon at the right time to avoid both an early and abusive surgery or to operate an already complicated patient.

Conflicts of Interest

The authors don't declare any conflict of interest.

Contributions of the Authors

Hakima Abid; Fatima Babakhouya, Ihssane Mellouki, Mounia El yousfi, Noureddine Aqodad, Dafr Allah Benajah, Adil Ibrahim, Mohamed El Abkari.

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