

## Predictive factors of glucocorticosteroid treatment failure in severe acute idiopathic colitis

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### Abstract

**Introduction :** The purpose of our study was to determine clinical, biological or endoscopic factors that could predict glucocorticosteroid treatment failure in acute colitis.

**Patients and Methods :** Fifty-four Tunisian Caucasian patients with acute idiopathic colitis (ulcerative colitis in 53 patients, Crohn's colitis in 1 patient) have been evaluated. Non-therapeutic response was defined as over 6 bowel movements per day, blood visible to the naked eye in stools on the fifth day after admission or the development of a complication inducing a resort to surgery. Predictive factors were assessed using bivariate and multivariate analysis.

**Results :** Thirty-nine patients (72.2%) had no medical response. In univariate analysis, predictive factors of therapeutic failure were : male sex, tobacco, previous history of colitis attacks, bowel movements per day over seven at admission and on day three, and pulse rate over 90/mn, temperature over 38°C, systolic blood pressure below 11 on day 3 and on day 5 after admission. In multivariate analysis, bowel movements over seven per day on day 3 of hospitalization and male sex independently predicted a failure of glucocorticosteroid treatment.

**Conclusion :** Bowel movements per day over seven on day 3 of hospitalization and male sex were the independently predictive factors of failure of glucocorticosteroid treatment. (*Acta gastroenterol. belg.*, 2005, 68, 226-229).

**Key words :** severe colitis, ulcerative colitis, Crohn's disease, medical treatment, glucocorticoids.

### Introduction

Severe acute idiopathic cryptogenetic colitis constitutes a medico-surgical emergency which is difficult to manage. Currently, the medical treatment using intravenous corticosteroid in non-complicated cases is justified (1). However, 25 to 86% of patients do not improve under this treatment (2,3) and have to undergo a subtotal colectomy in emergency (1,3). This colectomy has the inconvenience to include patients in whom the final diagnosis and classification of colitis are not definitely established. In fact, severe acute cryptogenetic colitis is inaugural in 35% of the cases (4) and severe colitis due to Crohn's disease seems to be more frequent (5). The reasons of failure of medical treatment remain unknown. A better identification of predictive factors of non-response to corticosteroid treatment could either allow an earlier resort to other regimens or more efficient treatments such as immunosuppressors, particularly cyclosporine, or an indication of earlier surgery (6-11). The aim of this study was to identify clinical, biological or endoscopic parameters that could predict the failure

of treatment by glucocorticosteroid in severe acute cryptogenetic colitis.

### Patients and methods

We included all Tunisian Caucasian patients hospitalized in the Gastroenterology or Surgery wards for non-complicated acute severe cryptogenetic colitis between January 1989 and December 2000. The diagnosis was based on at least two of the clinico-biological criteria of Truelove and Witts (11) and on normal radiological criteria such as the absence of pneumo-peritoneum or toxic megacolon at plain films of the abdomen. We excluded of the survey the patients who had a massive hemorrhage, those who had an infectious non-cryptogenetic, ischemic or post-antibiotic colitis, and those who had an unclassifiable inflammatory colitis as well as those who had received a medical treatment whose length was lower than 5 days.

Fifty-four patients (24 men and 30 women) were included in this survey ; 34 were known as affected by ulcerative colitis. All patients had a colonoscopy within 72 hours after the admission in order to search one or several of the following endoscopic signs : deep ulcerations unveiling the muscular sheet or deep ulcerations without visualization of muscular sheet, occupying more than 1/3 of the surface of the 4 colonic segments, or a mucosal detachment with or without ulcerations in well.

The files of these patients were reviewed retrospectively. The collected data were age, sex, tobacco addiction, alcoholism, profession, date of diagnosis, length of the last remission, maintenance treatment, maximal extension of the macroscopic lesions to the last hospitalization, etiology of the severe colitis, total number of thrusts in the antecedents, hemoglobin concentration, renal function, blood ionogram, sedimentation rate and endoscopic aspect of the colon at admission for severe attacks.

Some data were collected daily during the first 5 days after the admission : stool frequency, presence of visible

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Table I. — Univariate survey of the social and medical history of patients

	Therapeutic Response N = 15	Treatment Failure N = 39	P
SEX			
Male	3 (12.5%)	21 (87.5%)	0.025
Female	12 (40%)	18 (60%)	
Profession			
Steady	0	9 (23%)	NS
Intermittent	15 (100%)	30 (77%)	
Tobacco Addiction			
Yes	0	12 (100%)	0.015
No	15 (35.7%)	27 (64.3%)	
Alcoholism			
Yes	15 (28.3%)	38 (71.7%)	NS
No	0	1 (100%)	
History of Inflammatory Bowel Disease			
No	8 (47.1%)	9 (52.9%)	0.037
Yes	7 (19.4%)	30 (81.0%)	
Type of Colitis			
Ulcerative Colitis	7 (13.2%)	46 (86.7%)	NS
Crohn's colitis	0	1 (100%)	

blood in the stools, vital signs, temperature and state of the abdomen to the palpation.

The management of the severe acute idiopathic colitis was standardized including parenteral fluids (total parenteral nutrition was used if necessary) and intravenous corticosteroids using hemisuccinate of hydrocortisone with a mean dose  $313.8 \pm 58.09$  mg/24 hours (200-400 mg/24 hours). Antibiotics were associated in case of fever.

A therapeutic response to this intensive medical treatment justifying its continuation was defined by a reduced stool frequency lower or equal to 5 on the fifth day after the beginning of the treatment, which was maintained after the resumption of the oral food. The non-therapeutic response was defined by a number of stools superior or equal to 6 on the fifth day, the presence of blood macroscopically visible in the stools until the 5th day or the development of a complication imposing a colectomy.

The data was summarized at admission by descriptive statistics (means and frequencies) and analyzed with SPSS version 10. Then, all items associated with the main dependent variable (resulting of the glucocorticosteroid treatment) at the time of the univariate analysis, with a value of "P" lower to 20%, were included in a logistical regression model, which permitted to control confounding factors and to identify the items independently bound with the failure of the glucocorticosteroid treatment.

## Results

A therapeutic response to the steroids was noted in 15 patients (27.8%) and 39 patients (72.2%) were operated. The mean age of the non-operated patients was  $42 \pm 13$  years ; the mean age of the operated patients was  $38 \pm 12$  y ( $P = 0.2$ ). For operated patients, subtotal colectomy followed three months later by ileoanal anastomo-

sis was done in all cases except for two patients that had ileorectal anastomosis (Crohn's disease in one case, ulcerative colitis in one case). Three patients died of sepsis a few days after surgery. During the first six months after surgery, a pouchitis occurred in two cases, diarrhea in six cases and intestinal obstruction in one case.

## Univariate analysis

### – Medical history and habits of the patients

The failure of the glucocorticosteroid treatment was statistically more frequent in males than in females and in smokers than in non-smokers (table I). The way of installation of colitis (first inaugural attack or non severe previous attacks) appeared as well to be associated with a therapeutic failure (Table I)

– The signs of clinico-biological and endoscopic severity at admission :

Only a number of bloody stools exceeding 7 per 24 hours was associated with the absence of therapeutic response (Table II). On the other hand, no sign of endoscopic gravity was associated with a therapeutic failure at admission (Table III).

– The data collected daily during the first 5 days after admission :

On the third day of hospitalization, a number of bloody stools superior or equal to 7, a temperature superior or equal to  $38^{\circ}\text{C}$ , a systolic arterial pressure lower than 110 mm Hg, a tachycardia over 90 / minute were significantly associated with the absence of therapeutic response ( $P < 0.001$  for the two first variables and  $P = 0.036$  and  $P = 0.004$  for the two last variables, respectively). On the fifth day, a temperature superior or equal to  $38^{\circ}\text{C}$ , an arterial pressure lower than 110 mm Hg, a tachycardia over 90/minute appeared as predictive factors of the failure of medical treatment ( $P < 0.001$  for all comparisons cases).

Table II. — Univariate analysis of clinico-biological severity at admission

	Therapeutic Response N = 15	Treatment Failure N = 39	P
Number of bloody stools per day	7.27 ± 1.62	10.46 ± 2.94	< 10 <sup>-3</sup>
Pulse	90.80 ± 11.99	94.41 ± 12.78	NS
Temperature (C° celsius)	37.67 ± 0.54	37.77 ± 0.45	NS
Hemoglobin level (g/dl)	9.98 ± 1.52	10.09 ± 2.12	NS
Sedimentation rate (mm/hour)	62.47 ± 28.12	77.41 ± 28.19	NS

NS : Not significant.

Table III. — Univariate analysis of endoscopic signs of severity at admission

	Therapeutic response with steroids N = 15	Treatment failure with steroids N = 39	P
Deep ulcerations			
No	12	24	NS
Yes	3	14	
Mucous Detachment			
No	9	22	NS
Yes	6	14	
Naked Muscular layer			
No	13	27	NS
Yes	2	9	
Extended lesions			
No	8	15	NS
Yes	7	21	

Table IV. — Multivariate Analysis

	Adjusted Odds Ratio (OR a)	Interval of confidence on Odds Ratio to 95%	P
Sex	8.191	(1.209-55.478)	0.03
Deep ulcerations*	0.999	(0.108-9.192)	0.9
Number of stools on the 3rd day	21.043	(3.563-124.273)	0.001
Sedimentation rate*	2.241	(0.372-13.502)	0.3

\* Variables noted at admission.

## Multivariate analysis

It concerned the following variables : sex, deep ulcerations, sedimentation rate at the admission and number of stools on the third day of hospitalization. The sex and the number of stools superior to 7 on the third day were the independent variables of the non-therapeutic response to steroids with a P of 0.031 and 0.001, respectively (Table IV).

## Discussion

Treatment with intravenous corticosteroids is considered as the optimal therapy for severe acute colitis (11). For economical reasons, hemisuccinate of hydrocortisone was used in our hospital instead of methylprednisolone. The steroids interfere with the immune system that plays an important role in the mediation of the intestinal inflammation (12). A therapeutic response to the steroids in severe attacks has been noted in 27.8% of patients in this study. Remission in severe attacks was achieved in 55.7% of the patients in Janerot's study (13), and in 53% in D'Haens's study (14). In the Oxford stud-

ies, the remission rate was 73% (11) and 60% (15). These differences might be due to different proportions of patients with total ulcerative colitis or to a use of various definitions of severe attacks including or not endoscopic criteria (13).

The reasons of failure of the steroid treatment are still unknown. The in vitro survey of Hearing and al (16) suggests the existence of a T lymphocytes' resistance to steroids.

In the literature, the predictive factors of this failure are variable and sometimes discordant. In a recent meta-analysis (2) having regrouped 7 series including 306 patients affected by severe ulcerative colitis and 5 groups including 68 patients affected by Crohn's disease, no clinical or biologic predictive factor has been identified.

In the same way, in the survey of Linskens *et al.* (17), no relationship has been found between the parameters of coagulation, the products of degradation of fibrin and fibrinogen, the parameters of the inflammation and the evolution of the severe acute ulcerative colitis.

On the other hand, some factors have been recognized by other authors. In case of ulcerative colitis, these

factors were : a high frequency of stools per day, a high rate of C-reactive protein (CRP) and a low rate of albumin some days after an intensive medical treatment. (10,18-20). In case of Crohn's disease, the results are rather discordant and no factor could be identified (12). The relation between the presence of severe endoscopic lesions and the necessity of colectomy is not confirmed by all authors (3,17-21).

In this survey, a number of stools higher than 7 on the third day was a predictive factor of therapeutic failure in the multivariate analysis. This doorstep is variable in the literature for the ulcerative colitis ; it is of four by 24 hours on the third day of hospitalization for Lindgren *et al.* (19) and of eight by 24 hours on the third day of hospitalization for Travis *et al.* (20). Two parameters have not been included in our survey. These parameters were the CRP and albumin rate. The reasons were the impossibility to get the results during the first five days of hospitalization. No endoscopic severity sign has been kept in the multivariate analysis in our study (Table IV). The gender was an independent factor associated with therapeutic failure ; this finding has not been mentioned in the literature.

The axes of research are moving currently to other types of predictive factors (22). For example, Rees *et al.* (23) suggested that the absence of reduction of nitric oxide metabolites on the third day was predictive of therapeutic failure. Some genetic factors in experimental colitis were recently involved (24) ; their identification will be probably promising. There is now substantial human epidemiological data and several animal studies supporting the hypothesis that helminths protect the host from immunological disease (25,26). This hypothesis can explain the fact that the prevalence of inflammatory bowel disease is less frequent in Africa, especially in sub-Saharan Africa (25,26).

## Conclusion

A high number of stools, more than 7 per 24 hours, and the male gender were the independent predictive factors of glucocorticosteroid treatment failure in severe acute cryptogenetic colitis in our study. While waiting the identification of other notably genetic factors, we propose to take into consideration the number of stools per day to adjust the therapeutic attitude.

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