CHAPTER 156 ■ INFLAMMATORY BOWEL DISEASE AND TOXIC MEGACOLON

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FULMINANT COLITIS

Ulcerative colitis is characterized by a diffuse, continuous inflammatory process usually limited to the superficial mucosa of the colon. Crohn disease entails a more focal, transmural inflammation that can affect the colon either alone or accompanied by small bowel involvement. Both have the potential for severe, fulminating or toxic colitis (1). Since the original classification was published by Truelove and Witts in 1955, severe, acute, ulcerative colitis has been defined by the presence of six or more bloody bowel movements per day associated with temperature greater than 37.8°C, heart rate greater than 90 beats/minute, hemoglobin less than 10.5 g/dL, and/or an erythrocyte sedimentation rate (ESR) greater than 30 mm/hour (2). It has long been recognized that these criteria are indications for hospitalization and intravenous corticosteroid therapy (3,4).

However, it is apparent that the spectrum of ulcerative colitis extends beyond the severity to necessitate hospitalization to fulminant colitis and toxic megacolon, implying progression of mucosal inflammation into deeper layers of the colon wall (5), which is a medical emergency requiring more intense and combined medical and surgical management (6). In addition to the symptomatic criteria set forth by Truelove and Witts, patients with fulminant colitis or toxic megacolon have evidence of transmural inflammation, including more profound tachycardia (heart rate greater than 120 beats/minute), fever (greater than 38°C), hypotensive bowel sounds, hypoalbuminemia, and metabolic alkalosis, accompanied by radiologic and endoscopic evidence of transmural disease and circular muscle paralysis, which precipitates dilatation (7) (Table 156.1). Approximately 15% of patients with ulcerative colitis will have a severe flare-up that will require hospitalization (3,8). Between 6.3% and 9% will have severe colitis as their initial presentation (8). Mortality from severe colitis is less than 2%, with a colectomy rate of about 30% (2,3). The risks of surgery or colectomy with fulminant colitis or toxic megacolon have not been independently assessed, but their prognosis is, most certainly, worse than patients presenting with criteria for severe colitis alone (7).

Clinical Features

In contrast to patients with severe colitis, those with fulminant colitis are characterized by having more than ten bowel movements per day, rectal urgency, continuous bleeding, abdominal pain and distention, fevers, weight loss, and dehydration (3). On physical examination, patients present with fever, tachycardia, abdominal tenderness and mild distention, tympany, and decreased bowel sounds (9). Laboratory abnormalities include leukocytosis, anemia (hemocrit concentration must be taken into account), hypalbuminemia, hypokalemia, hyponatremia, and elevated sedimentation rate and C-reactive protein (CRP). The degree of metabolic alkalosis correlates with the severity of colitis (7).

A plain abdominal radiograph can determine the extent of ulcerative colitis by the absence of fecal material distal to the margin of disease and the presence of air outlining normal hauntrations proximal to the disease margin (10,11). Radiologic features of fulminant colitis include wall thickening, with islands of edematous mucosa surrounded by deep ulcerations (9,12,13). The presence of colonic dilatation greater than 5.5 cm is predictive of the presence of—or evolution to—toxic megacolon (9).

A limited proctoscopic examination or flexible sigmoidoscopy with minimal air insufflation may be performed safely to evaluate the mucosa for pseudomembranes or ischemia (11). Examination generally shows extensive ulceration with friable, bleeding mucosa. In rare instances, however, such as with rectal enema therapy or in the setting of Crohn disease, the rectum may be normal. In patients whose initial presentation of inflammatory bowel disease is severe colitis, biopsies should be performed to evaluate for Crohn disease and to rule out acute self-limited colitis. In those with an exacerbation of known diagnosis, biopsies can help to exclude Clostridium difficile or cytomegalovirus (14). More extensive endoscopic examinations (15) are generally contraindicated due to the risk of perforation or inducing toxic megacolon. However, they have been performed safely in some experienced centers (7). If performed, the presence of severe colitis (deep penetrating ulcers) in conjunction with clinical features of severe disease is a poor prognostic sign (9,13,15,16). Similarly, the presence of extensive and deep ulcerations is a poor prognostic marker in Crohn disease (12).

Stool analysis for ova and parasites, C. difficile, Escherichia coli O157:H7, Campylobacter, Salmonella, and Shigella should be performed as part of the diagnostic workup (7,17).

Management

Few medical emergencies require as close cooperation between medical and surgical personnel as does fulminant colitis. A team approach with early management and continuous assessment by both groups is vital not only to determine whether surgery is indicated, but also to support critically ill patients preoperatively and postoperatively. Early recognition and
institution of therapy by an experienced team can alter the outcome of this life-threatening illness (3,4,7,17).

**Medical Treatment**

Resuscitative measures, including vigorous fluid, electrolyte, and blood replacement to maintain the serum hematocrit at approximately 50%, are paramount. The goal of fluid replacement should be to restore previous losses and continue replenishing those that are ongoing from diarrhea, fever, and third spacing of fluids (7). Despite the fact that bowel rest is an ineffective primary therapy for severe colitis, oral intake of fluids should be discontinued in fulminant colitis or once colonic dilatation is recognized (18). Parenteral nutritional support in attempts to correct malnutrition and electrolyte and acid-base balance—including repletion of phosphate, calcium, and magnesium—should be initiated. Although severe hypokalemia may not be present, total body potassium depletion is common and may be exacerbated by glucocorticoids such that resuscitative measures should include adequate potassium replacement (7).

Aminosalicylates, a mainstay of maintenance therapy and the treatment of mild to moderate disease, have no role in the treatment of fulminant colitis (3,4,7,17). These limited activity on superficial inflammation is insufficient to abort or control the transmural disease, and potential adverse effects (e.g., nausea, vomiting, or worsening colitis) may confound the clinical picture. These drugs should be withheld until the patient has recovered and resumed a normal diet.

Corticosteroids have long been used in the management of ulcerative colitis as well as in Crohn colitis (3,4,7,17). There is no general agreement regarding which corticosteroid preparation or dose should be given. Usual doses employed for severe fulminating colitis range from 40 to 80 mg of methylprednisolone (in Europe, often 1 mg/kg) or 400 mg of hydrocortisone provided in divided doses or continuous infusion (3,4,7,17,19). Prednisone, 25 mg intravenously every 6 hours, and methylprednisolone, 6 to 15 mg every 6 hours, are both available for intravenous administration. There is no advantage to doses greater than 60 mg of methylprednisolone daily (19,20). A continuous infusion of corticosteroids may be beneficial to maintain steady plasma levels; however, a recent trial did not identify a difference between twice-daily intravenous dosing versus continuous infusions (21). The use of adrenocorticotropic hormone (ACTH) has not been shown to be superior to corticosteroids and, although it may be preferred in patients not previously exposed to corticosteroids, at a dose of 100 to 150 U per day (22), its use has become an anachronism.

The response to corticosteroids in the setting of severe fulminant colitis has remained constant for the past several decades (19), with approximately 75% of patients respond (13,19,23) and less than half failing to achieve remission (17). The presence of hypoaalbuminemia, high CRP, short duration of illness, and prior corticosteroid use are predictors of medical failure (25,26). In addition, ex-smokers have a worse prognosis (27). Short-term prognosis to corticosteroids in severe disease can be predicted as early as 24 hours. Persistence of more than nine stools per day, an albumin less than 3 g/dL, or a pulse rate greater than 90 beats/minute was predictive of greater than 60% risk of colectomy (9). Patients with greater than eight stools per day and a CRP greater than 4.5 mg/dL by day 3 had greater than 90% likelihood of requiring colectomy (11) or cyclosporine therapy. Continuation of intravenous corticosteroids beyond 7 to 10 days does not provide any additional benefits (19,28) and may increase morbidity and surgical risks (29).

Patients who improve, as evidenced by restoration of formed bowel movements with the absence of bleeding and ability to pass flatus without using the toilet, are then transitioned to oral prednisone at the same daily dose used to achieve the clinical remission. They may be discharged from the hospital when tolerating a low-residue diet with formed stools without out blood or rectal urgency; premature discharge is doomed to failure and readmission. Aminosalicylates are added as a maintenance therapy once patients are tolerating oral steroids and a full diet. The long-term prognosis after hospitalizations for severe colitis requiring corticosteroid therapy is not as promising as once considered (30–32). The impact of the addition of immunomodulators or biologics has not been assessed in this population.

**Cyclosporin A**, administered as a continuous IV infusion, either alone (33) or in combination with corticosteroids, has
been effective in treating severe ulcerative colitis (28). Although initial studies employed a 4 mg/kg dose as a continuous infusion (28), subsequent trials have confirmed similar results and less toxicity with doses of 2 mg/kg (34). Immediate response rates up to 85% to 92% have been reported (35) and, similar to the experience with the “intensive intravenous corticosteroid” regime, failure to improve—as defined by having eight or more stools per day or persistence of CRP elevation after 3 days of cyclosporine—is predictive of the need for colectomy (11). Careful daily monitoring for serious side effects of nephrotoxicity, infection, and seizures must be carried out when using cyclosporine (36).

Once patients have responded to intravenous cyclosporine with achievement of a clinical remission—again, defined as formed bowel movements without bleeding or rectal urgency—they are transitioned to oral cyclosporine by doubling the intravenous dose for twice-daily oral administration (e.g., if the intravenous dose is 100 mg/24 hours, the oral dose would be 200 mg twice daily) (36). Patients receiving a combination of corticosteroids and cyclosporine should receive Pneumocystis prophylaxis with sulfamethoxazole-trimethoprim three times weekly (37). Forty to fifty percent of patients treated with intravenous cyclosporine experience long-term remission (37–40). Improved outcomes are reported for patients who have been transitioned to oral cyclosporine with the addition of 6-MP or azathioprine (37,41).

Most recently, infliximab, a chimeric anti tumor necrosis factor (TNF) monoclonal antibody, has been shown to be effective as outpatient therapy for patients with moderate to severe ulcerative colitis (42). The role of infliximab in fulminant ulcerative colitis has been debated; the controversy is likely related to the severity of the disease (43–45). The largest clinical trial enrolled outpatients with moderate to severe disease. Subsequent, smaller trials in hospitalized patients have demonstrated conflicting results (46–49). It appears that infliximab will be more effective for patients in the moderate to severe spectrum (47–49), whereas the results with fulminant disease are less convincing (43,47,48). In choosing between infliximab and cyclosporine therapy, the former has been more effective and easily administered (less therapeutic monitoring), whereas the results with cyclosporine have been more consistent in the sicker group of patients (7,17,48).

**Surgical Management**

Persistence of medical therapy in the setting of fulminant colitis must be balanced against the potential for a surgical “cure” of the disease. Indications for surgery in fulminant colitis include clinical deterioration or failure to respond to medical therapy (3,4,7,17). Although the medical management of fulminant colitis is similar to that for toxic megacolon, the absence of acute colonic dilatation may permit delay of surgical intervention. However, the timing of surgical intervention in these less urgent cases requires experienced clinical judgment. Early intervention to reduce mortality must be balanced against the potential for intensive medical management to control the inflammatory process and complications, thereby potentially preventing the psychosocial and medical stigma of colectomy. Generally, in the absence of colonic dilatation, medical management may be continued for 5 to 7 days in a further attempt to reverse transmural inflammation, as long as the patient is stable and improving. Patients with fulminant colitis who do not begin to respond to the intensive intravenous steroid regimen, as described above, should be referred to a center experienced in cyclosporin therapy or undergo colectomy.

The type of operation performed has treatment of fulminant colitis depends on the clinical status of the patient and experience of the surgeon (7,17,50–52). A one-stage procedure that cures ulcerative colitis without the need for a second operation is appropriate for older patients or those not desiring restorative ileal pouch–anal anastomosis. Most surgeons prefer a limited abdominal colectomy with ileostomy, leaving the rectosigmoid as a mucous fistula or the rectum alone, using a Hartmann procedure (53). This approach has the advantages of limiting the lengthy pelvic dissection in acutely ill patients while allowing for the option of a subsequent restorative, sphincter-saving procedure (ileoanal anastomosis) (54). In patients with indeterminate colitis or Crohn disease, preservation of the rectum may provide the opportunity for an eventual ileorectal or ileoanal anastomosis to preserve anal continence after temporary diversion and pathologic review of the colectomy specimen (1,55).

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**TOXIC MEGACOLON**

Toxic megacolon refers to acute nonobstructive dilatation of the colon, generally as a complication of ulcerative colitis, but it may occur with any severe inflammatory colitis (56). This condition has been described with idiopathic and infectious colitis, including ulcerative colitis, Crohn disease (57), amebic colitis (58), pseudomembranous colitis (59), and other infections (Shigella, Salmonella, Chagas disease, and cytomegalovirus [CMV]) (14,60). Toxic megacolon has been reported to complicate 1% to 13% of all ulcerative colitis cases (61,62) and 2% to 3% of Crohn colitis cases (62). Although mortality in early series was as high as 25%, reaching 50% if colonic perforation occurred, early recognition and management of toxic megacolon has substantially lowered mortality to below 15% (62) generally and, in experienced centers, usually below 2% (63). Factors associated with increased mortality include age older than 40 years, the presence of colonic perforation, and delay of surgery (62). Colonic perforation, whether free or localized, is the greatest risk factor leading to increased morbidity or death.

**Predisposing Factors**

The severity of disease activity is the most important predictor of toxic megacolon, which is more common in extensive colitis than in proctitis or proctosigmoiditis (64). However, limited right- or left-sided colitis (61,62) has been associated with toxic megacolon (64,65).

Toxic megacolon typically occurs early in the course of ulcerative colitis, usually within the first 3 years of disease; 22% to 40% of cases present with the initial attack (62,64–66). The onset of toxic megacolon has been temporally linked to diagnostic examinations such as barium enemas or colonoscopy, suggesting that manipulation of the inflamed bowel or vigorous laxative preparation may exacerbate the process, possibly through electrolyte imbalance (62,64).

Certain drug therapies have been implicated in the development of toxic megacolon. Difenoxin/atropine sulfate (Lomotil), loperamide, and other inhibitors of colonic motility such as opiates and narcotics may contribute to the...
development of toxic megacolon by inhibiting colon muscle function in severe transmural disease. Electrolyte and pH disturbances are risk factors for toxic megacolon (7). Severe potassium depletion, secondary to significant diarrhea or corticosteroid therapy, or both, is known to inhibit colonic motility. Despite early speculations regarding the role of corticosteroids in inducing toxic megacolon (67,68), most no longer accept the implication that corticosteroids or adrenocorticotropic hormone are precipitating factors (7,17,66,69,70). Concern remains, however, that corticosteroids may suppress signs of perforation, thereby delaying surgical therapy.

CMV infection may contribute to fulminant colitis or toxic megacolon (71–74). There are no controlled trials regarding the utility of treating CMV and, often, in the absence of systemic manifestations of CMV (e.g., fever, hepatitis), no treatment is necessary (7,17), although there are reports of successful intervention targeting CMV if identified in colon biopsies.

### Clinical Features

Toxic megacolon usually occurs in the background of chronic inflammatory bowel disease (66,68,75). Jalan et al. described the most accepted clinical criteria based on signs, symptoms, and diagnostic abnormalities for toxic megacolon (36,62) (Table 156.2). The presentation typically evolves with progressive diarrhea, bloody stools, cramping abdominal pain, and abdominal distention. Impaired consciousness and lethargy may be present and are ominous signs (62). Occasionally, in chronically treated patients, a paradoxical decrease in stool frequency with passage of only bloody discharge or bloody membranes may be an ominous sign. Therapeutically, clinical signs of toxemia, including pyrexia (temperature greater than 38.5 °C) and tachycardia, develop as abdominal pain and distention become progressive and bowel sounds diminish or cease. On physical examination, peritoneal irritation, including rebound tenderness and abdominal guarding, represent transmural inflammation with serosal involvement, even in the absence of free perforation. Conversely, peritoneal signs may be minimal or absent in elderly patients or those receiving high-dose or prolonged corticosteroid therapy. In such patients, loss of hepatic dullness may be the first clinical indication of colonic perforation. Mental status changes, including confusion, agitation, and apathy, are occasionally noted (66). Leukocytosis, defined as total white blood cell count greater than 10,500 cells/μL, with a left shift, anemia, hypokalemia, and hypoalbuminemia are common laboratory findings (56).

### Diagnosis

Plain films of the abdomen are usually sufficient radiographic studies, revealing loss of haustration with segmental or total colonic dilatation (76) (Table 156.2). Clinical studies have demonstrated a strong correlation between colonic dilatation and deep ulceration involving the muscle layers (13). The magnitude of dilatation may not be severe, averaging 8 to 9 cm (normal is less than 5–6 cm), although colonic diameter may reach 15 cm before rupture. Maximal dilatation can occur in any part of the colon. Accompanying mucosal thumbprinting or pneumatosis cystoides coli reflects severe transmural disease.

Free peritoneal air should serve as an immediate indication for surgery (62,66). Infrequently, retroperitoneal tracking of air from a colonic perforation may produce subcutaneous emphysema and pneumomediastinum without pneumoperitoneum (77). In patients with severe colitis, small bowel ileus may herald toxic megacolon (78,79) and is a bad prognostic sign for medical success (63). Discrepancies may exist between physical and radiographic findings. Abdominal distention by physical examination can be minimal despite massive colonic dilatation. Conversely, physical findings may dominate the presentation, and peritoneal signs in the absence of free air or dilatation should not be ignored.

### Management

Just as in fulminant colitis, a coordinated team approach between medical and surgical services to management and monitoring is necessary in patients with toxic megacolon.

### Medical Treatment

The initial treatment is supportive and similar to treatment outlined for fulminant colitis. Aggressive resuscitation with fluids, electrolytes, and blood is necessary. Patients with nausea and vomiting or significant abdominal pain should be on complete bowel rest. Anticholinergic and narcotic agents should be discontinued immediately. In the presence of small bowel ileus, a nasogastric tube is usually placed, and despite a lack of clear evidence for the placement of long intestinal tubes, they are advocated by some (80). Patient repositioning from front to back or prone knee–elbow position may redistribute colonic air and assist in decompression (81,82). Rarely, patients with dilatation in the absence of toxic signs or symptoms may benefit from rectal tube decompression.

Broad-spectrum antibiotics, with adequate Gram-negative and anaerobic coverage, are considered standard therapy and should be administered without delay once transmural inflammation or toxic megacolon is suspected (56). Antibiotics should be continued until the patient stabilizes over several days to a week or through the initial postoperative period. Whether antibiotics help arrest progression of toxic megacolon is not known.

### TABLE 156.2

**JALAN’S CRITERIA FOR DIAGNOSIS OF TOXIC MEGACOLON**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
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<tbody>
<tr>
<td>1. Radiographic evidence of colonic dilatation</td>
<td>1</td>
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<tr>
<td>2. At least three of the following:</td>
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<tr>
<td>a. Temperature greater than 38.5 °C</td>
<td>1</td>
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<tr>
<td>b. Heart rate greater than 120 bpm</td>
<td>1</td>
</tr>
<tr>
<td>c. White blood cell count greater than 10.5 (x 10³/μL)</td>
<td>1</td>
</tr>
<tr>
<td>d. Anemia</td>
<td>1</td>
</tr>
<tr>
<td>3. At least one of the following:</td>
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<tr>
<td>a. Dehydration</td>
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<tr>
<td>b. Mental status changes</td>
<td></td>
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<tr>
<td>c. Electrolyte disturbances</td>
<td></td>
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<tr>
<td>d. Hypotension</td>
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</tbody>
</table>

Generally, most patients with inflammatory bowel disease (IBD) will have been receiving corticosteroids before toxic megacolon developed, in which case they should be continued. There is no evidence that corticosteroids precipitate or worsen outcome in toxic megacolon. Similar to therapy for fulminant colitis, augmented doses of corticosteroids should be administered in view of the additional stress of the toxic state. There is concern that corticosteroids could mask signs of perforation or peritonitis, so close monitoring is necessary. In cases of toxic megacolon caused by infectious etiologies, corticosteroids should not be used. Just as in fulminant colitis, there is no consensus regarding the corticosteroid preparation for treatment in toxic megacolon.

Surgical Management

After 12 to 24 hours of intensive medical management, if no improvement or deterioration occurs, surgical intervention is required for toxic megacolon. Some physicians actually view early surgical management of toxic megacolon as the conservative approach, noting that delay of operative therapy may promote higher mortality. Evidence of colonic perforation is an unequivocal indication for emergent surgery. If physical signs of perforation are absent, 12- to 24-hour radiographic surveillance is necessary. Perforation is associated with severe complications, including peritonitis, acute fluid and electrolyte imbalance, and hemodynamic instability. Early recognition of perforation should lessen morbidity or mortality. Other indications for emergent surgery precluding prolonged medical management include signs of septic shock, multiorgan dysfunction (7), and imminent transverse colon rupture (diameter greater than 12 cm) (56). Hypoalbuminemia, persistently elevated C-reactive protein or erythrocyte sedimentation rate, small bowel ileus, and deep colonic ulcers are poor prognostic factors for successful medical therapy (11,63,83,84).

The surgical management of toxic megacolon must be individualized for each patient. The type of operation is dependent on the clinical condition of the patient and the experience of the surgeon (51,52,85). The types of surgery are outlined in the fulminant colitis section. Rarely, “blow-hole” colostomies may be useful in highly selected individuals with poor operative prognoses (86).

COMPLICATING SCENARIOS IN INFLAMMATORY BOWEL DISEASE

Thrombosis

Massive gastrointestinal bleeding is an unusual complication in inflammatory bowel disease, occurring in 0.9% to 6% of patients (105,106). The general management is the same as in non-IBD patients. Resuscitation is the first step, followed by diagnostic evaluation—usually with endoscopy—to localize the site of bleeding. In one case series, colonoscopy identified the source of bleeding in 60% of IBD patients, and angiography was used in cases where colonoscopy was not diagnostic (107). Conservative therapy has been advocated, but surgery is indicated when bleeding is not stabilized by transfusions or if recurrent massive bleeding is present. Principles of management of gastrointestinal bleeding are discussed elsewhere in this text.
PEARLS

Management of Fulminant Colitis and Toxic Megacolon

- Team approach including medical and surgical personnel
- Intravenous fluid resuscitation
- Supplemental parenteral nutrition
- Bowel rest in the presence of vomiting, abdominal pain, or hemorrhage
- Evaluate for enteric pathogens, C. difficile, and CMV
- Abdominal girth measurement
- Decompression
  - Nasogastric tube (des) or repositioning maneuvers (colonoscopic dilatation)
- Medical treatments
  - Specific treatments for infections
  - Intravenous corticosteroids for inflammatory bowel disease
  - Cyclosporin or infliximab in selected patients not responding to intravenous corticosteroids after 3 to 7 days
- Broad-spectrum antibiotics if toxic
- Blood transfusions to maintain hematocrit at about 30%
- Radiology
  - Daily to frequent abdominal radiographs
  - Computed tomographic scan as needed for management
- Surgical indications
  - Failed medical therapy
  - Progressive dilatation or toxicity
  - Shock or multiorgan dysfunction
  - Persistent hemorrhage
  - Evidence of perforation

References

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