Medical Management of Chronic Ulcerative Colitis

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Stefan D. Holubar and Mattias Soop

Key Concepts

- CUC is highly prevalent in North America and Europe, and its incidence is increasing globally.
- CUC has an unknown etiology, but the pathogenesis is believed to be multifactorial, with an impaired mucosal immune regulation and unknown environmental conditions or trigger(s).
- Surgeons must be familiar with the numerous medical treatments for CUC, including their side effects.
- Mild-to-moderate CUC is typically treated in a bottom-up manner with oral aminosalicylates, and if steroids are required for flares, then the patient is transitioned to AZA/6MP or a biologic agent to wean the steroids.
- Moderate-to-severe disease is typically treated in a top-down manner with combination therapy with a biologic agent and immunomodulator, often under the cover of temporary steroid treatment.
- Patients may require surgery and should be aggressively optimized in terms of anemia, malnutrition, and VTE prophylaxis.
- Pouchitis is common and responds promptly to oral antibiotic use. Patients with "Crohn's-like" picture of the pouch may benefit from additional medical therapy.

Part 1: Defining CUC

Introduction

- Chronic ulcerative colitis (CUC) is an idiopathic, recrudescent chronic disease of colonic mucosal ulceration (Fig. 46.1) with a prevalence of well-over 600,000 affected persons in North America.
- CUC is one end of the spectrum of idiopathic inflammatory bowel disease (IBD) (Fig. 46.2).
- The vast majority of patients with CUC will require multiple medications to control disease over the course of their lifetime.

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- Symptoms include chronic diarrhea, often bloody, accompanied by tenesmus, defecatory frequency and urgency.
- The urge incontinence that many patients experience is often the most troubling symptom.
- Extraintestinal manifestations are numerous and summarized in Fig. 46.3.

Diagnosis

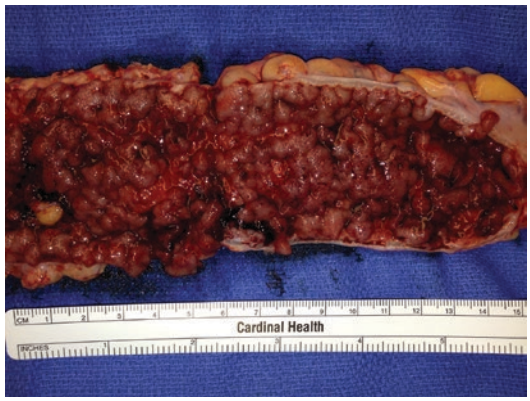

Fig. 46.1 Operative specimen, gross photo. Note ulcerated, hemorrhagic mucosa with severe pseudopolyposis and exposed muscularis, slightly (chronically) thickened bowel wall. (Courtesy of Dr. Stefan D. Holubar MD, MS)

- CUC is diagnosed using a combination of history, physical exam, and colonoscopic and histologic appearance (Fig. 46.4).
- Conditions that may need to be ruled out in the differential diagnosis include irritable bowel syndrome, celiac sprue, and the other colitides.
- Relatives and siblings of patients with IBD may also have either CUC or Crohn's disease.

Colonoscopy

- Mucosal inflammation starts in the rectum (not the anus) and progresses continuously proximally a variable distance.
- Inflammation may be mild, with a granular mucosa with contact bleeding, to more severe with linear ulcerations, to fulminant with severe pseudopolyposis (Fig. 46.1).
- In patients with long-standing disease, the colon may be foreshortened, ahaustral ("lead-pipe colon").
- Biopsies demonstrate acute and/or chronic colitis, with inflamed lamina propria and

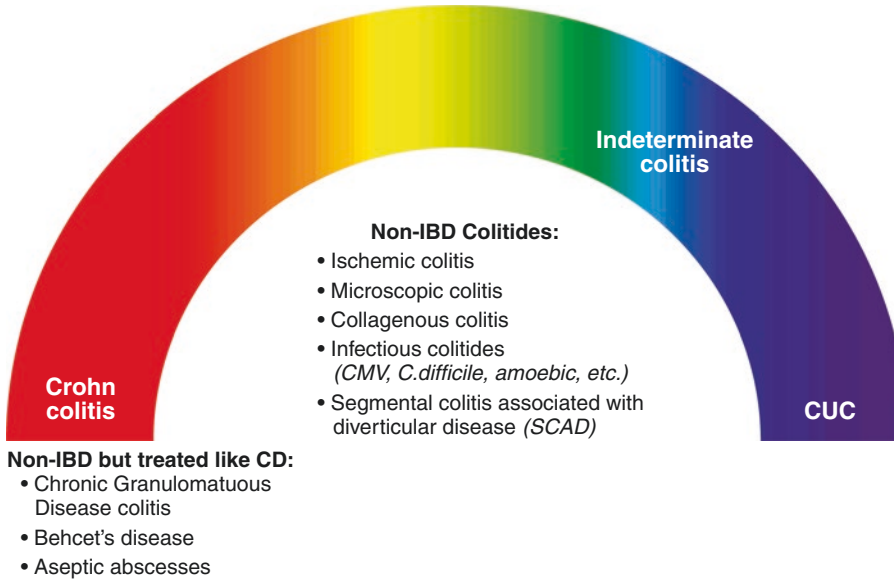

Fig. 46.2 Auto-inflammatory colitis spectrum

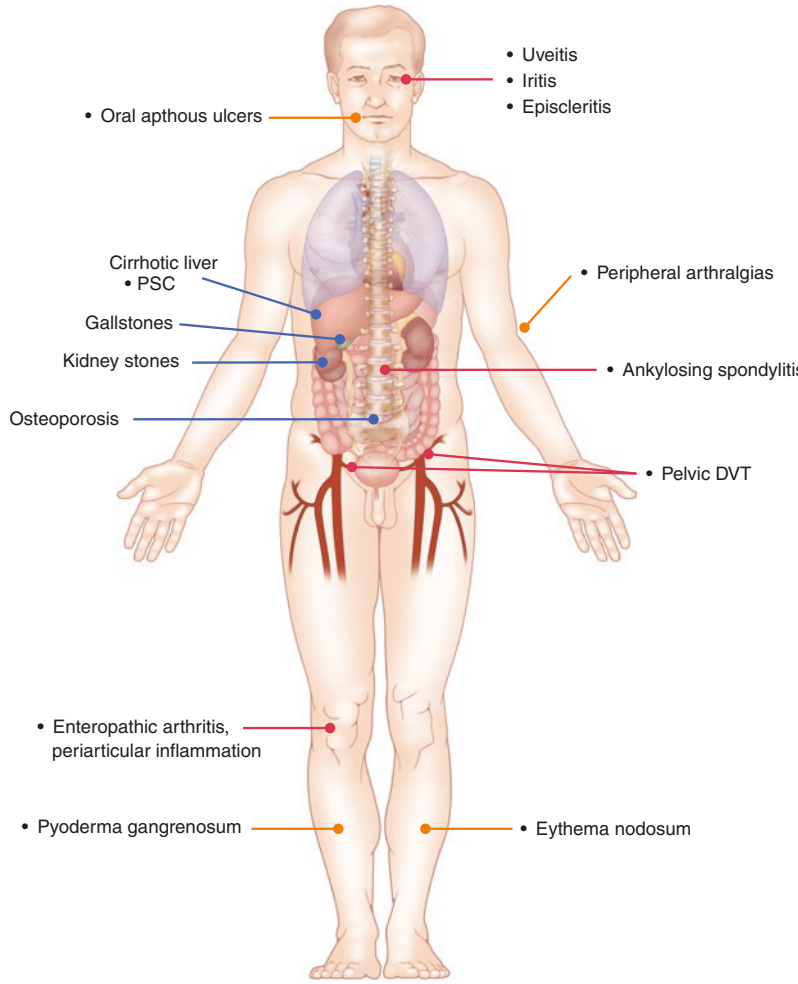

Fig. 46.3 Schematic representation of common extraintestinal manifestations in CUC

distorted crypt architecture. The presence of granulomas generally indicates CD (Fig. 46.4: photomicrograph of CUC vs. CD with granuloma).

Imaging

- Imaging studies such as fluoroscopic small bowel follow-through, magnetic resonance enterography (Fig. 46.5), computed tomographic enterography (CTE, Fig. 46.6), or capsule endoscopy (Video 46.1) may be used to assess for stigmata of Crohn's disease.
- CT and MRI may also demonstrate the extent and severity of colitis. Findings include an edematous, thickened rectal and colonic wall with mucosal hyper-enhancement.

Serology

- Nonspecific serologic inflammatory markers include white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).
  - Both ESR and CRP are sensitive markers of inflammation, inexpensive, and available

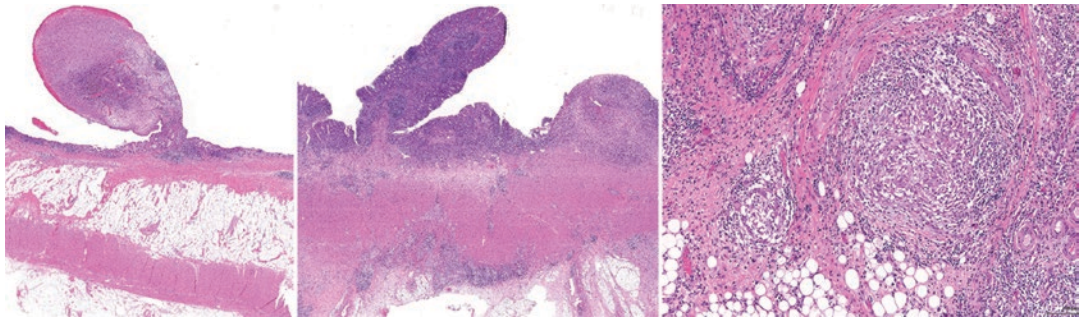

Fig. 46.4 Photomicrograph of CUC vs. CD. H&E stain. Top panel shows severe transmural inflammation and granulomas consistent with Crohn's disease; middle panel shows severe mucosal ulceration consistent with ulcerative colitis; bottom panel shows mucosal inflammation and a pseudopolyp consistent with ulcerative colitis. (Courtesy of Dr. Anthony Senagore)

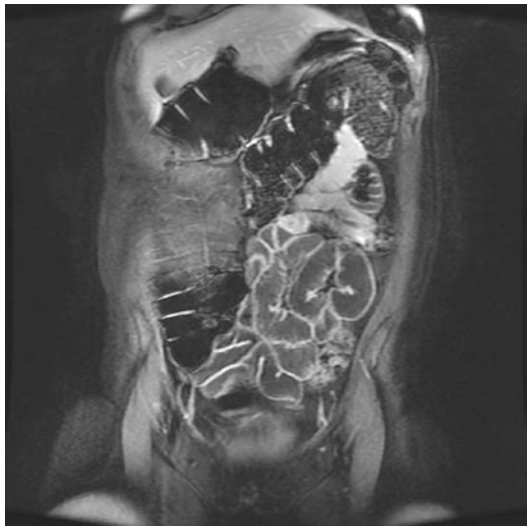

Fig. 46.5 Magnetic resonance enterography, LAVA sequence 70 s post-contrast. Note the normal appearance of the small bowel wall in a CUC patient prior to total colectomy. Specifically the small bowel wall is of normal thickness, and the lack of mucosal or bowel wall hyper-enhancement, with no demonstrable fistula, strictures, or abscesses

in most centers. The main difference is ESR's longer half-life.

  - Fecal calprotectin can predict and follow the trajectory of disease flares and predict mucosal healing.

- Prometheus® antigen testing is reserved for cases that are difficult to classify based on traditional criteria.

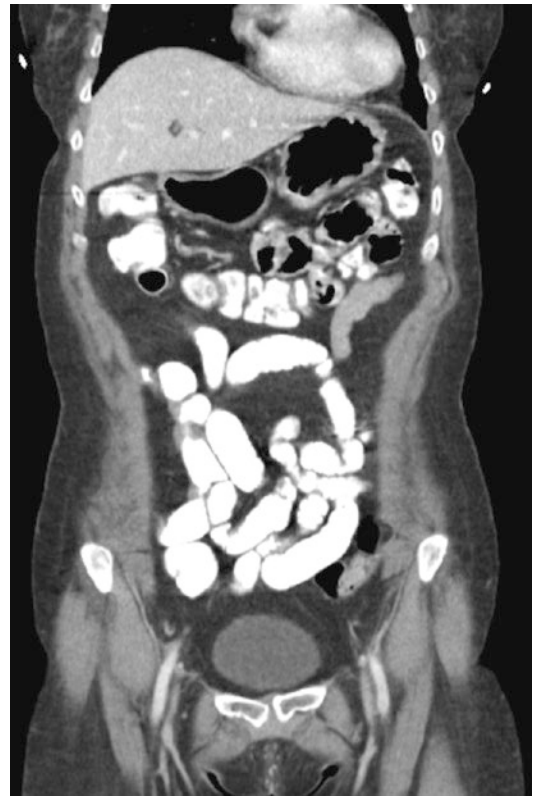

Fig. 46.6 Computed tomographic enterography. Note the normal appearance of the small bowel wall in a CUC patient prior to total colectomy. Specifically the small bowel wall is of normal thickness, and the lack of mucosal or bowel wall hyper-enhancement, with no demonstrable fistula, strictures, or abscesses

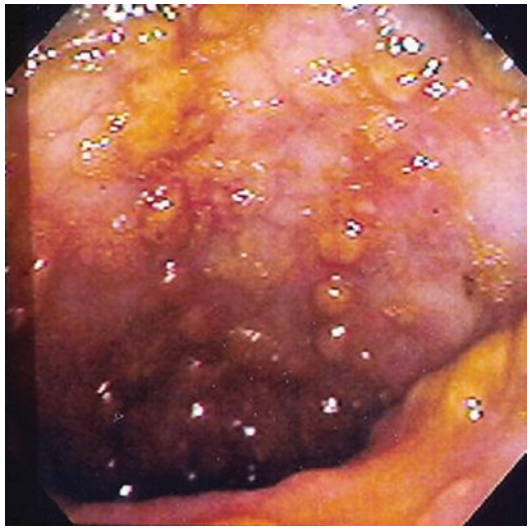

Fig. 46.7 Colonoscopic appearance of pseudomembranous (*Clostridium difficile*) colitis. Note the pale white appearance of the pseudomembranes. (Courtesy of Dr. Anthony Senagore)

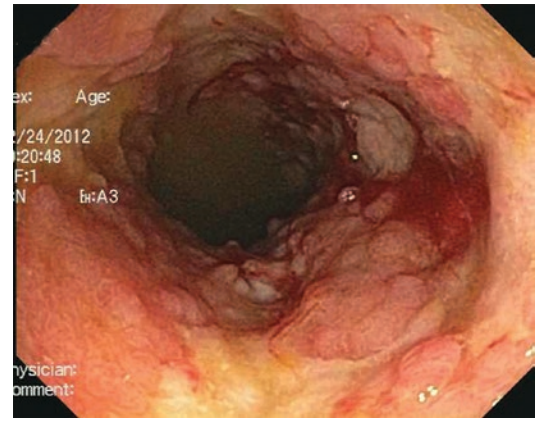

Fig. 46.8 Colonoscopic appearance of CMV colitis in a patient with CUC. Note the classic "punched-out" ulcerations (bottom center of photo) in a background of pseudopolypsis. (Courtesy of Dr. Anthony Senagore)

Infectious Work-Up

- For patients presenting with bloody diarrhea, infectious colitides should be considered.
- Standard stool studies for ova and parasites mainly to assess for *Giardia lamblia* or cryptosporidium in the case of immunosuppressed patients are appropriate.
- *Clostridium difficile* is seen with increased frequency in IBD and can be assessed by endoscopic appearance (Fig. 46.7) or molecular testing.
- Cytomegalovirus (CMV) colitis (Fig. 46.8), with its characteristic "punched-out" ulcerations, is also seen with increased frequency.

Epidemiology

- North America has a relatively high incidence of 8–15 cases per 100,000 persons per year.
- It is estimated that 50,000 new individuals are diagnosed in North America yearly, with an estimated point prevalence of more than 600,000 persons at any given time.
- The incidence of CUC in western societies continues to rise. Risk factors for CUC are summarized in Table 46.1.
- Approximately 70–75% of CUC patients will never require colectomy.
- Unfortunately, the proportion of patients with prolonged remission is only 10%, highlighting the waxing and waning nature of this illness. Approximately 1% of patients live with continuously active disease.

Colorectal Adenocarcinoma

- Patients with CUC are at increased risk of developing colorectal cancer. A rule of thumb is the risk of developing colorectal cancer (CRC) in CUC is 0.5–1% per year after the first 10 years of disease.
- Currently it is recommended that surveillance should commence 8–10 years after onset of colitis (rather than the time of diagnosis).
- Young age at diagnosis, longer disease duration, severity and extent of inflammation, family history of CRC, and the presence of primary sclerosing cholangitis (PSC) are risk factors.

Table 46.1 Epidemiologic risk factors for development of CUC

Category	Risk factor(s)	Comments
Age	Median age of diagnosis = 33 years	Larger studies have disproven bimodal distribution
Gender	Slight male preponderance	–
Genetics	Monozygotic twin concordance = 14–19%, dizygotic concordance 0–7%	If one sibling with CUC, other sibling(s) with 7–17 relative risk of CUC
Geography	Higher prevalence in Northern developed countries but is worldwide	Highest risk areas appear to be North America, UK, Northern Europe, and Scandinavia; rising incidence of CUC in developing countries typically precedes that of CD by 1–2 decades
Race/ethnicity	Caucasians, Ashkenazi Jewish ("Jews of Europe"); incidence rising in Asians and Hispanics	Migration studies suggest that geography is a more important risk factor than race as low-risk groups who migrate to higher prevalence areas then develop a higher prevalence independent of race
Socioeconomic status (SES)	Possible association between increased SES and increased risk of CUC	–
Cigarette smoking	Highly characterized strong, inverse relationship with current smokers at 40% risk reduction for development of CUC	Current smokers with CUC less likely to require hospitalization or colectomy relative to non-smokers
Appendectomy	Highly characterized strong, inverse relationship with patients who have had appendectomy with a 70% risk reduction for development of CUC	Patients who have had appendectomy who do develop CUC may have less severe disease
Antibiotics	Oral antibiotics in prior 2–5 years modestly increase the risk of IBD development	Probable dose-response relationship i.e., the more prescriptions for prior antibiotics, the higher the likelihood of developing IBD
Oral contraceptives	No significant relationship for CUC	Earlier studies suggested a modest increased risk for CUC in prior oral contraceptives
Diet	No significant relationship for CUC	Some studies suggested a link between refined sugar and CD not CUC
Infection	No significant relationship for CUC	Conflicting data for CD but no effect for CUC

Adapted from Loftus EV. Epidemiology of inflammatory bowel disease. In: Talley NJ, editor. GI epidemiology. 2nd ed. Hoboken, NJ: Wiley Blackwell; 2014. p. 273–84

Classification of CUC

- Historically, disease activity was measured by the criteria outlined by Truelove and Witts (Table 46.2).
- More recently the Montreal classification of IBD has become the preferred way to specify disease activity (Fig. 46.9).

Severity

- S0 = clinical remission
- S1 = mild disease: <4 bowel movements per day, no serologic or systemic signs of inflammation
- S2 = moderate: >4 stools per day, some signs of inflammation
- S3 = severe: > = 6 bloody stools daily, pulse >90 beats per minute, temperature > 37.5°C, hemoglobin <10.5 g/100 ml, and ESR > 30 mm/h

Extent

- E1 = ulcerative proctitis
- E2 = left-sided colitis
- E3 = pancolitis
- Endoscopic classification is facilitated by the Mayo Severity Index (Table 46.3).
- The Simple Clinical Colitis Activity Index (SCCAI, Table 46.4) is useful for following patient's symptoms over time.

Table 46.2 Modified Truelove and Witts criteria

Variable	Mild disease	Severe disease	Fulminant disease
No. of stools/day	<4	4–10	> = 10
Blood in stool	Intermittent	Frequent	Continuous
Temperature	Normal	>37.5	>37.5
Pulse	Normal	>90	>90
Hgb	Normal	<75% of normal	Requiring transfusions
ESR (mm/h)	Normal = <30	>30	>30
Abdominal X-ray	Normal	Edema/thumbprinting	Dilation
Abdominal pain	None	Mild diffuse tenderness	Distension and tenderness

Adapted from Mahadevan U. Medical treatment of ulcerative colitis. Clin Colon Rectal Surg. 2004;17(1):7–19
Note moderate disease with features of mild and severe disease

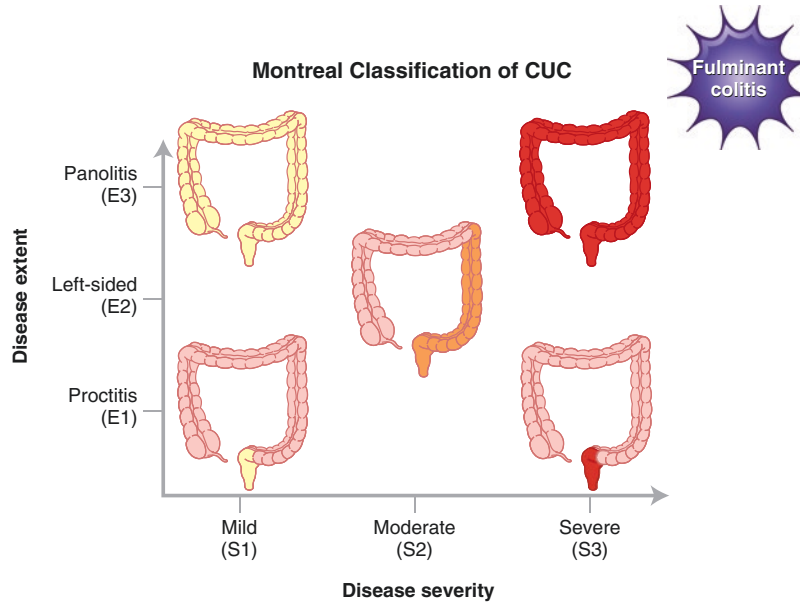

Fig. 46.9 Diagrammatic representation of the Montreal classification of CUC disease severity and extent

Table 46.3 Mayo Severity Index

Variable	Points (range 0–12)			
	0	1	2	3
BM frequency	Normal	1–2 BM > normal	3–4 BM > normal	> = 5 > normal
Bleeding	None	Streaks <50% of BMs	Obvious blood with most BMs	Blood alone
Endoscopy	Normal	*Mild*: erythema, decreased vascularity, mild friability	*Moderate*: marked erythema, lack of vascular pattern, friability	*Severe*: spontaneous bleeding, ulceration
Physicians Global Assessment (PGA)	Normal	Mild	Moderate	Severe

Adapted from Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317(26):1625–9

Table 46.4 Simple clinical colitis activity index

	Points (range 0–15)				
Symptom(s)	0	1	2	3	4
Daytime BM frequency	1–3	4–6	7–9	>9	
Nocturnal DM frequency	None	1–3	4–6		
Fecal urgency	None	Hurry	Immediately	Incontinence	
Bloody stools	None	Trace	Occasional frank	Usually frank	
General well-being	Very well	Below average	Poor	Very poor	Terrible
EIMs	1 point per extraintestinal manifestation				

Adapted from Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. Gut. 1998;43(1):29–32

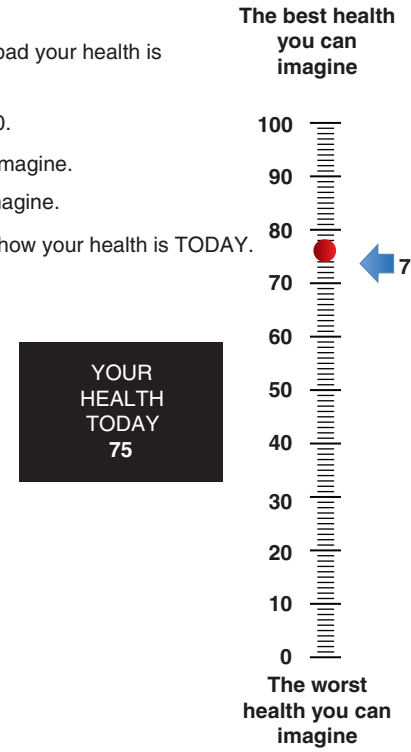

Fig. 46.10 EuroQoL 5D visual analog scale, an example of a rapid, easily administered and interpretable instrument which assesses global health-related quality of life. © Stichting EuroQol Research Foundation

Treatment Endpoints

- The goals of medical therapy include induction of remission, avoiding steroids and improving quality of life (QoL) while avoiding toxicity and preventing neoplasia.
- Maintenance of remission often requires ongoing medical therapy.
- Symptomatic improvement can also be assessed by measuring quality of life (QoL). Instruments to assess QoL may include measures of overall QoL (such as the SF-36 or EuroQoL-5D VAS [Fig. 46.10]), disease (IBD-Q), or symptom-specific (FISI/FIQL).

Cost Considerations

- CUC is known to be a costly disease with medical patients on average consuming $6586 dollars per year, increasing to $15,732–$20,131 in the years prior to surgical intervention.
- The cost-effectiveness of surgery compared with biologic therapy has also been studied,

Table 46.5 Sensitivity analysis of the effect of duration of disease on the cost-effectiveness of infliximab and surgery for severe ulcerative colitis. Quality-adjusted life years based on EuroQoL-5D visual analog scale

Model length	Dominant strategy	Cost of IFX strategy (US dollars)	Cost of surgery strategy (US dollars)	Effectiveness of IFX strategy[a]	Effectiveness of surgery strategy
1 year	IFX	$26,698.45	$63,721.15	0	0
2 years	IFX	$63,648.51	$74,090.32	0.78	0.76
3 years	Surgery	$91,515.26	$82,364.24	1.51	1.50
4 years	Surgery	$112,938.29	$90,277.08	2.19	2.21
5 years	Surgery	$129,786.88	$97,911.94	2.84	2.89
10 years	Surgery	$179,816.82	$132,325.91	5.65	5.98
Lifetime	Surgery	$305,691.59	$270,477.74	16.58	18.34

[a] Quality-adjusted life years based on EuroQoL-5D Visual analog scale

Reproduced with permission from Holubar SD, Piazik B, Xu Kathleen, Dulai P, Tosteson A, Siegel C, Finlayson S. Cost-effectiveness of infliximab versus colectomy for severe ulcerative colitis: a Markov analysis: P-108. Inflamm Bowel Dis. 2012. 7;18:S57–8. © Wolters Kluwer

and early colectomy was found to be a cost-effective treatment compared to maximal medical therapy.

- A sensitivity analysis comparing the cost-effectiveness of infliximab and surgery for severe CUC showed that after 2 years of IFX therapy, surgery increasingly became the dominant strategy (Table 46.5).

Part 2: Specific Treatments

Bottom-Up Versus Top-Down Strategies

- An overview of available medical therapy is shown in Table 46.6.
- "Bottom-up" therapy starts with less expensive, less effective medications which are sequentially added until the desired clinical endpoint is achieved.
- "Top-down" strategy is when patients are initially placed on more aggressive therapies in order to achieve rapid remission, and then agents are sequentially weaned.
  - An example of top-down therapy would be inducing the patient on a biologic and a thiopurine and then attempting to remove the biologic after the patient is clinically improved.

Aminosalicylates (5-ASA Moieties)

- Multiple forms of 5-ASA medications have been developed, mainly in an attempt to reduce side effects.
- 5-ASA medications are administered via enteral or topical formulations.
- There are three release mechanisms: pH (e.g., Asacol®, Lialda®), time release (e.g., Pentasa®), and bacterial cleavage release (e.g., Azulfadine®); these mechanisms dictate the target area of bowel (ileum, colon, or rectum).
- Oral 5-ASA products have been shown to be effective for induction of remission in mild-to-moderate CUC.
- "Bidirectional therapy" with both enteral and per rectal preparations is more effective than either alone.
- Side effects, which are dose-dependent, are mainly dermatologic and gastrointestinal toxicity.

Immunomodulator Therapy (6-MP, Azathioprine)

- Azathioprine (AZA) is the prodrug of 6-mercaptopurine (6-MP), and both act as an immunomodulator and weak immunosuppressant.
- It is important to understand the TMPT metabolic pathway in order to prevent severe toxicity, including life-threatening leukopenia, pancreatitis, and hepatitis (Fig. 46.11).
- In TMPT-deficient patients (prevalence 1 in 300 persons), active metabolites are not efficiently degraded resulting in supra-therapeutic AZA concentrations. Thus, TMPT testing is an integral part of initiating TP therapy.

Table 46.6 Overview of clinical pharmacotherapy for CUC

Class (effect)	Indication	Examples	Dose
5-Aminosalicylates (enteric/topical anti-inflammatory)	Induction *and* maintenance of remission for mild-to-moderate colitis/proctitis	Sulfasalazine	4–6 g PO daily
		Mesalamine Canasa® suppositories	PO: 2.4–4.8 g PO daily PR: 500 mg–1 g per rectum daily
		Olsalazine	1.5–3 g PO daily
		Balsalazide	6.75 g PO daily
Topical corticosteroids (anti-inflammatory)	Maintenance of remission for mild-to-moderate colitis	Budesonide	9 mg PO daily, rectal foam now available
Thiopurine immunomodulators (block purine metabolism)	Induction *and* maintenance of remission for moderate-to-severe colitis	Azathioprine (AZA) 6-MP	AZA: 2.5 mg/kg PO daily (50–150 mg PO q24) 6MP: 1.5 mg/kg daily
Biologic agents (block TNF or leukocyte rolling and adhesion)		Anti-TNF-alpha Antibodies	IFX: 5–10 mg/kg, weeks 0, 2, and 6 and then every 4 weeks Adalimumab: 160 mg week 1, 80 mg week 2, and then 40 every other week
		Anti-integrin Antibodies	Golimumab: 200 mg week 0 and then 100 mg every other week Vedolizumab: 300 mg IV weeks 0, 2, and 6, then every 8 weeks
Systemic corticosteroids (anti-inflammatories)	Rescue therapy for severe colitis[a]	Prednisone	5–40 mg PO daily
		Hydrocortisone	20–300 mg IV daily
Calcinurin inhibitors (immunosuppressives)	Rescue therapy for steroid-refractory severe colitis[a]	Cyclosporine Tacrolimus	2–4 mg/kg daily 0.05 mg/kg twice daily

[a]indicated for induction of remission *not* maintenance of remission. Inability to wean from these agents is an indication for surgery

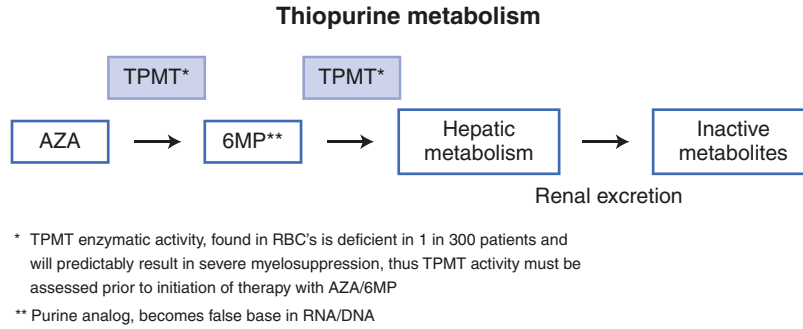

Fig. 46.11 Schematic representation of in vivo thiopurine metabolism

- Immunomodulator therapy may be associated with a marginally increased risk of lymphoma, but the absolute risk is small.
- TPs are effective steroid-sparing medications. They are often started upfront with steroids to induce remission. The steroids are then weaned, and the TP is used as a maintenance drug.
- TPs are often used in combination with biologics in part to prevention of anti-TNF immunogenicity. Thiopurines, in the setting of combination therapy, may also represent an "exit strategy" from chronic biologic therapy.

Biologic Agents

Anti-TNF-Alpha Antibodies

Infliximab (Remicade®)

- IFX is a chimeric mouse/human monoclonal anti-tumor necrosis factor (TNF) alpha antibody. IFX was FDA approved for CUC in 2005 and is now indicated for the treatment of mild-to-severe UC in both adults and children.
- In the ACT-1 and ACT-2 randomized trials assessing the efficacy of IFX for inducing and maintaining remission, 60–69% of patients had successful induction, compared with 29–37% response for placebo.
- The typical loading dose is 5 mg/kg IV at weeks 0, 2, and 6, switching to maintenance dose of 5 mg/kg IV every 8 weeks starting at week 14.
- If a loss of responsiveness occurs and symptoms flare, then the IFX dose can be increased to 10 mg/kg IV every 4–8 weeks.
- Serum drug trough levels are monitored to assure proper dosing; ensuring adequate trough levels may be associated with increased efficacy and decreased risk of colectomy.
- The best outcomes of IFX therapy are seen in combination with other medications such as TPs as demonstrated by the UC-SUCCESS trial with 40% of patients achieving a steroid-free remission, compared with only 2% on monotherapy with either agent; similarly mucosal healing was observed in 63% of combination therapy patients compared with 55% on IFX alone.
- The most widely recognized side effect of IFX is activation of latent infections most notably TB. Thus prior to initiation of IFX therapy, patients are screened with the QuantiFERON® gold assay.
- IFX can make active infections worse and can exacerbate hepatitis B.
- Other adverse reactions include infusion reactions, which can result in flash pulmonary edema or hypersensitivity including anaphylaxis.
- It is highly controversial whether or not biologic agents, and IFX in particular, increase the complication rate of surgery. The half-life of the agents (Fig. 46.12) may provide some guidance for timing of elective surgery.

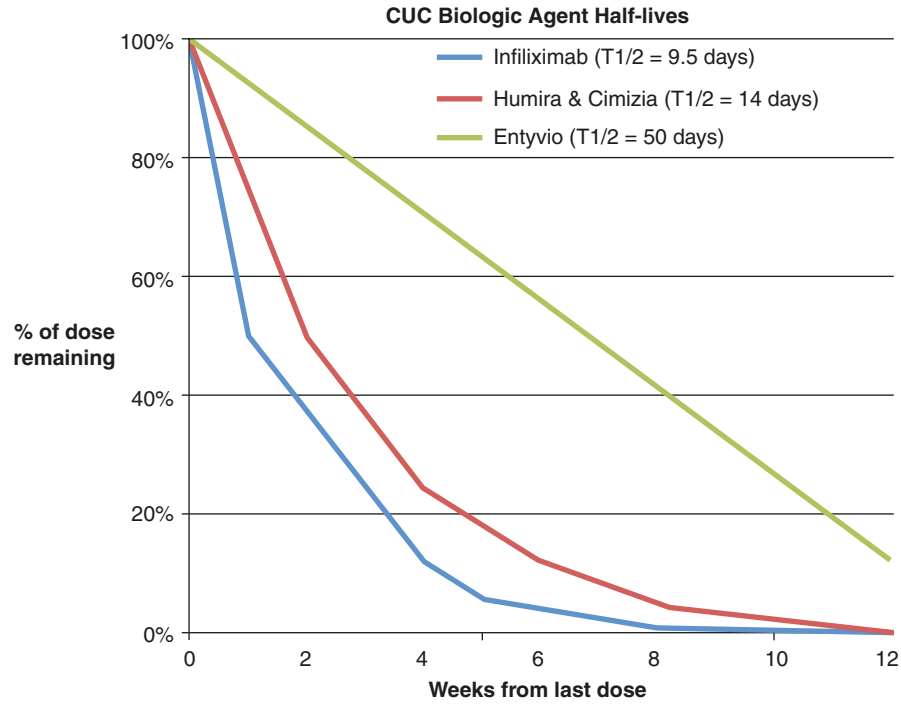

Fig. 46.12 Graphical representation of the theoretical in vivo half-lives of biologic agents used to treat CUC. Note this graph assumes first-order elimination pharmacokinetics

Adalimumab (Humira®)

- This humanized antibody is indicated for induction and maintenance of remission in adults with moderate-to-severe CUC.
- The ULTRA-1, ULTRA-2, and ULTRA-3 trials demonstrated that in patients with moderately to severely active CUC, adalimumab is efficacious in both short- and long-term maintenance of remission for up to 4 years in 60% of patients.
- Loading doses are used (week 0,160 mg; week 2,80 mg; maintenance week 4,40 mg SQ every other week subcutaneously).
- If a sub-optimal response is observed, the dosing interval is often increased to weekly.
- As in IFX, trough levels can be used to monitor and optimize therapy.
- Also as in IFX, the best outcomes are seen with combination therapy with TPs.
- The humanization of the antibody has reduced the side effect profile relative to IFX. Adverse reactions are generally similar to those of IFX and also include local injection site reactions and loss of responsiveness.

Certolizumab Pegol (Cimzia®)

- Cimzia is a partially humanized Fab fragment of an anti-TNF antibody, which is PEGylated.
- Presently it is FDA approved for CD (and RA), *but not approved for CUC*.

Golimumab (Simponi®)

- Simponi is another humanized anti-TNF Ab, which was FDA approved for the induction and maintenance of remission in adults and for patients with loss of responsiveness to IFX and Humira.
- In the PURSUIT-SC study, golimumab was effective for the induction of remission in moderately to severely active CUC, with >51% of patients achieving remission compared with 30% of placebo patients.
- Dosing is usually 200 mg subcutaneously at week 0 and then 100 mg subcutaneously every other week.

Anti-integrin Antibodies

Vedolizumab (Entyvio®)

- Entyvio is an intravenously administered monoclonal antibody to integrin $\alpha 4\beta 7$.
- In 2014, it was FDA approved for the induction and maintenance of remission of both CUC and CD in adults and also for patients with loss of responsiveness to other biologic medications.
- In the GEMINI-I and GEMINI-II studies, vedolizumab resulted in induction of remission in 47% of patients, compared with 25% of placebo, and maintenance of remission in 41% vs. 15% with placebo.
- Dosing, which is intravenous, is 300 mg IV at weeks 0, 2, and 6 and then every 8 weeks.

"Rescue" Therapy

Corticosteroids

- Corticosteroids represent the mainstay of rescue therapy for otherwise medically refractory CUC.
- The mechanism of action is that of nonspecific immunosuppression and immunomodulation.
- Steroids are associated with significant side effects, and they should not be used for maintenance therapy.
- Various formulations are converted to hydrocortisone equivalent doses using readily available online conversion calculators.
- Side effects of steroids include adrenal suppression, water retention, moonlike facies, psychological distress (ranging from agitation and insomnia to frank psychosis), rosacea, buffalo hump, abdominal striations, and osteoporosis.
- One of the most serious and potentially nonreversible adverse effects is osteoporosis, which may not be responsive to calcium or vitamin D supplementation. Patients on repeated courses of corticosteroids need bone density monitoring with dual-energy X-ray absorptiometry (DEXA) scans.

- The CORE-1 study showed that budesonide MMX 9 mg was effective at indication of remission in mild-to-moderate CUC but more limited in maintenance of remission.
- Long-term (2 years) budesonide use was shown to be safe based on bone density and protective if steroid naive.
- Oral steroids are typified by prednisone. Most patients with CUC respond to oral steroids, with only 16% not responding acutely.
- However, systemic steroids have no role for maintenance of remission due to their relatively severe side effect profiles.
- Long-term (> 1 year) corticosteroid treatment is generally contraindicated; inability to wean off chronic steroids represents an indication for surgery.
- IV steroids are indicated for those refractory to outpatient medical therapy. Maximum effective dose is 300 mg hydrocortisone per day. An estimated 60% of patients will respond, usually within 5–7 days.

Cyclosporine/Tacrolimus

- These drugs, used for prevention of graft rejection in solid organ transplantation, are calcinurin inhibitors.
- Calcinurin inhibitors are reserved for use as a rescue agent for severe, otherwise medically refractory, CUC.
- These medications carry a risk of opportunistic infections and are associated with a host of specific adverse reactions; they are potentially nephrotoxic, hepatotoxic, and neurotoxic and may exacerbate hypertension and hyperlipidemia.

Methotrexate (MTX)

- MTX is an antimetabolite, specifically inhibiting folic acid metabolism by competitive inhibition of dihydrofolate reductase (DHFR).
- Aside from being hepatotoxic and myelosuppressive, MTX is also an FDA category X drug, meaning it is teratogenic.

Part 3: Medical Management of Mild-to-Severe CUC

Mild-to-Moderate Distal Colitis/ Proctitis (Fig. 46.13)

- Topical mesalamine is the first-line treatment both for inducing and maintaining remission of distal mild or moderate colitis.
  - Foams reach the sigmoid colon, and enemas may even reach the splenic flexure; compliance can be an issue.
  - Although oral aminosalicylates are less effective than topical mesalamine, most patients prefer oral formulations. In moderately severe cases, combining topical and oral therapy is more effective than topical mesalamine alone both in achieving and maintaining remission.
- Topical corticosteroids have similar efficacy in achieving remission in active disease and are an alternative to topical mesalamine. They should not be used for maintenance, however.

Mild-to-Moderate Extensive Colitis (Fig. 46.13)

- For mild or moderate colitis, oral salicylates induce clinical improvement in 60–80% of cases within 4 weeks of therapy.
- In either distal or extensive colitis not responding to 4 weeks of aminosalicylate therapy, a course of oral steroids is indicated.
  - When a clinical response has been achieved, the dose is tapered over several weeks. Although the response rate is around 70%, ~20% develop steroid dependency and cannot be weaned without relapse of symptoms.
- In nonresponders, and in patients who become steroid-dependent, therapy should be started to aid in weaning of prednisone. The two main options at this stage are TPs and biologics.
  - Azathioprine is effective in inducing and maintaining remission, but its effects are

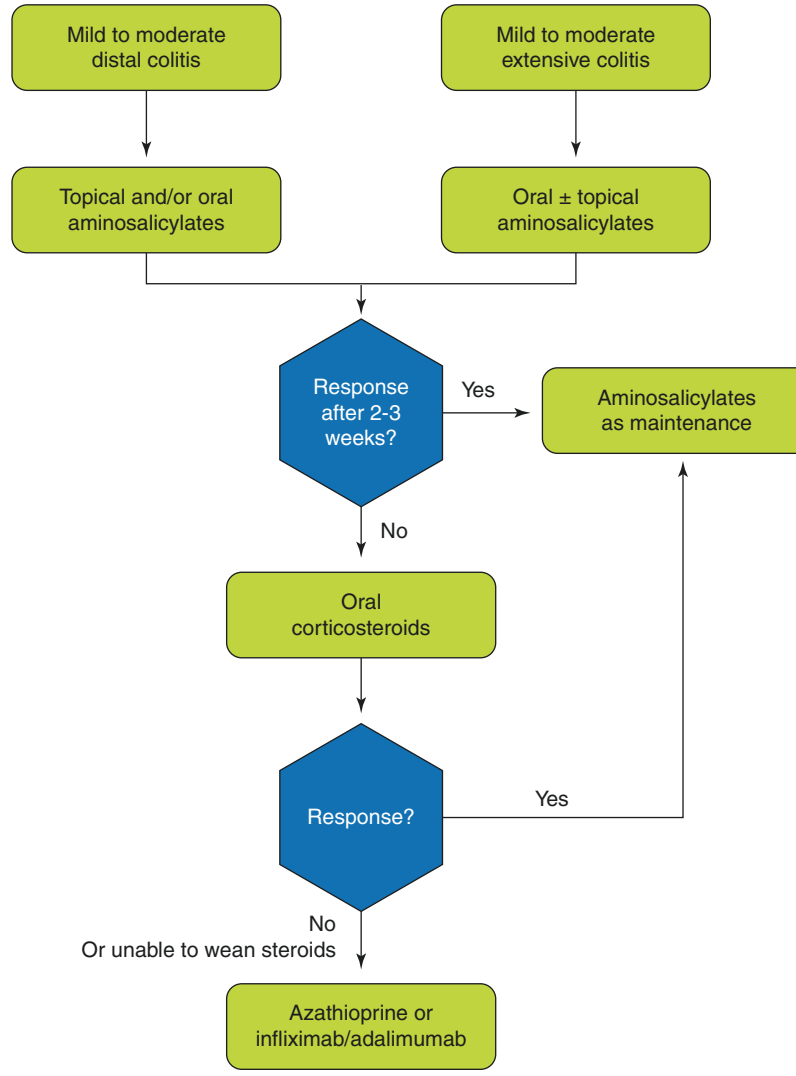

Fig. 46.13 Standard "bottom-up" approach to the management of mild-to-moderate CUC (based on the American College of Gastroenterology 2010 Practice Guidelines)

slow with the time of onset measured in months, requiring overlap with an extended course of oral prednisone.

– Infliximab has been well studied in steroid-refractory mild and moderate colitis; 69% of patients respond to induction treatment. Co-administration of infliximab and azathioprine may be associated with an increased clinical response rate and mucosal healing in moderate and severe steroid-refractory colitis compared to monotherapy with either drug.

- Remission in mild and moderate extensive colitis can be maintained either by oral aminosalicylates, TPs, or infliximab.

Severe Colitis (Fig. 46.14)

- Most patients with severe colitis require hospitalization for stabilization and a course of intravenous corticosteroids, regardless of the extent of disease.

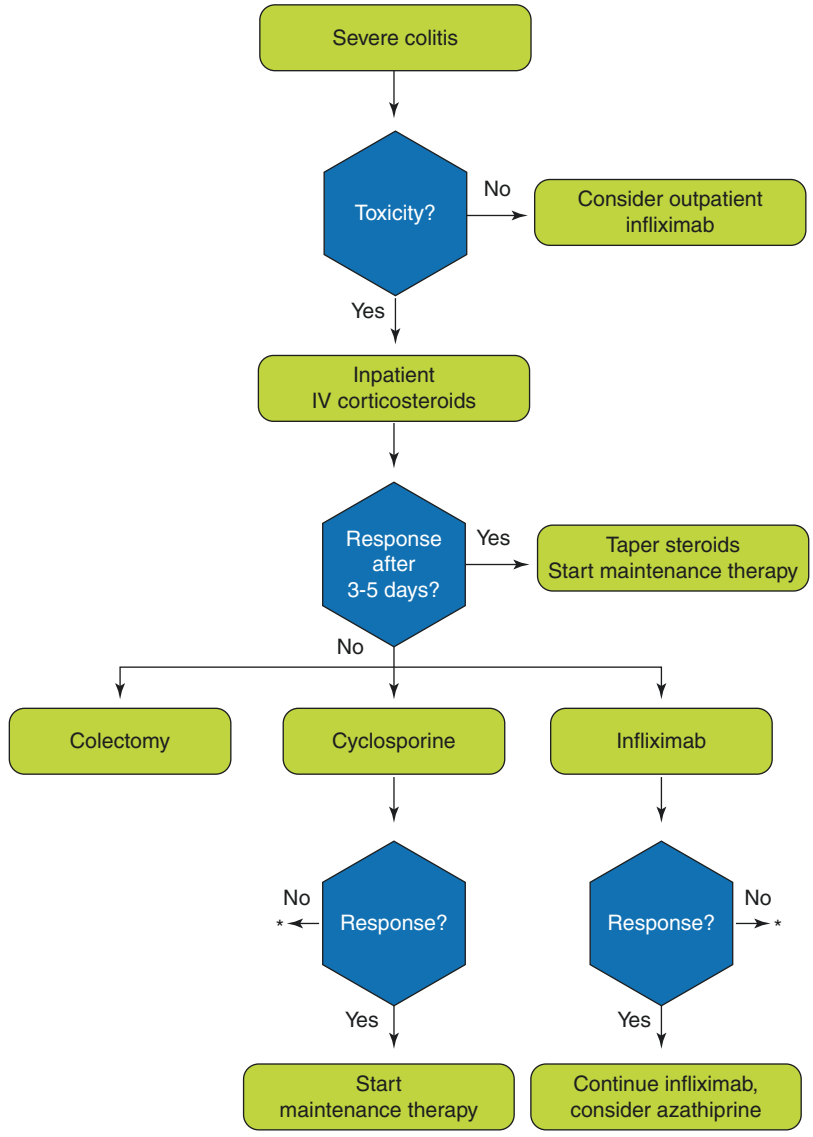

Fig. 46.14 Standard "bottom-up" approach to the management of severe CUC (based on the American College of Gastroenterology 2010 Practice Guidelines)

* Colectomy. Selected patients in specialized IBD units may respond to switching from infliximab to cylosporine or vice versa

- A course of 3–5 days is given with close clinical observation. Consultation with a colorectal surgeon and a stoma therapist is typically advisable during this stage, so that the patient can be in a position to make an informed decision about the next steps by day 3–5 should steroid therapy fail; 20–40% of patients with severe UC will fail to improve on IV corticosteroids.
- Patients will often need supplemental parenteral nutrition support. Continued oral diet is encouraged in most patients, due to the theoretical advantages of short-chain fatty acid provision to the colon. However, bowel rest may be indicated if bowel movements are excessive.
- Thromboembolic prophylaxis is routinely given, and anticholinergic and opioid medications are avoided as possible.

- Importantly, gut infections may exacerbate ulcerative colitis, and treating those aggressively may facilitate induction of remission.
  - Stool samples are obtained for *Salmonella*, *Yersinia*, *Shigella*, and *C. difficile* toxin.
  - Colonic CMV disease is best demonstrated by immunohistochemistry of classic "punched-out" mucosal ulcer biopsies obtained on flexible sigmoidoscopy; leukocyte CMV PCR is sometimes used as a surrogate marker.
- Broad-spectrum antibiotics are often given to patients with toxicity owing to concern about bacterial translocation.
- Patients with megacolon (often defined as colonic dilatation to a diameter > 6 cm) require additional caution.
  - Oral intake is stopped, abdominal signs are closely monitored, and daily plain abdominal films are obtained to assess progression.
  - Failure to respond to corticosteroids is an indication for urgent colectomy after 24–48 h, as is progressive dilatation.
- Fulminant colitis is the advanced form of severe acute colitis and is typically defined as toxic colitis, i.e., colitis with signs of systemic toxicity such as peritonitis, hypotension, impending perforation, and/or end-organ damage such as renal failure.
- Rescue therapy for steroid-refractory severe UC typically includes three options: colectomy, cyclosporine, and infliximab.
  - Intravenous cyclosporine is highly effective in steroid-resistant severe UC, with response rates up to 83%. The issue of recrudescence of colitis following rescue therapy with cyclosporine, in combination with a significant toxicity profile, has led to a reduction in its usage in the biologic era, and presently it is only offered at select centers.
  - Infliximab has emerged as a widely used rescue therapy with response rates in the 50–71% range. One important advantage is that infliximab can be continued long term to maintain remission.
  - A direct comparison confirmed that both cyclosporine and infliximab have high initial response rates when used as rescue therapy in steroid-refractory severe colitis (85 vs. 86%); colectomy rates were also similar at 3 months (18 vs. 21%).
  - The strategy of using surgery as the last resort may actually increase CUC-related mortality, and an undue delay may increase postoperative complications. Patients should be educated about the role and outcomes of surgery.