Compagnoni et al., Res Rep Gastroenterol 2020, 4:4
DOI: 10.37532/rrg.2020.4(1).112

Research and Reports in Gastroenterology

Review Article

A SCITECHNOL JOURNAL

Toxic Megacolon: Management Challenges

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Received date: June 15, 2020; **Accepted date:** June 25, 2020; **Published date:** July 5, 2020

Abstract

Toxic Megacolon (TM) is a non-obstructive dilatation of the colon, either total or segmental, associated with systemic toxicity. Even though it is best known as a consequence of Inflammatory Bowel Diseases (IBD) and it is mostly related to Ulcerative Colitis (UC), it may be also a complication of other conditions, such as infectious diseases. In fact, the epidemiology of TM has lately changed: there has been a recent increase in the number of reports of TM associated with pseudomembranous colitis (PMC) and, hereupon, the Clostridium difficile has spread as one of the most important causes of TM. However, more precise data about the epidemiology of TM should be collected. Due to its systemic involvement, TM is a severe and life-threatening condition that still represents a big challenge for both physicians and surgeons. A multidisciplinary team should take care of the patient with a close monitoring and the surgeons should be involved from the very onset of TM, since it often requires a surgical treatment and the establishment of the right timing to perform it can be very difficult. Even though the mainstay of the therapy is the treatment of the underlying cause of TM, the milestones of the current therapy are mostly extrapolated from old trials about IBD patients, especially those who are affected by severe UC. Therefore, one of the main difficulties about management of TM is the lack of recent randomized clinical trials comparing different approaches to TM.

Keywords Toxic Megacolon; Inflammatory Bowel Diseases; Clostridium difficile colitis

Epidemiology

TM is defined as a total or partial non-obstructive dilatation of the colon, equal or larger than 6 cm, and the additional presence of systemic toxicity[1]. The incidence of TM depends on the etiology and, since there are many different causes of TM, precise data about its epidemiology are still lacking and there are not many recent studies available. In literature, most of the studies involve patients affected by IBD and TM is more frequently related to UC. A retrospective study conducted in 1985 reported that among 1236 patients with IBD,75 developed TM (6%); more specifically 10% of those affected by UC and 2,3% of those with Crohn's disease[2]. A more recent prospective study analyzed 45 patients with severe UC: 24 of them (53%) had gastrointestinal distension and 7 of these 24 (15% of 45 patients) had TM on admission or developed it few days later[3].

Another study reported that TM was the first clinical presentation of an undiagnosed UC in 13% of the patients[4]. The prevalence of TM is higher among women (56.4%) than men (43.6%), it is more common among whites (79.7%) and the average age of onset is 62.4 years. Also, the most common causes of hospitalization are IBD (51.6%), septicemia (10.2%) and intestinal infections (4.1%), with an overall in-hospital mortality of 7.9%[5]. Nonetheless, during the last years, the epidemiology of TM has been changing, with an increase of its incidence associated with infectious conditions, especially C. difficile colitis: the changes might be due to the more frequent use of broad-spectrum antibiotics and the emergence of a hyper virulent C. difficile strain (BI/NAP1/027)[6]. According to several studies conducted in 2008, the incidence of TM in pseudomembranous colitis is between 0.4% and 3%. Also, the mortality rate of TM secondary to C. difficile colitis is considerable and varies from 38% to 80%[7-9].

Etiology

Besides IBD, and more specifically UC, there is a wide array of conditions that may be complicated by colonic dilatation. In fact, a study conducted in 2006 retrospectively examined 70 patients surgically treated for TM between 1985 and 2004, with UC emerging as the main cause (46%), followed by infectious colitis (34%) and ischemic colitis (11%); only one case (2%) was related to Crohn's disease [4]. Among the infectious conditions, there are bacterial colitis (C. difficile, Salmonella, Shigella, Campylobacter), viral colitis (Cytomegalovirus(CMV))and parasitic colitis (Entamoeba) [10-14]. In particular, CMV has been associated to TM in IBD [15]. C. difficile and CMV infections are the main cause of TM in patients with HIV infection and AIDS [16]. There are also case reports of TM in patients affected by Aspergillosis, Rotavirus infection and a toxic colonic dilatation developed in a case of Hemolytic-Uremic Syndrome caused by E. Coli O157[17-19]. Further etiological factors include ischemic colitis, Behçet's disease and malignancies such as colonic lymphoma and Kaposi's sarcoma [20-23]. Also cytotoxic chemotherapy is reported as a potential cause of TM and a case series describes TM after an autologous transplantation in four patients with amyloidosis [24,25].

Pathogenesis

The exact mechanisms causing TM are not fully understood, yet. The association between an inflammatory condition of the colon and the decreased contractility of smooth muscle is well established. Different inflammatory mediators, such as vasoactive intestinal polypeptides, substance P and leukotrienes, may be involved in TM development: the change of the colonic response to these chemical mediators is related to a decreased smooth muscle contraction and may inhibit colonic motility[26-28]. Also nitric oxide (NO) induces colonic smooth muscle relaxation[29]. An increased expression of inducible nitric oxide synthase (iNOS) has been found in animal models of colitis, in specimens of the colonic mucosa of patients with UC and also in the muscularis propria of patients with TM[30-32]. It has also been reported that the mucosal cells of patients with UC release significantly higher levels of H_2O_2, interleukin (IL)-1β and NO into the submucosal layer compared to the mucosal cells of control patients[33]. Precipitating factors for TM include medications which reduce the gut motility (narcotics and anticholinergics), electrolytic

doi: 10.37532/rrg.2020.4(1).112

derangements (e.g. hypokalemia) and diagnostic procedures such as barium enema and colonscopy [34].

Diagnostic Approach

The diagnosis of TM is based on a combination of clinical signs of systemic toxicity and signs of colonic dilatation in imaging investigations.

Table 1 Table 2

History
Signs of IBD and acute colitis
Abdominal pain
Bloody diarrhea
Vomiting
Weight loss
History of previous exacerbations
Extraintestinal manifestations
Possible exposure to enteric pathogens
Family, environment
Recent travels
Medications, especially:
Antibiotics
Antidiarrheals
Anticholinergics
Opiates
Immune status
Chemotherapy, malignancy
HIV
Physical examination
Abdominal pain, tenderness, distension
Constipation, obstipation
Reduced bowel sounds
Fever
Tachycardia, hypotension
Mental changes
Laboratory investigations
Inflammation
Elevated white blood cells count
Elevated C-reactive protein
Elevated erythrocyte sedimentation rate
Anemia
Electrolyte imbalances
Blood culture
Fecal screening for pathogens
Stool sample for Clostridium difficile culture and A/B toxin assay

Table 1: Diagnostic Approach to Toxic Megacolon.

Clinical conditions and laboratory findings

The most used criteria for the diagnosis of TM are: (a) radiographic evidence of colonic dilatation greater than 6 cm, especiallyin the transverse colon; (b) any three of the following: fever (>38.6 °C, 101.5 °F), tachycardia (>120 beats/min), leukocytosis>10500/μl, anemia; and (c) any one of the following: dehydration, altered level of consciousness, electrolyte imbalances, hypotension[35]. Frequent clinical findings are abdomen tenderness and reduced bowel sounds, while signs of peritonitis may indicate perforation. As concern laboratory findings, there are several but non-specific abnormalities which reflect systemic toxicity: increased erythrocyte sedimentation rate and elevated C- reactive protein are common features. Electrolyte imbalances are one of the main criteria, and hypokalemia and hypoalbuminemia are associated with severe diarrhea, volume depletion and a poor prognosis. Even though a severe hypokalemic alkalosis has been considered a relevant marker of severity and it can be used during the follow up of these patients, it is not considered mandatory[36].

Clinical criteria for toxic megacolon (by Jalan 35)
Main criteria (at least 3 of the following)
Fever > 38,6°C
Tachycardia > 120 bpm
Leukocytosis >10500/μl
Anemia
In addition, at least one of the following:
Dehydration
Altered level of consciousness
Electrolyte imbalances
Hypotension
Imaging studies
Plain abdominal imaging
Colonic dilation > 5,5 cm
Disturbances or loss of colonic haustration
Air-fluid levels
Small bowel distension
Additional CT findings
Colonic wall thickening
Pericolic stranding
Complications: abscesses, perforation
Abdominal Ultrasound

Table 2: Diagnostic criteria of Toxic Megacolon.

Imaging and endoscopy

Abdominal radiograms

Typical features in plain abdominal radiograms include dilatation greater than 6cm and ascending and transverse colon are usually the most dilated tracts; air-fluid levels and loss or disturbance of colonic haustration could also be found. In pediatric IBD patients over 11 years old with clinical signs, a transverse colonic dilatation greater than 56 mm is indicative of TM, while in younger patients a dilatation greater than 40 mm is unlikely[37&38]. Abdominal radiograms should be repeated every 24 hours in order to evaluate the response to medical therapy.

Ultrasounds

There are not specific ultrasonographic features for TM, but ultrasounds may be used if TM is suspected, due to the wide availability of this technique. Possible US findings may be increased diameter (≥ 6cm) of the colon, thin colonic walls and the loss of the haustration[39].

CT scans

It has been showed that CT scans can be useful to detect signs of severe colitis (diffuse colonic wall thickening, thickened haustra with high- and low-density bands, multilayered appearance, hyperemic mucosa, pericolic stranding) and the additional detection of colonic dilatationis indicative of developing TM. CT scans are also more reliable than plain abdominal radiograms, as they can find abdominal complications both clinically silent and not evident on radiograms[40]. However, CT scanning has been proved not to make a real contribution in the management of patients with severe acute colitis, since it does not help to differentiate patients who need medical or surgical intervention[41].

Colonscopy

Endoscopic examination is generally contraindicated because of the high risk of colonic perforation, but sigmoidoscopy without air inflation might be valuable to exclude pseudomembranous colitis, together with C. difficile toxin assays[42].

Management of Toxic Megacolon

One of the main difficulties in the management of TM is the lack of recent randomized controlled trials investigating new treatments and comparing them with the current ones. Because of the severity of this condition, a multidisciplinary team approach with close monitoring and supportive care is fundamental: surgeons should be consulted from the very beginning and the coordination of medical and surgical team is the mainstay to avoid delays in the treatment and fatal complications.

Medical management

The main goals of medical therapy are the treatment of the underlying cause of TM and the avoidance of further complications, especially colonic perforation. Since TM is more common in IBD patients, TM in acute severe UC must be treated with high-dose intravenous (IV) steroids, which should be started immediately: the recommended dose is 400 mg/die of hydrocortisone (100 mg every 6 hours) or 60 mg/die of methylprednisolone for maximum 5 days [1,4,43]. There is no evidence of benefit in higher doses or longer therapy [44-46]. Nevertheless, it must be remembered that the failure rate of intravenous steroids in severe colitis is about 20%-40% and physicians cannot predict response to therapy based upon individual's clinical features or previous presentations [47]. Other measures that are considered appropriate in addition to IV steroids include intravenous fluids and electrolytes replacement (especially correction of hypokalemia and hypomagnesaemia, since they can promote colonic dilatation) [48]. Hemoglobin levels should be maintained above 8 g/dl [49]. Medications like anticholinergics, opiates and non-steroidal anti-inflammatory drugs must be discontinued, as they are considered to worsen the course of the disease [1, 50-54].Prophylaxis of deep vein thrombosis with low-dose heparin should be administered in patients with TM complicating an IBD, which is itself an independent risk factor for venous thromboembolism [55-59]. In acute severe UC bowel rest is not generally recommended, since there are no significative differences in remission rate and need for surgery between patients treated with enteral nutrition and those treated with parenteral nutrition: enteral nutrition is safe and associated with fewer complications than parenteral nutrition in these patients [60&61]. However, bowel rest is usually necessary to reduce colonic atony in the setting of TM and colonic dilatation. Even though broad-spectrum antibiotics are largely introduced at the onset of TM, it must be pointed out that controlled trials with oral or intravenous antibiotics (metronidazole, tobramycin, ciprofloxacin or vancomycin) added to conventional therapy in patients with severe UC have shown no changes in the outcome [62-64]. Conversely, if TM in patients with IBD is supposed to be related to C. difficile infection, stool cultures and toxin assay should be performed and empirical oral vancomycin should be given until the infection is excluded, since C. difficile has been associated with an increased morbidity and mortality. Patients affected by IBD who develop a C. difficile infection are frequently treated with antibiotics and immune modulators, but this combination is often associated with a worse outcome, so immunosuppressive therapy should be stopped when possible [65-69]. Also CMV infection must be investigated and treated– if positive – with ganciclovir (5 mg/kg i .v. 2 times per day) or valganciclovir (900 mg 2 times per day) until the virus is not detectable anymore or until clinical remission is achieved after at least three weeks of treatment. In fact, CMV often occurs in patients with acute severe UC and it is usually associated with a steroid-refractory disease course. Active CMV infection in IBD patients is commonly associated to a poor outcome and surgical treatment is often required [70-74]. As already said, many patients do not respond to intravenous steroids. Even if a rescue therapy is often attempted in patients with severe steroid-refractory UC, there are no strong evidences in literature about the efficacy of infliximab or cyclosporine in IBD patients who already have developed TM and it may be imprudent to delay surgery in favour of a medical rescue therapy. Moreover, TM itself is one of the complications for which an emergency surgical treatment is indicated, such as perforation and profuse bleeding. As concern C. difficile infection, it is recently spreading as a cause of TM also in non-IBD patients and it should be investigated. The treatment consists in oral vancomycin 500 mg 4 times a day and intravenous metronidazole 500 mg 3 times a day. The combination of these two antibiotics has been proved to reduce mortality from 36% to 16% [75]. However, regardless of the cause of TM, it must be remembered that there is a very limited window of opportunity for medical treatment to work and, without clinical and radiological improvement within 24-48 hours, early colectomy will be necessary.

Surgical therapy

Even though a prompt medical therapy is the mainstay to avoid surgery, a delay of surgical treatment can increase the risk of complications. Therefore, the choice of the optimal timing to perform surgery can be very challenging. Different results in literature lead to different attitudes towards the surgical approach, even though several authors agree that surgical therapy should be offered as soon as possible – since it is considered to decrease operative mortality from 20% to 7% and overall mortality from 11,3% to 4,5% having a more favorable outcome– and medical treatment should be mostly thought as a preparation for impending surgery [76-78]. Colonic perforation is the most important predictor of mortality, but also female gender, age over 40 years old, hypo albuminemia, high blood urea and low serum carbon dioxide levels are also associated with higher mortality in patients undergoing surgery [2]. Also neurological disorders,

doi: 10.37532/rrg.2020.4(1).112

coagulopathies, chronic pulmonary disease, congestive heart failure and renal failure represent independent predictors of in-hospital mortality [5]. Surgery in C. difficile infections complicated by TM is a rare eventuality because of the effectiveness of specific anticlostridial therapy. It is required in about 20% of the patients with severe infection but it frequently leads to a fatal outcome [79 & 80]The most common surgical procedure in emergent setting of TM is total abdominal colectomy with end ileostomy. Proctectomy should not be performed because it increases the procedural time, risk of injury to pelvic nerves, risk of bleeding, and negatively affects the future of ileal-pouch-anal-anastomosis (IPAA) [81]. In fact, the staged approach decreases the incidence of pelvic sepsis caused by anastomotic leak at the ileal-anal anastomosis and its resultant long-term effects on pouch function [82]. The three-staged (total colectomy and end ileostomy; proctectomy, IPAA and DLI; DLI reversal) has been compared to the two-staged procedure (total proctocolectomy and IPAA with diverting loop ileostomy (DLI); DLI reversal):the overall complication rates were similar, while infectious specific complications were higher in the two-stages group (38.2% vs 21% in the three-stages group, $p< 0.05$). The three-stages approach provides also an opportunity to optimize the patient's nutritional status and wean off medical therapy after total abdominal colectomy, prior to proceeding with completion proctectomy and IPAA creation [83]. Therefore, in emergency surgical treatment, three-staged operations are widely performed. Emergency colectomy in UC is associated with a mortality rate of 5-8% and morbidity rates of 27-51% and a study showed a lower mortality rate when surgery was performed within 5 days from the beginning of intensive medical therapy [84-86]. Mortality rates are higher in case of colonic perforation. Risk factors that increase morbidity are protracted medical management and hospitalization prior to surgery.Age over 64 years, presence of more than 2 comorbidities and emergency colectomy are independent predictors of post-operative complications [87].

Conclusion

The management of toxic megacolon (TM) still represents a great challenge in medicine.

In fact, not only TM is a life-threatening condition itself, but also the lack of recent data makes its management even more difficult. The most important approach is the identification and the treatment of the underlying condition; also, a strict surveillance should be performed by a multidisciplinary team of expert physicians, radiologists and surgeons, who must be involved from the very onset of TM. Since TM is more frequent in IBD patients, the mainstay of the current protocols is the administration of high doses of intravenous steroids (100 mg of hydrocortisone every 6 hours or 60 mg/die of methylprednisolone)and an intensive monitoring of fluids and electrolyte balance. Hemoglobin levels must be maintained above 8 g/dl and prophylaxis of deep vein thrombosis with low-dose heparin should be also administered. When suspected, C. difficile infection must be investigated and an empirical treatment with oral vancomycin should be administered until the infection is excluded. Also CMV infection should be considered and eventually treated with ganciclovir or valganciclovir. Bowel rest is usually necessary to reduce colonic atony. Moreover, it must be remembered that the epidemiology of TM is changing, with an increase of severe infections caused by C. difficile. Therefore, C. difficile must be suspected especially in patients who went under antibiotic therapies; in this case, steroids must be avoided and antibiotics must be administrated (oral vancomycin 500 mg 4 times a day and intravenous metronidazole 500 mg 3 times a day).Even though medical therapy usually represents the first approach to TM and it may improve the clinical conditions of the patient, TM represents an indication for surgery in patients with IBD or severe C. difficile colitis. The best surgical technique is the three-staged total colectomy with end ileostomy and the decision about the best timing to perform it may be not so easy. It must be also pointed out that TM may have different causes, e.g. ischemic colitis and other bacterial and viral infections, but their role is still to be clarified. In conclusion, there are not many recent studies about medical therapy of TM (since a delay in surgical treatment can be fatal) and the few available information's are extrapolated from trials conducted among patients with severe UC or C. difficile colitis. In any case, TM therapy must be targeted to its cause and further prospective studies about its pathogenesis and treatment are highly desirable.

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