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REVIEW

Toxic Megacolon: Background, Pathophysiology, Management Challenges and Solutions

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Abstract: Toxic megacolon (TM) is one of the fatal complications of inflammatory bowel disease (IBD) or any infectious etiology of the colon that is characterized by total or partial nonobstructive colonic dilatation and systemic toxicity. It is associated with high morbidity and mortality, and surgical management is necessary for the majority of the cases. An accurate history and physical examination, plain radiographs of the abdomen, sigmoidoscopy, and, most important of all, awareness of the condition facilitate diagnosis in most cases. Operative intervention is warranted when massive hemorrhage, perforation, or peritonitis complicate the clinical scenario or medical therapy fails to control the disease. We sought to review the management challenges of TM and its possible management strategies in this article.

Keywords: toxic megacolon, inflammatory bowel disease, management challenges and solutions for toxic megacolon, *Clostridium difficile* colitis, nitric oxide synthase

Introduction

Toxic megacolon (TM) is a potentially fatal condition defined as an acute colonic dilatation, greater than 6 cm in diameter, of the transverse colon, and loss of haustration on radiologic examination in a case of severe colitis.[1,2] Despite its low prevalence, the outcomes are still unsatisfactory, with in-hospital mortality of 7.9%.[3,4] Our review aims are to highlight the crucial aspects and recent advancements regarding epidemiology, pathogenesis, and management of TM.

Epidemiology

The exact prevalence of TM is underreported. However, the prevalence continues to increase with age. The most common cause of hospital admission included IBD (51.6%), followed by septicemia (10.2%) and intestinal infections (4.1%).[4] Some studies reported that the incidence of TM is higher in patients with Ulcerative Colitis (UC) compared to Crohn's disease (CD) (8–10% in UC compared to 2.3% in CD).[5,6] In contrast, others reported its incidence in CD to be higher than in UC (4.4–6.3% in CD compared to 1–2.5% in UC).[7] Incidence of TM due to *Clostridium difficile* (*C. diff*) was estimated to be 0.4–3% before 1990; however, it is 4.3% after 1990.[5,6] Female gender, age more than 40 years, hypoalbuminemia, acidosis, and high blood urea nitrogen levels are associated with high mortality in a previous study.[8] The mortality rate in patients with TM is variable. Before 1976, the mortality rate for TM was 27% in medically managed cases, however, as low as 19% in surgically managed cases, which dropped dramatically to a mere 0–2% in

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patients with IBD. Early identification and intensive management may have contributed to the reduced incidence and mortality of TM in IBD.[9] Patients with fulminant infection require surgical intervention in up to 20% of cases, carrying mortality rates between 35 and 80%.[10,11] Colonic perforation is one of the most important predictors of mortality; 44% of patients underwent emergent colectomy after perforation, while only 2% of patients without perforation needed the procedure.[8]

Etiology

UC and CD are important etiologies for TM making it evident that any inflammatory condition of the colon could predispose to TM.[5,25,26] TM is a rare but potentially lethal complication of any disease that causes inflammation of the colon, including IBD and Infectious etiologies such as *C. diff* and cytomegalovirus colitis.[5,27,28] Other precipitating factors for TM include anti-motility agents, such as anticholinergic medications and narcotics, electrolyte derangements, such as hypokalemia, and diagnostic procedures like barium enema and colonoscopy.[29]

Pathogenesis

The Massachusetts General Hospital reported its isolated cases of TM from in 1933, 1936, and 1941.[12] In 1956, Bockus et al drew attention to it in their study. They described it as "toxic aganglionic megacolon," referring to what they suggested about its pathogenesis, which was described as destructive changes in the nerve plexus in the distal colon.[13] The mechanism involved in the development of TM remains unclear; however, changes in colonic response to chemical mediators result in defective smooth muscle contraction and lowered basal pressure of the colonic lumen, which may play an essential role in the development of TM.[14–17] NO is an inhibitory neurotransmitter that is known to cause relaxation of the colonic smooth muscles.[18] NO synthase is expressed more in the inflamed mucosa of UC patients compared to noninflamed mucosa, which subsequently leads to suppression of colonic contraction.[19–21] Selective inhibition of NO synthase reportedly improves the motility, diameter, and intracolonic pressure in animal models with colitis.[22] Enemas containing NO synthase inhibitor revealed a clinically significant benefit in a patient with TM due to UC.[23] In contrast to what was suggested by Bockus et al, the inflammation in the case of TM is reportedly caused by the neuromuscular transmission rather than degeneration of the neurons.[24]

Clinical Manifestations

TM affects both gender and all ages; however, complications can present earlier in patients with IBD. TM occurs in around 5% of a severe attack of UC. Approximately half of the patients with TM develop this complication in the first three months of their IBD diagnosis.[30] TM usually occurs in patients with pancolitis, but patients with only left-sided colitis also can develop it. The most common presenting symptom is severe bloody diarrhea. With the clinical decline, patients can also develop hypotension, tachycardia, fever, diffuse abdominal tenderness with distention, and sluggish bowel sounds. One study revealed that patients with TM secondary to *C. diff* colitis had diarrhea as a complaint in all cases, abdominal pain, and distention in up to 82 percent of the cases and the malaise in 91 percent of the cases.[31] Other laboratory parameters showing progressive systemic toxicity include significant leukocytosis, metabolic alkalosis, and electrolyte derangements.

Nevertheless, strong analgesics or altered mentation might conceal the signs or symptoms of TM. Free perforation can also occur without dilatation of the colon. It is a rare complication, developing in approximately 1% of patients with UC without TM.[32,33] Typical presentation of peritonitis may be absent, primarily due to the masking effect of steroid therapy. It is crucial to look for hepatic dullness daily, especially in patients with severe colitis, and are on steroid therapy as they might have a free perforation and not have typical signs of peritonitis. For the same reason, a daily x-ray of the abdomen is recommended.

Diagnosis

As per the description of Jalan et al, the diagnostic criteria of TM include (a) radiographic evidence of colonic dilatation of more than 6 cm especially in the transverse colon; (b) any 3 of the following: fever (> 38.6 °C, 101.5 °F), tachycardia (> 120 beats/min), leukocytosis (> 10.5 × 103/μL), or anemia; and (c) any of the following: hypotension, hypovolemia, altered mental status, or electrolyte disorders.[12] The diagnostic purpose of TM is mainly for the diagnosis of the condition and the underlying etiology. Imaging studies are required for the diagnosis of TM as a "megacolon" is defined radiographically by a maximum diameter of >6 cm. Computed tomography of the abdomen with contrast helps establish the diagnosis and also evaluating for complications that may require immediate

surgery. Baseline and serial abdominal x rays help follow the progression of colonic dilatation. Typical features might include dilated transverse or right colon (more than 6 cm) more frequently compared to descending colon, sigmoid colon or rectum; deep mucosal ulcerations, segmental colonic wall thinning, air-fluid levels with abnormal haustral pattern and nodular pseudo polyps on radiologic exam. Common nonspecific lab abnormalities associated with TM include leukocytosis with prominent neutrophilia, especially in *C. diff* colitis cases, anemia from gastrointestinal blood loss, metabolic alkalosis secondary to volume depletion, hypokalemia, hypoalbuminemia and elevated inflammatory markers including ESR and CRP.

A complete colonoscopy is extremely risky in patients with TM because it can cause colonic perforation. A limited endoscopic examination without bowel preparation (eg, proctoscopy or sigmoidoscopy) is safer compared to complete colonoscopy. It is useful to diagnose an inflammatory (eg, [IBD]) or infectious process (eg, cytomegalovirus [CMV] or *C. diff* colitis) in the rectum or sigmoid colon. Nevertheless, a sigmoidoscopy can miss CMV inclusion bodies as classic ulcers are generally present in the ascending colon in a majority of the cases.[34]

Treatment

The main objective for the treatment of TM is to reduce the inflammation, improve the motility of the colon, and to prevent free perforation. If UC gets complicated with colonic dilatation, fluid replacement and intravenous steroid therapy is recommended, along with addressing electrolyte derangements aggressively. Bowel rest and nasogastric decompression can also help in the reduction of air and fluid within the GI tract. Both medical and surgical teams should co-manage patients on admission with daily evaluation.

Inpatient evaluation, preferably in the closed observation unit, with periodic examinations, help assess for signs of toxicity. Serial labs, including CBC and Electrolytes, along with clinical abdominal x-ray, should be performed twice a day initially upon admission and subsequently daily as the condition improves. Maneuvers to decrease abdominal distension by permitting the redistribution or passing of colon gas could be another conservative management strategy. Encouraging patients to walk around, using knee-elbow maneuver in the prone position, rotating patient who is bed-bound and inserting a rectal tube helps reducing bowel distension.[30] Enteral feeding can be initiated as soon as the patient shows signs of improvement to promote gut motility. Total parental nutrition (TPN) is of limited value in patients with TM from any cause. TPN provides no proven clinical benefit in terms of avoiding surgical intervention in patients with colitis due to UC.[35] When it comes to the specific medical or surgical therapy for TM must target the underlying etiology:

Inflammatory bowel disease — 5-ASA compounds and Sulfasalazine have no role in patients with IBD-related TM and should be commenced only after the acute attack resolves. In a few cases, an acute attack of TM might co-occur with the initiation of 5-ASA compounds.

Glucocorticoids

Intravenous glucocorticoids (hydrocortisone 100 mg every 6 to 8 hours) are the mainstay of therapy for all patients with TM secondary to IBD and are not associated with a higher risk of perforation.[36] However, this approach is based on limited observational data and clinical experience. Dexamethasone, by diminishing the expression of NO synthase, has been reported to decrease the colonic diameter. Most providers consider methylprednisolone because of its lower potassium wasting and sodium retaining properties, while others prefer prednisolone as the oral and parenteral doses are the same.

Infliximab or Cyclosporine

Patients with IBD-related TM who are refractory to three days of intravenous glucocorticoid therapy should receive either Infliximab or Cyclosporine as the second-line therapy. Infliximab is the preferred second-line treatment for all patients with IBD-related TM. Cyclosporine should be reserved for those who cannot tolerate Infliximab, and there is only evidence for its effectiveness in UC, not CD. (See Table 1) Data suggest that cyclosporine may provide an initial response rate of as high as 80%. After a follow-up period, the response rate decreases to approximately 40%. Although further studies are required, cyclosporine therapy may prevent the need for urgent surgery, allowing an elective surgery to be performed under the more controlled scenario. Most patients who develop IBD-related TM have UC; some have indeterminate colitis or Crohn's colitis. Since these three conditions may not be readily distinguishable during an acute flare-up such as TM, many authors suggest treating all IBD-related TM with the same approach.

Table 1 Different Medication Use for the Treatment of Toxic Megacolon

Medication	Indications	Mechanism of Action/Dosages	Therapeutic Benefits/Risks/ Complications
Sulfasalazine/ 5-ASA compounds	-In IBD related Toxic megacolon not as first line, after attack resolves	-Anti-inflammatory effects	-No enough data supporting beneficial use in IBD related toxic megacolon, it can be used after initial attack resolves
Glucocorticoids	-First-line therapy for all patients with IBD-related toxic megacolon -Methylprednisolone due to its lower sodium retaining and potassium wasting properties, while other clinicians prefer prednisolone since the parenteral dose is equal to the oral dose	-Decreases diameter of colon by reducing nitrous oxide synthetase -Hydrocortisone 100 mg IV every 6 to 8 hours -Methylprednisone 60 mg daily for 5 days[37,38]	-Not associated with risk of colonic perforation
Cyclosporine	If no response to Glucocorticoids within 3 days	-Inhibits T-lymphocyte function that is essential for the propagation of inflammation -Rapid response 4 mg/kg per day; 82% with clinical improvement with possibility of avoiding colectomy[39]	-Cyclosporine should be reserved for those who cannot tolerate infliximab and there is only evidence for its effectiveness in ulcerative colitis, not Crohn's disease -Cyclosporine better to be avoided in elderly patients with significant co-morbid conditions as well as patients in whom colectomy is likely to be necessary in near future
Infliximab	If no response to Glucocorticoids within 3 days	-Blocks the action of TNF-α by preventing it from binding to its receptor in the cell, but it also causes programmed cell death of TNF-α-expressing activated T lymphocytes that mediate inflammation -Infliximab 5 mg/kg (2 or 3 infusions)[40]	-Effective as rescue therapy for severe steroid refractory colitis in up to 70% of instancing -Clinical response usually occurs within 3 to 7 days of treatment - Infliximab also appears to induce a long-term remission comparable to that seen with cyclosporine

C. difficile colitis

For patients with TM due to severe *C. diff* colitis, the inciting antibiotics should be withdrawn immediately. Steroids are contraindicated in TM due to an infectious etiology, including *C. diff*colitis.

Empiric antibiotics are indicated as mortality due to TM correlates with the development of sepsis. Approximately half of the acute dilatation cases resolve with medical therapy alone.[32] Perforation of colon is the most critical predictor of mortality (44% of cases require emergent surgical intervention following perforation vs only 2% of cases requiring it without perforation),[9] a critical aspect of management is to decide the optimal time for surgical intervention. Generally, cases that do not improve after 2–3 days of medical management require a surgical evaluation.[41]

Surgery is indicated in patients with colonic perforation, necrosis, or full-thickness ischemia, intra-abdominal hypertension or abdominal compartment syndrome, clinical signs of peritonitis, or worsening abdominal exam despite adequate medical therapy, and end-organ failure. Besides, white blood cell count >50,000 cell/mL and serum lactate level of >5 mmol/L are relative indications for surgical intervention. The timing of surgery in TM is still a matter of controversy and varies by the underlying etiology of the TM. Although the main objective of all medical therapy is to avoid the need for surgical management, delaying surgery may ultimately increase the risk of complications such as abdominal compartment syndrome or perforation. Careful monitoring for any signs of impending perforation is vital. Patients developing abdominal distention, rebound tenderness, or hemodynamic instability require emergent surgical intervention. Further management is debatable for patients who achieve remission with medical management. According to one study, almost half of the patients who were managed successfully for TM

Table 2 Different Surgical Intervention for the Management of Toxic Megacolon

Surgical Intervention Indications	
- Failure to respond to one of the second-line agents (infliximab or cyclosporine) for three days.	
- Toxic megacolon while on either infliximab or cyclosporine should undergo surgery right away	
- Patients with colonic perforation, abdominal compartment syndrome, full thickness colonic wall ischemia, worsening clinical status despite proper medical management, Leukocytosis >50,000 cell/mL and serum lactate level of >5 mmol/L are relative indications for surgery.	
-Early surgical intervention before colonic perforation has a lower mortality rates compared to colectomy after perforation (8 versus 40 percent)[9]	
Surgical Intervention	**Description**
Subtotal colectomy with end-ileostomy	Urgent surgery of choice for toxic megacolon secondary to either Crohn's disease or Ulcerative colitis.[6] - Compared to single stage proctocolectomy, it has lower mortality (9%) with possibility of anastomosis subsequently in most patients - Common complications include small bowel obstruction (20%), wound infection (18%) and intraabdominal abscess (17%).
Total abdominal colectomy	Recommended procedure for patients with perforated colon, abdominal compartment syndrome or colonic necrosis.
Partial or segmental colectomy	No longer performed due to a higher mortality and reoperation rate.
Diverting loop ileostomy/colonic lavage	An alternative surgical intervention that has been associated low mortality in some studies.[43]

eventually required surgical intervention.[42] Because of these facts, some providers offer elective surgical evaluation after the resolution of an acute attack of TM. Early surgical intervention before colonic perforation has a lower mortality rate compared to colectomy after perforation (8 versus 40 percent).[9] (See Table 2).

Additional Therapies

Leukocytapheresis (LCAP) is useful in the management of TM. A series of six patients whose conditions had failed to improve after treatment with high-dose steroids and antibiotics were enrolled in a study. In four cases, the TM resolved by the morning after initiation of treatment with LCAP. In two patients, the TM resolved approximately 40 hours later. Improvement continued in four out of the six patients.[44]

Shetler et al reported that colonoscopic decompression and intracolonic vancomycin administration in the management of acute pseudomembranous colitis associated with TM is safe and effective in approximately 57–71% of the cases.[45]

Hyperbaric oxygen therapy has also been reported to be effective in the management of TM, but further studies are needed to confirm these results.[46]

Tacrolimus was successfully used in 1 case study in a patient with steroid-refractory UC complicated by TM. However, further studies are required to validate its use.[47]

Intravenous immune globulin (IVIG) may potentially be an adjunct therapy in patients with severe C diff infection with megacolon, taking into account the possibility of adverse effects.[48]

Special Populations

HIV/AIDS patients

An aggressive exploration of infectious and noninfectious etiology is a must, including radiological imaging and early limited endoscopic workup. Patients with cytomegalovirus (CMV) colitis or *C. diff* infection respond poorly to medical management only and often require surgical intervention.[49,50] Critically ill patients with advanced AIDS who are poor surgical candidates could be managed by supportive therapy, antibiotics, and careful colonic decompression.

Pregnant women

Women with known risk factors for TM (most commonly UC) should plan conception during a state of remission.[51] Patients who are in remission at the conception are likely to remain in remission during pregnancy. In the case of TM in pregnancy primarily due to UC, high-dose intravenous glucocorticoids therapy is effective in three-fourth cases of severe colitis, the remainder requiring either Infliximab or emergent surgical intervention.[52,53]

Management of fulminant colitis during pregnancy is challenging as the gravid uterus can restrict a thorough abdominal examination, and diagnostic radiation could be teratogenic.[54] In pregnancy, hemoglobin, and serum albumin level drop, while other inflammatory markers, including the ESR and CRP rise; so, these blood tests are not reliable measures of disease activity. Urgent colon surgery can increase the risks of preterm delivery and spontaneous abortions.

Prognosis

The mortality rates for TM are inconsistent. Before 1976, the death rate in 604 cases of TM was 27 percent (43 out of 160) for patients who were managed medically and 19 percent in 444 patients who underwent surgical intervention.[55] The in-hospital mortality for TM further decreased from 9.2 to 6.5 percent in 2010 through 2014.[4] Colonic perforation is associated with a significantly worse prognosis, with the mortality rate increased by three- to fivefold.[6,8]

The etiology of TM can also affect the prognosis, TM secondary to infectious etiology has a better prognosis than patients with TM secondary to IBD who have been treated with biologics; however, this result is mainly based upon a small group of studies. The prognosis is especially good when colonic dilatation complicates acute self-limited colitis and is managed promptly.[56] Nevertheless, the mortality rates dropped significantly to less than 2 percent in patients with IBD, probably related to diverse factors, including early identification of TM, the rapid escalation from glucocorticoid therapy to biologics (or cyclosporine), increasing use of biologics and accelerated dosing, aggressive medical management, prompt surgical intervention, and better post-surgical care.[9]

A review of patients with TM due to *C. diff* infection between 1968 and 1992 revealed an overall mortality of 31 to 35 percent.[31] In other studies, the overall mortality from TM secondary to severe *C. diff* infection was 64 to 67 percent, and 71 to 100 percent in cases which were managed surgically.[31,57] These studies show that patients with TM due to *C. diff* infection will do better with medical management alone, and surgery may offer a nominal benefit. However, surgery should not be postponed in acutely sick patients.

The difference in mortality rates may also be due to the biases of medical or surgical providers. Two studies have revealed that 68 to 75 percent of cases of TM managed medically did not require a surgical intervention later and have maintained remission for up to six years.[6,9] Surgical studies reveal up to a 50 percent rate of future surgical intervention, including colectomy in patients with TM who initially responded well to medical treatment alone.[55,58] Timely surgical interventions decreased the mortality rate significantly from 22 to 1.2 percent in one report.[59] The key points of this review article have been summarized in Table 3.

Table 3 Key Points to Keep in Mind when managing Toxic Megacolon

Key points of the Review Article:
1. Toxic megacolon (TM) was thought to be a complication for ulcerative colitis (UC) specifically. Later on, the Crohn's disease (CD) was found to be a cause, and gradually it becomes evident that any inflammatory condition of the colon could predispose to TM.
2. Accurate history and physical examination, plain radiographs of the abdomen, sigmoidoscopy and, most important of all, awareness of the condition facilitate diagnosis in most cases.
3. The most common cause of hospital admission included Inflammatory bowel disease (IBD) (51.6%), followed by septicemia (10.2%) and intestinal infections (4.1%).
4. Computed tomography of the abdomen with contrast is usually performed to establish the diagnosis and also evaluating for complications that may require immediate surgery. Baseline and serial abdominal x rays are then performed to follow the progression of colonic dilatation.
5. Patients should be admitted and evaluated, preferably in the intensive care unit, with frequent examinations to assess for signs of toxicity.
6. Both medical and surgical teams should co-manage patients on admission with daily evaluation.
7. Female gender, age more than 40 years, hypoalbuminemia, acidosis, and high blood urea nitrogen levels are associated with high mortality in a previous study. This patient population requires a special attention from the admission.
8. It is important to examine the abdomen for hepatic dullness every day in patients who have severe colitis and are taking high-dose glucocorticoids because they might have a free perforation and not have classic signs of peritonitis.
9. The main goal for treatment for TM is to treat the underlying inflammation, restoring colonic motility, and preventing free colonic perforation.
10. In HIV infection patients with TM, an aggressive search for infectious and noninfectious causes is essential, including early limited endoscopy and imaging studies. Patients with cytomegalovirus (CMV) colitis or *C. difficile* infection respond poorly to medical therapy and often require emergent subtotal colectomy and ileostomy.
11. Women with known risk factors for toxic megacolon (most commonly ulcerative colitis) should plan conception during a state of remission.

Conclusion

TM is a condition best approached through the combined efforts of the medical and surgical team working with the patient. Medical therapy is the first-line treatment in most cases, but objective measures of improvement should be discussed before treatment initiation. If the patient manifests signs of hemorrhage, peritonitis, or perforation, surgery is

emergently indicated. Subtotal/total colectomy and ileostomy is the procedure of choice in most instances, and a laparoscopic approach is potentially favored when possible and feasible.

Abbreviations

TM, toxic megacolon; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; *C. diff, Clostridium difficile*; NO, nitric oxide; TPN, total parenteral nutrition; LCAP, leukocytapheresis.

Disclosure

The authors have nothing to disclose.

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