Review article

# Current Status of the Treatment of Fulminant Colitis[☆]

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## ARTICLE INFO

## ABSTRACT

Fulminant colitis is not a well-defined entity that constitutes a severe complication. It usually occurs in the course of ulcerative colitis and *Clostridium difficile* colitis. A multidisciplinary management combining a gastroenterologist and surgeons is crucial with intensive medical treatment and early surgery in non-responders. It is important to distinguish if we are facing a flare of IBD or, on the contrary, it is an infectious colitis, due to the fact that although general therapeutic measures to adopt will be the same, they will demand opposed specific measures.

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## Estado actual del tratamiento de la colitis fulminante

### RESUMEN

La colitis fulminante es una entidad cuya definición no está bien establecida y que supone una complicación grave. Sus principales causas son la colitis ulcerosa y la infección por *Clostridium difficile*. El manejo multidisciplinar integrado por gastroenterólogos y cirujanos es fundamental, con un tratamiento médico intensivo de inicio y cirugía precoz en los pacientes que no responden. Es importante dilucidar si nos encontramos ante un brote de EII o por el contrario, se trata de una colitis infecciosa, ya que aunque las medidas terapéuticas generales a adoptar serán las mismas, exigirán medidas específicas opuestas.

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## Introduction

The exact definition of fulminant colitis (FC) has not been well established. The first definition from 1950 described an acute severe colitis that was rapidly progressive, resulting in death within the first year.[1] It is generally accepted that this term refers to acute severe inflammation of the colon, associated with systemic toxicity either with or without colic dilatation.[2] Nonetheless, it is an imprecise definition, and it is often difficult to determine what is considered severe colitis and what is FC, with the currently preferred term of acute severe colitis.[3,4] In ulcerative colitis (UC), according to the diagnostic criteria of Truelove and Witts,[5] acute colitis is defined when patients present more than 6 bloody stools per day, tachycardia, hypotension, high fever, changes in mental state, anemia requiring transfusion, pain and abdominal distension, and water-electrolyte imbalance. In the context of colitis due to Clostridium difficile (CD), Dallal[6] defined FC according to the existence of tachycardia, need for mechanical ventilation, oliguria, and hypotension requiring vasopressor treatment.

When associated with total colic dilatation or segmental dilatation of more than 6 cm in the absence of obstruction, the condition is considered a toxic megacolon. This entity, unlike FC, is perfectly defined and requires surgical treatment within 24–72 h.[7] Both are serious situations that require specialized hospital care with intensive monitoring by gastroenterologists and surgeons.

This manuscript is a review of the relevant articles obtained from a search of the literature on the MEDLINE database between 1990 and 2014, using the search terms: ''fulminant colitis'', ''toxic megacolon'', ''severe colitis'', ''ulcerative colitis'', ''severe ulcerative colitis'', and ''Clostridium difficile colitis''.

## Etiology

The most frequent causes of fulminant colitis are UC and infectious colitis, although there are reports of cases caused

Inflammatory causes:

- Ulcerative colitis
- Crohn's disease

Infectious causes:

- Bacterial: pseudomembranous colitis due to Clostridium difficile, Salmonella, Shigella, Yersinia, Campylobacter, etc.
- Viral: Cytomegalovirus
- Parasites: Entamoeba histolytica, Cryptosporidium

Other causes:

- Ischemia
- Drugs
- Radiotherapy

**Fig. 1 – Causes of fulminant colitis.**

by Crohn's disease, ischemic colitis, radiation colitis, and colitis induced by drugs or vasculitis[2] (Fig. 1).

Historically, it had been almost exclusively associated with inflammatory bowel disease (IBD) and specifically UC. In recent decades, however, the incidence of infectious FC has increased[8–10] along with the higher incidence of colitis due to CD, which is more aggressive and refractory.[11,12] Nonetheless, in our setting, infection due to CD is a much less frequent cause of infectious colitis and severe colitis than in the United States. While their incidence has not been properly evaluated, existing data show that we are still far from the problem seen in American hospitals, although we have also witnessed a progressive increase.[13] Clostridium difficile is a spore-forming, Gram-positive anaerobic bacillus that grows by forming colonies and can cause anywhere from diarrhea without colitis to FC. Approximately 3%–8% of CD disease develops FC and many of these patients require urgent colectomy.[14] The main risk factor for developing CD disease is prior antibiotic use. Clindamycin, cephalosporins, and fluoroquinolones present the highest risk. Other risk factors have been reported, such as advanced age, prolonged hospitalization, immunosuppression, IBD and the use of protein pump inhibitors.[11,14] Other infectious agents have also been less frequently implicated in the cause of FC, including bacteria (Salmonella,[15] Shigella,[16] and Campylobacter[17]), as well as viruses (Citomegalovirus[10] [CMV] and Herpes simplex[18]), and parasites (Entamoeba hystolytica[19]).

The possible role of some infections as triggering factors for episodes in patients with IBD has not been clearly proven,[8,9] although it is recommended to rule out a possible overinfection in patients with active IBD.[20] The most frequently involved agents are CD and CMV.[21] The increased incidence of CD infection among patients with IBD is well known, and IBD is an independent risk factor for infection.[11,14] Patients with UC in treatment with corticosteroids or immunosuppressants present elevated risk for CMV infection.[10,21]

## Diagnosis

Patients with FC present a series of dilemmas for the specialists who treat them. The first is to determine whether it is an IBD exacerbation, in which case the immunosuppressant treatment should be intensified, or, on the contrary, an infectious colitis, in which case this strategy can worsen the patient's condition. This doubt can arise at the onset or in a patient who has been previously diagnosed with IBD.

The first step should be a thorough, detailed patient medical history to acquire information about any known personal or family history of IBD, epidemiologic data that raise the suspicion of an infectious origin (contact with other people with diarrhea, trips or previous antibiotic use), use of medications or drugs that could cause colitis (non-steroid anti-inflammatories or cocaine), or vascular diseases or vasculitis that could be related with an ischemic origin.

Lab work usually detects anemia and leukocytosis with neutrophilia (occasionally leucopenia due to the septic state). Electrolytic alterations are common due to dehydration, as is hypokalemia due to the increased excretion of potassium or colon mucous inflammation. Hypoalbuminemia is also

common, especially in chronic patients. Erythrocyte sedimentation rate and C-reactive protein are usually high, as both are systemic inflammation markers.

Likewise, fecal samples should be taken for culture and for CD toxin determination. The diagnosis of CD is established by a combination of clinical and laboratory findings. Cytotoxicity assay, with its very high sensitivity and specificity, is considered the gold standard laboratory test. But, given its laborious nature and response time of more than 48 h, ELISA is usually used in clinical practice for the detection of toxins A and B; it provides results that are quick and easily reproducible, although less sensitive. PCR (polymerase chain reaction) is a sensitive and specific molecular biology technique, although it is more expensive.[22–24]

Simple abdominal radiography is useful for detecting and monitoring colonic dilatation, estimating the extension of the inflammatory process and ruling out complications. Abdominal computed tomography (CT) is used to determine etiology, identify possible complications and define the differential diagnosis. The findings are usually nonspecific: wall thickening, colonic dilatation, accordion sign, target sign, ascites, etc.[25] CT scans are essential in seriously compromised patients that do not present diarrhea.

Complete colonoscopy is absolutely contraindicated; sigmoidoscopy with biopsy is usually sufficient for histologic and microbiologic studies and has less risk. Nonetheless, there are authors who defend the safety of a complete colonoscopy in these situations.[26] It is essential for an etiologic diagnosis, with the finding of endoscopic patterns that detect possible IBD and pseudomembranous or ischemic colitis. Infectious colitis can imitate the endoscopic findings of IBD and should be differentiated with clinical, stool culture and histologic findings.

## General Treatment

In the treatment of FC, it is essential for there to be a close collaboration between physicians and surgeons, along with a strict follow-up by both. The patient should know his/her options, as well as their positive and negative aspects.[2] Time is crucial when deciding on a surgical approach; hasty surgery without previous medical treatment can be detrimental to the future quality of life of the patient, but it is less dangerous than a surgical decision made after the onset of complications. If the patient requires surgery due to the presence of perforation, mortality can reach 30%.[27]

The objectives are to reduce colonic distension in order to avoid perforation, correct water–electrolyte imbalance and nutritional alterations, and treat precipitating factors and systemic affectation.

Treatment begins with close monitoring of the patient, including daily evaluation of the clinical situation, abdominal examination, level of consciousness and vital signs. Likewise, lab work is recommended every 48 h as well as radiographic studies in cases of bowel dilatation.[28]

Electrolytic alterations should be identified and corrected as soon as possible with adequate fluid and electrolyte replacement, especially potassium and magnesium, as their deficiencies can precipitate toxic megacolon.[29] Blood

transfusion should be restricted and used only in cases of severe anemia.[20]

The use of antibiotics in non-infectious colitis is still controversial. Although some authors justify their use due to the risk of transmural extension, microperforation, and bacteremia, the recommendation for their use cannot be generalized given the heterogeneity of the available studies.[30,31] Nonetheless, in severe cases with a high risk of perforation, and especially in cases of megacolon, practically all experts recommend using antibiotic treatment aimed at anaerobes and Gram-negative germs. Depending on the local rates of resistance, cefotaxime and metronidazole, ciprofloxacin and metronidazole, imipenem, meropenem or piperacillin–tazobactam are recommended.[30]

Nutritional support is important. *Nil per os* is not effective as a primary therapy and, except in cases of absolute oral intolerance, intestinal obstruction or extremely severe patient condition, oral intake should not be suspended.[32] If complete nutritional and caloric content cannot be guaranteed, enteral nutrition is preferable, either as a supplement or as the only nutritional source. Parenteral nutrition is more expensive and entails a higher risk of infection and of thromboembolic phenomena.[33]

Antiperistaltic agents and narcotics should be avoided as they can contribute to ileus, exacerbate colitis and precipitate toxic megacolon.[29]

Antithrombotic prophylaxis with low molecular weight heparin is required in all patients.[34]

## Specific Treatment

### Colitis Due to Inflammatory Bowel Disease

In severe cases of UC, the patient should be hospitalized.[4,20] While immediate measures are being taken, a strategy should be developed that includes additional options in case the initial measures fail, as well as possible mid- to long-term treatment. In doing so, it is necessary to review all the diagnostic information and data that may be of interest in the decision-making process. Furthermore, it is practical to include diagnostic procedures that analyze the adverse effects of infliximab, cyclosporine, or azathioprine, as this would allow the treatments to be begun with greater safety, and any necessary preventive measures could be taken.[28]

In most cases, the initial treatment is based on the administration of intravenous corticoids at a dose of 1 mg/kg/day of prednisone[35,36] (Fig. 2), except in situations of absolute contraindication due to previous acute toxicity or surgical emergencies. Corticoids can be administered in single or fragmented doses or in continuous perfusion, and no differences have been demonstrated between these different methods.[35] In patients who cannot be treated with steroids, cyclosporine (4 mg/kg) can be used as a first line of treatment with similar results.[37]

From day one, it is recommended to set a time to evaluate response. This is usually done between the third and fifth days after the start of treatment, and most authors tend to do an initial evaluation after 72 h.[28] If remission is not reached, there are several indices that are able to predict the probability of
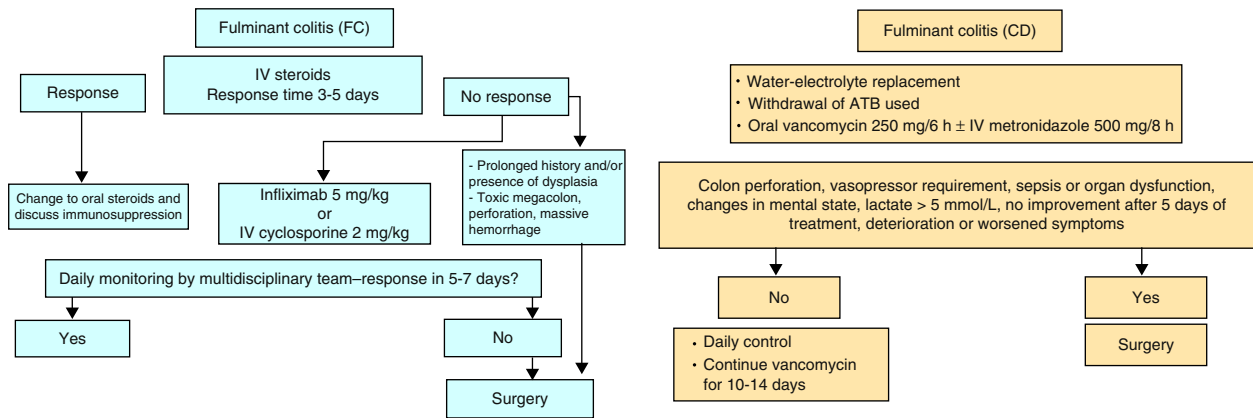
**Fig. 2 – Medical treatment of fulminant colitis.**

response if the corticosteroid treatment was prolonged. The Ho index estimates the probability of response to corticoids according to the number of stools, the presence of colonic dilatation and hypoalbuminemia.[38] Another simple model based on 4 parameters (rectal bleeding, PCR, platelet count and number of stools) evaluated on the third day can precisely predict if the patient needs a change in treatment.[39] On occasions, the situation is very clear, and it is proposed to initiate a new treatment between the third and fifth days. In other instances, the decision is not as clear, and a reevaluation is made between the 5th and 7th days. If remission is not reached by the 7th day, it is best to initiate an alternative treatment.

Having reached this point, it is very important to rule out other causes of resistance to corticosteroid treatment, especially CMV or CD infection, by means of rectal biopsy and fecal determination of toxins, respectively.

When corticoid treatment fails, there are 3 alternatives: cyclosporine, infliximab or surgery. There are no studies comparing these options, which would enable us to make clear recommendations. The decision should be made by the team, and it is also very important to take into consideration the patient's opinion. Factors that favor surgery include a long history of disease or the presence of dysplasia in previous examinations, as well as 3 clinical situations: toxic megacolon, perforation, and massive hemorrhage. In almost all cases, however, and excluding these 3 situations, medication options should be attempted, opting for 2 possible second lines of treatment: cyclosporine and anti-TNF biological agents.

Cyclosporine at a dose of 4 mg/kg/day (intravenous) has been demonstrated to be effective at inducing the remission of corticosteroid-resistant severe UC.[40] Lower doses of 2 mg/kg/day have shown a similar efficacy with fewer side effects,[41] so they are currently recommended. The dose can be adjusted individually up to a maximum of 4 mg/kg/day depending on the levels obtained and toxicity.

From among the available anti-TNF, infliximab offers the greatest clinical experience. It has been shown to be more effective than placebo in severe episodes of UC, specifically in those that are corticosteroid-resistant, with an induction dose of 5 mg/kg, followed by another dose 2 weeks later and a third dose after 6 weeks.[42] There has only been one clinical trial

about adalimumab in UC which showed it to be more effective for achieving clinical remission in moderate to severe episodes that did not respond to corticosteroids or immunomodulators (although with small differences versus placebo).[43] Nonetheless, we do not have data for severe episodes. For some months now, there is a third anti-TNF available for the treatment of moderate-severe ulcerous colitis: golimumab.[44]

The choice between infliximab and cyclosporine cannot be based on efficacy since the studies that compare them show similar results.[45] If the patient develops an acute episode while already in treatment with thiopurines, infliximab is indicated. In the remaining cases, either of the 2 could be chosen depending on local factors, such as experience and availability of blood level determinations for cyclosporine, and clinical factors that could contraindicate one or another treatment.

Regardless of the medication option chosen, another evaluation time must be planned, and the most reasonable moment is 7 days after the start of the new treatment. At this point, once again there are no set rules; if the patient's status worsens or there is a total lack of improvement, surgery is a reasonable option; if there is remission, the next step is maintenance. Nevertheless, intermediate situations are rather frequent. Thus, patients who do not respond to cyclosporine may avoid surgery with the use of infliximab; on fewer occasions, the opposite has been true.[46]

As for the use of other treatments, more studies are needed to obtain consolidated conclusions. Oral tacrolimus seems effective at inducing a response in acute episodes of UC, even those that are corticoid-resistant, but the quality and quantity of the evidence available are limited. In a single controlled trial in hospitalized patients with active moderate-severe UC (corticosteroid-resistant or corticosteroid-dependent), only at high doses was it significantly superior to placebo with a dose–response effect.[47] In a systematic review of the observational series available, without defining how many patients were severe or resistant to corticosteroids, 53% of patients treated reached remission.[48] Although some authors defined leukocytapheresis as an innocuous and effective system, most of the studies done are poor in quality. Response measurements were heterogenous, and assignment to treatment groups or concomitant treatments was not blinded, so proper assessment is difficult. The data from the only blinded

randomized study do not confirm their effectiveness,[49] so they cannot be recommended for inducing remission, especially in severe episodes.

Surgery is usually reserved for patients who do not respond to treatment, although the possibility of surgical intervention should be assessed from day one. The most commonly performed procedure is subtotal colectomy and end ileostomy. Once the patient has recovered, the intervention is completed with proctectomy, and ileoanal pouch anastomosis.[27]

In the prebiological era, it is estimated that only 60% of patients who responded to medication were colectomy-free after 2 years. Therefore, some authors recommended elective proctocolectomy with ileoanal anastomosis in patients with a good initial response to conservative treatment, which is a surgery with less morbidity and better quality of life than emergency procedures.[50] Nonetheless, today's biological treatment has improved the short-term prognosis of these patients, and the 2-year colectomy rate has dropped to 10%–20%,[51] so the aforementioned recommendation is no longer valid. Studies are needed to analyze the long-term impact of prolonged biological treatment in the natural history of patients with severe UC.

### Clostridium difficile Colitis

Many cases of infectious colitis are self-limiting, but others can become complicated and lead to FC. In addition to the previously commented measures, once the pathogen is identified, specific antibiotic treatment should be initiated. In the case of colitis due to CD, the previously used antibiotic that triggered the symptoms should be withdrawn.[52]

The antibiotics recommended for the treatment of colitis due to CD are metronidazole and vancomycin (Fig. 2). In mild or moderate cases, both are equally effective, with no demonstrated superiority of either one; therefore, the choice is usually oral metronidazole, which is much less expensive. In acute colitis, however, oral vancomycin is superior to metronidazole, with a response rate of 90%–100%, making it the option of choice.[53] Intravenous vancomycin is not effective; in patients who do not tolerate oral intake, vancomycin can be administered with a nasogastric catheter or even by enema.[54] In fulminant disease, its effectiveness can be increased by adding intravenous metronidazole.[11]

The treatment recommended for refractory FC is unknown. New strategies as well as antibiotics (fidaxomicin,[55] tigecycline,[56] and rifaximin[57]) and immunoglobulins[58] have been used with different results, although there are no data about severe cases. Fecal microbiota transplantation has shown promising results in the treatment of recurrences, but there is likewise no experience in severe colitis.[59]

In patients who do not present improvement in 24–48 h, surgical assessment is necessary. Early diagnosis and surgical treatment with subtotal colectomy and end ileostomy are important to reduce mortality.[60,61] Surgical treatment must be considered in cases of colon perforation, vasopressor requirements, sepsis or organic dysfunction, mental changes, leukocytosis higher than 50 000/mL, lactate >5 mmol/L, lack of improvement after 5 days with medication and worsening clinical tests.[62]

Neal[63] and other authors propose a less invasive laparoscopic alternative involving colonic lavage with polyethylene glycol through a loop ileostomy and follow-up with vancomycin enemas and IV metronidazole, which has provided good results (mortality 19% and only 3 subtotal colectomies).

Different studies have demonstrated that early intervention before the onset of shock and organ failure can improve survival in FC due to CD. Different risk factors have been proposed for the development of FC in the context of colitis due to CD,[64] as well as predictive factors for mortality after colectomy.[65] Neal et al.[63] propose a scoring system based on 12 clinical criteria to identify severe patients in whom it is necessary to consider colectomy: (1) immunosuppression (1 point); (2) abdominal distension or pain (1 point); (3) hypoalbuminemia <3 g/dl (1 point); (4) fever (1 point); (5) ICU admittance (1 point); (6) wall thickening or ascites on abdominal CT scan (2 points); (7) leukocytes >15 000 or <1500 (2 points); (8) decline in renal function with an increase of 1.5 times baseline creatinine (2 points); (9) signs of peritoneal irritation (3 points); (10) need for vasoactive drugs (5 points); (11) need for ventilation (5 points); and (12) disorientation, confusion (5 points). The condition is then classified as mild (1–3 points), severe (4–6 points) and complicated severe (7 or more points), thus identifying the patients who would most benefit from early surgical assessment.

## Conclusion

FC is a serious condition that requires intensive management by a multidisciplinary team of surgeons and gastroenterologists. From the beginning, it is necessary to define a strategy to follow, including additional options if the immediate measures fail, along with mid- and long-term treatment.

In our setting, the most frequent etiologies are UC and infectious colitis; with regards to the latter, we are currently seeing an increase in the incidence and severity of colitis due to CD.

During diagnosis, it is very important to determine whether the condition is an IBD exacerbation or infectious colitis, since the general therapeutic measures will be the same but will require diametrically opposed specific measures.

In UC, the initial treatment is based on the administration of intravenous corticosteroids. It is very important to evaluate early response in order to establish a second line of treatment with cyclosporine or infliximab, except when there is a complication that indicates surgical treatment, which will also be indicated if these latter measures fail.

In severe colitis caused by CD, the recommended treatment is oral vancomycin associated with intravenous metronidazole. Early patient response should be monitored intensively in case it was necessary to perform colectomy.

## Conflict of Interests

The authors have no conflict of interests to declare.

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