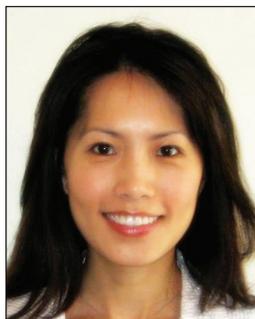Seymour Katz, M.D., Series Editor

Practical Treatment of Ulcerative Colitis

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The initial approach to ulcerative colitis patients requires the exclusion of other causes of bloody diarrhea, followed by the determination of the extent and severity of disease. Patients with mild-to-moderate UC are treated initially with oral 5-ASA medications combined with 5-ASA or steroid suppositories plus 5-ASA enema or steroid foam preparations. The oral 5-ASA preparations should then be continued for maintenance of remission. For patients with moderate-to-severe UC, oral steroids are used initially, followed by 6-MP or azathioprine for maintenance in the traditional step-up therapeutic strategy. For the patient with acute, severe UC, who has not responded to IV steroids for five-to-seven days, treatment choices are either IV cyclosporine or IV infliximab or colectomy. Alternatively, for patients with severe UC, infliximab is effective using a top-down strategy in order to more rapidly achieve response and remission. For UC patients who have not responded adequately to medications, colectomy with IPAA is appropriate because the diseased colon is removed and the medications with their potential side effects are avoided.

INTRODUCTION

Before choosing the initial therapeutic approach for the patient with ulcerative colitis (UC), three issues must be clarified: 1) demonstration that the diagnosis is ulcerative colitis and not another cause of bloody diarrhea, 2) determination of clinical and endoscopic disease severity, and 3) documentation of disease extent.

An accurate diagnosis remains the foundation for a successful therapeutic plan and therefore all other possible causes of bloody diarrhea must be excluded expeditiously. Infectious colitides that may present with colonic mucosal ulcerations and bloody diarrhea include: *Clostridium difficile*, *E. coli* 0157: H7, CMV, *Salmonella*, *Shigella*, and amoebiasis. Non-infectious causes of bloody diarrhea in the differential diagnosis include: ischemia, radiation, NSAIDs, oral contraceptives, hormone replacement therapy, medications, and Crohn's disease. Please refer to Table 1.

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Table 1
Differential Diagnoses: Bloody Diarrhea, Mucosal Ulcerations

- *Clostridium difficile*
- CMV; Hemorrhagic *E. coli* 0157:H7; *Solmonella; Shigella; Amebiasis*
- Ischemia; Radiation
- NSAIDs; Antibiotics; Oral Contraceptives; Hormone Replacement Therapy
- Crohn's Disease

Clinical assessment of disease activity in the patient with ulcerative colitis includes both a careful history and laboratory studies. Patients with less than four bowel movements per day, small amounts of rectal bleeding, normal inflammatory indices (sedimentation rate, C Reactive Protein, Platelet Count), and no evidence of toxicity are classified as having mild UC. Patients with four-to-six bowel movements per day, moderate rectal bleeding, normal inflammatory indices, and evidence of mild toxicity are classified as having moderate UC. Patients with 6 to 10 bowel movements per day, large amounts of rectal bleeding, anemia, elevated inflammatory indices, and/or evidence of significant toxicity are classified as having severe UC. Patients with greater than 10 bowel movements per day, continuous rectal bleeding, severe anemia that may require blood transfusions, high inflammatory indices, and/or evidence of severe toxicity such as abdominal tenderness, abdominal distension and/or colonic dilation on radiologic examination, are classified as having fulminant UC. Overall, approximately 20% of UC patients at presentation will have mild disease activity, 75% moderate to severe disease activity, and 5% fulminant disease activity.

Colonoscopic evaluation plays a vital role in confirming the diagnosis of UC, excluding other possible causes of bloody diarrhea, and determining disease extent and severity. Biopsies and aspirates are needed to exclude infectious colitides and to rule out co-infection with *C. difficile* or CMV. Aspirates should be obtained at the time of colonoscopy and sent immediately to the laboratory for determining whether or not *Clostridium difficile* is present. This is important, because *Clostridium difficile* in IBD often occurs in the absence of pseudomembranes. In the patient with severe acute ulcerative colitis, a full colonoscopy should be avoided due to safety considerations. However, a limited (20 to 40 cm) unprepped flexible sigmoidoscopy with aspirates and biopsies, combined with abdominal CT imaging can usually provide the necessary information. With regards to disease extent, approximately 45% of patients will have UC involving the rectum and sigmoid colon, 40% of patients will have UC involving the rectum, sigmoid, and descending colon (left sided colitis), and 15% of patients will have UC involving the entire colon.

For patients in whom clinical and colonoscopic features do not definitively distinguish between UC and Crohn's colitis, serum assays for perinuclear anti-cytoplasmic antibodies (pANCA) and anti-*Saccharomyces cervisiae* antibodies (ASCA) may facilitate the distinction. For example, the presence of a positive pANCA and a negative ASCA in a patient with clinically and colonoscopically indeterminate colitis has a positive predictive value of 75% for the diagnosis of ulcerative colitis; conversely, the occurrence of a negative pANCA and a positive ASCA yields an 86% positive predictive value for the diagnosis of Crohn's colitis (1). Although this distinction is not uniformly requisite, it may occasionally influence medical and/or surgical treatment decisions (1).

MILD TO MODERATELY ACTIVE UC

Aminosalicylates have been used for the treatment of mild to moderately active UC for many years. Sulfasalzine is comprised of 5-aminosalicylic acid (5-ASA, mesalamine) linked to sulfapyridine by an azo bond (2). Sulfasalazine is cleaved in the colon by bacterial azoreductase into 5-ASA and sulfapyridine (2). Sulfasalazine has been demonstrated to induce and maintain remission in UC (2-4). The 5-ASA component is responsible for the clinical efficacy of sulfasalazine for the treatment of UC (2). Because sulfapyridine causes most of the toxicity of sulfasalazine (2), alternative preparations that deliver mesalamine (5-ASA) to the colon are now predominantly used for our UC patients. Nevertheless, because of its proven effectiveness and low cost, sulfasalazine continues to be used for a significant number of UC patients.

Currently available 5-ASA formulations, sans sulfapyridine, include Asacol, Pentasa, Dipentum, Colazal, and Lialda. Asacol utilizes a pH-dependent acrylic resin (Eudragit-S), which dissolves at a pH greater than 6.0, allowing delivery of 5-ASA to the terminal ileum and colon. Pentasa allows the time release of mesalamine, resulting in delivery of 5-ASA to both the small intestine and colon. Balsalazide (Colazal) links a 5-ASA molecule to an inert carrier molecule via an azo bond, resulting in release of 5-ASA in the colon, after cleavage by bacterial azoreductases. Olsalazine (Dipentum), consists of two 5-ASA molecules linked via an azo bond, which is cleaved by bacterial azoreductases in the colon, allowing release of 5-ASA in the colon. Lialda utilizes MMX delayed release technology to allow 5-ASA release to the colon. 5-ASA can also be delivered topically to the rectum and left colon, by either enema or suppository preparations.

Oral 5-ASA medications have proven to be very effective in inducing response and maintaining remission in a high percentage of UC patients (2-4). For most patients, doses of 2.4 Gm to 4.8 Gm per day will induce an excellent response within six weeks and maintain a durable long-term remission. In a meta-analysis, the efficacy of 5-aminosalicylates compared to placebo in inducing remission in UC has been confirmed (4). Therefore, in the treatment of mild to moderately active UC, oral 5-ASA medications are the first line therapy of choice (Figure 1).

Patients with mild to moderate UC of the rectum, sigmoid colon, or left colon can also be effectively treated with topical corticosteroid and 5-ASA suppository, enema, and foam preparations (Figure 1). Since there can be significant steroid absorption from hydrocortisone enemas, we usually use 5-ASA enemas plus 5-ASA suppositories or topical steroid foam plus steroid suppositories. A double-blind study of patients with mild to moderate distal UC compared oral (2.4 g/day) versus rectal (4 g/day) versus combination therapy (5). In this six-week trial, the percent of patients who responded and achieved remission was significantly higher in the combination group when compared to either rectal or oral therapy alone. Therefore, initial combination therapy with oral 5-ASA medications plus topical, rectal 5-ASA enemas and/or suppositories, should strongly be considered initially in patients with

mild to moderate UC of the rectum, sigmoid colon, or left colon (Figure 1). Patients with mild to moderate left sided UC who do not respond to standard doses of topical 5-ASA therapy may respond to increased doses and frequency of treatment (6). After response and remission have been achieved, long-term oral 5-ASA therapy alone can be used for maintenance of remission.

MODERATE TO SEVERE UC

Systemic corticosteroids have long been utilized in the treatment of moderate to severe UC. Prednisone 40 mg po daily is effective for the induction of response and remission in 80% of moderate to severe UC patients (Figure 1). Tapering of the prednisone by decreasing the dose by 5mg every one to two weeks can begin after the patient has been stable for two to four weeks. Oral corticosteroids are not effective for maintenance of remission and their long-term use is associated with major side effects. Therefore, after inducing remission with steroids, we need to employ different effective treatment strategies to maintain remission including oral and/or topical 5-ASA products, immunomodulators, and/or biologic agents (Figure 1).

For patients with mild to moderate UC, who are refractory to 5-ASA products, and for patients with moderately severe UC, who require steroids for induction of response and remission, immunomodulators are appropriate as the next step in therapy. This is the traditional step-up approach, which has been used for many years (Figures 1, 2). In contrast, for patients with severe UC, a top-down approach using biologics as the next step may be appropriate (Figures 1, 2).

The immunomodulators azathioprine (AZA) and 6-mercaptopurine (6-MP) have been demonstrated to successfully maintain remission in patients with moderate to severe ulcerative colitis (7,8). AZA or 6-MP are usually begun after successful induction of remission with steroids and are therefore primarily used for maintenance of remission and as steroid sparing agents for long-term control of UC. AZA and 6MP may not achieve their maximal benefit for four-to-six months and therefore are usually used in patients who have had either an excellent partial response or who are in remission after induction with steroids (7,8).

Some of the potential side effects of AZA and 6MP include fever, rash, pancreatitis, infections and lym-
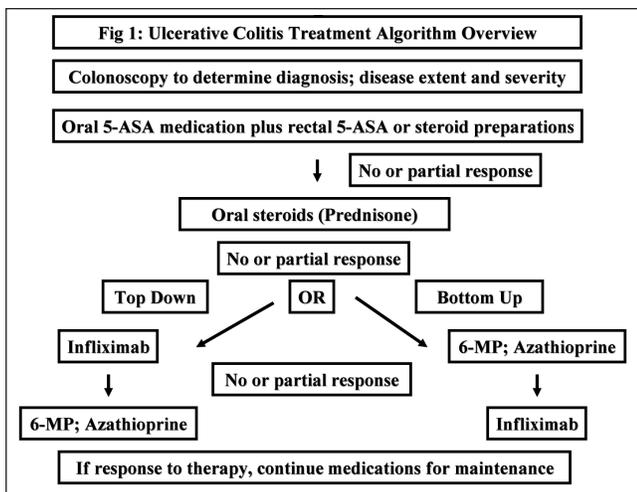
Fig 1: Ulcerative Colitis Treatment Algorithm Overview

Colonoscopy to determine diagnosis; disease extent and severity

Oral 5-ASA medication plus rectal 5-ASA or steroid preparations

↓ **No or partial response**

Oral steroids (Prednisone)

No or partial response

Top Down | **OR** | **Bottom Up**

Infliximab | **No or partial response** | **6-MP; Azathioprine**

6-MP; Azathioprine | **Infliximab**

If response to therapy, continue medications for maintenance

Figure 1. Treatment algorithm overview for the outpatient with ulcerative colitis (UC). Initially a colonoscopy is performed to rule out other diagnoses as well as to determine the extent and severity of the UC. If the patient does not respond to initial therapy with oral 5-ASA medications combined with 5-ASA or steroid suppositories plus steroid or 5-ASA foam or enema preparations, treatment with prednisone is appropriate. For UC patients with mild to moderate disease activity who do not respond or who only partially respond to prednisone, a trial of 6-MP or azathioprine is appropriate, followed by a trial of infliximab if 6-MP or azathioprine fails (traditional step-up therapy). For UC patients with severe disease activity who do not respond or who only partially respond to prednisone, infliximab is appropriate, followed by a trial of 6-MP or azathioprine if infliximab fails (top-down therapy). If remission is able to be achieved using any of the therapeutic regimens discussed above other than prednisone, then the medications are continued long-term to maintain remission.

phoma (9). Leukopenia and hepatitis correlate with the levels of the metabolites 6-thioguanine (6-TG, bone marrow suppression) and 6-methylmercaptopurine (6-MMP, liver toxicity). 6-TG and 6-MMP are generated by the thiopurine s-methyltransferase (TPMT) enzyme (10,11). TPMT genotype and/or TPMT enzyme activity phenotype testing should be obtained prior to the initiation of AZA or 6MP therapy to identify the 0.3% of the population with low or absent TPMT enzyme activity, in order to decrease the risk of potentially life-threatening bone marrow toxicity (10,11). These patients should not receive AZA or 6MP. Patients with intermediate enzyme activity, which comprises 11% of the population, can begin therapy with a low dose of AZA or 6MP
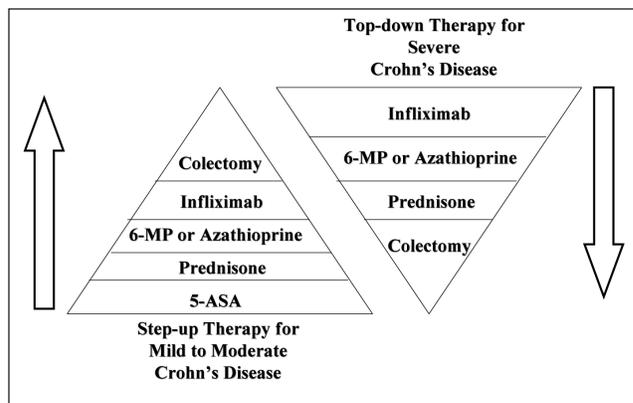
Top-down Therapy for Severe Crohn's Disease

Infliximab / 6-MP or Azathioprine / Prednisone / Colectomy

Colectomy / Infliximab / 6-MP or Azathioprine / Prednisone / 5-ASA

Step-up Therapy for Mild to Moderate Crohn's Disease

Figure 2. Step-up therapy for mild to moderate Crohn's disease versus top-down therapy for severe Crohn's disease. The traditional step-up approach begins with first line therapy including oral 5-ASA medications combined with 5-ASA or steroid suppositories plus steroid or 5-ASA foam or enema preparations. For UC patients who fail first-line therapy, oral prednisone is then used. After the patient responds or is in remission due to prednisone, a trial of 6-MP or azathioprine is used to maintain long-term remission. For patients who fail 6-MP or azathioprine, trial therapy with infliximab is appropriate. For patients with UC, who have not responded or only partially responded to 6-MP (or azathioprine) and/or infliximab, colectomy with either ileostomy or ileal pouch-anal anastomosis is important to consider. In contrast to the traditional step-up algorithm described above, patients with severe UC are appropriate candidates for top-down therapy, beginning with infliximab. If a patient fails therapy with infliximab, 6-MP or azathioprine can then be used. For UC patients who fail both infliximab and 6-MP or azathioprine, prednisone is appropriate. If necessary, colectomy should be considered.

(10,11). Patients with normal TPMT genotype or activity can commence with higher doses of AZA (2–2.5 mg/kg/day) or 6MP (1–1.5 mg/kg/day) (10,11).

6-TG is the active moiety which is responsible for the clinical efficacy of AZA/6MP. 6-TG levels can assist in dosage titrations of AZA/6MP to optimize efficacy and minimize toxicity (10,11). Bone marrow toxicity due to an elevated 6-TG level necessitates AZA or 6-MP dose reduction. Alternatively, a low or absent 6-TG level in a non-responder, indicates noncompliance (10,11). AZA/6MP hepatotoxicity appears to be associated with higher mean 6-MMP levels (10,11). Despite the availability of 6-TG and 6-MMP levels, they do not

replace CBC or liver chemistries, which should be obtained weekly to biweekly during the first month of therapy, and then every one-to-two months when the patient has demonstrated stable blood counts (10,11).

The increased risk of lymphoma in IBD patients on AZA or 6MP has raised concern, especially in patients positive for Epstein Barr virus (12). A meta-analysis of six studies on patients with Crohn's disease on 6MP or azathioprine demonstrated a four-fold increase in the incidence of lymphoma by discovering one lymphoma per 2,000 patient years of follow-up in Crohn's patients on AZA/6MP v. one per 8000 years of follow up in those who were not on AZA/6MP (12).

Infliximab (Remicade) is an anti-TNF alpha chimeric (75% human, 25% mouse) monoclonal antibody which has been shown to be effective in chronic, severe UC. The ACT 1 and ACT 2 trials have substantiated the efficacy of infliximab in steroid refractory UC patients (13). Therapy is begun with a dose of 5 mg/kg IV given at weeks zero, two, and six for induction of response and remission, with maintenance infusions given at six-to-eight week intervals (13). The potentially serious adverse effects of infliximab include major infections such as primary and disseminated tuberculosis (TB), pneumonia, sepsis, urinary tract infections, abscesses, and peritonitis. Systemic fungal infections such as histoplasmosis, coccidiodomycosis, aspergillosis, candidiasis, and *Pneumocystis carinii* pneumonia (PCP) have also been reported. The potential for these and other well known side effects should be discussed with the patient, and this discussion should be documented before proceeding with infliximab therapy. In order to decrease side effects, it is important to use infliximab as monotherapy, without concomitant immunomodulators or steroids. Thus, after beginning infliximab, tapering and discontinuation of steroids needs to occur as rapidly as possible.

ACUTE SEVERE (FULMINANT) UC

The value of IV corticosteroids in acute, severe UC has been demonstrated in clinical trials (14). In patients with acute severe (fulminant) UC, up to 75% will exhibit a partial or complete response within one week to intravenous corticosteroids. For the other 25%, steroid refractory UC is defined as the absence of a response to treatment within five-to-seven days and

the therapeutic choices are cyclosporine-A, infliximab, or colectomy (Figure 3).

Cyclosporine-A (CsA) can be considered in patients with acute, severe steroid refractory UC (15,16; Figure 3). CsA is used as a bridge to AZA or 6MP maintenance therapy (17). Thus, in the patient with acute, severe steroid refractory UC, the CsA can be initiated along with AZA or 6MP; the steroids can then be tapered rapidly and the CsA discontinued, at which time the AZA or 6MP is used as maintenance therapy (15–17). The potential adverse effects of CsA are significant and include severe opportunistic infections such as PCP, nephrotoxicity, hypertension, seizures, peripheral neuropathy, anaphylaxis, colonic perforation, and increased postoperative mortality (15,16). Cholesterol levels
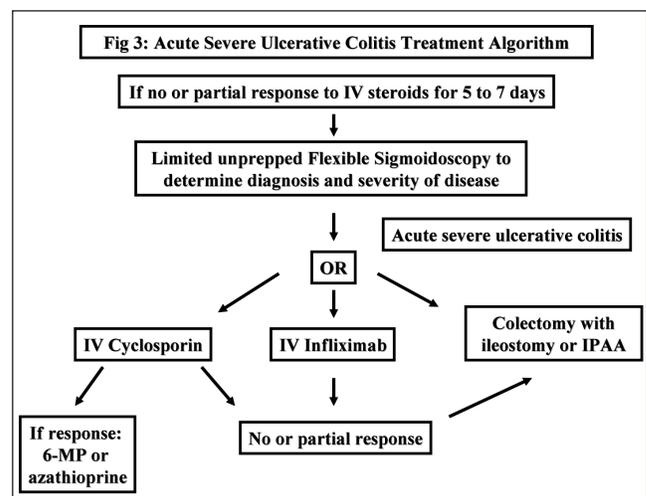

Figure 3. Treatment algorithm for the inpatient with acute severe ulcerative colitis (UC). If the patient does not respond to IV steroids after five-to-seven days, a limited unprepped flexible sigmoidoscopy is performed to rule out other causes of severe UC and to determine disease severity. For the patient with acute severe UC, possible treatment choices include either IV cyclosporine or IV infliximab or colectomy. If the patient responds to IV cyclosporine, maintenance of remission by bridging the patient to 6-MP or azathioprine should be used. If the patient responds to infliximab, long-term remission should be maintained with infliximab infusions on a regular basis. For patients with acute severe UC, who do not respond or only partially respond to IV cyclosporine or IV infliximab, colectomy with ileostomy or ileal pouch-anal anastomosis should be considered, because the disease is removed and major complications, including death, from the severe acute ulcerative colitis can be avoided.

Table 2
Severity and Nature of Colitis

	Mild-Moderate	Moderate-Severe	Acute Severe (Fulminant)	Maintenance of Remission
Oral 5ASA or Sulfasalazine	++++	++	No	++++
Topical 5ASA	++++	++	No	++
Topical steroids	++++	++	No	No
Immunomodulators	+	++++	No	++++
IV steroids	No	No	++++	No
IV cyclosporine	No	No	++++	No
Infliximab	No	++	++++	No

should be measured prior to initiating CsA therapy, since low cholesterol levels can predispose to seizures. During therapy, CsA levels should be carefully monitored. Additionally, those patients who concomitantly take CsA plus corticosteroids should receive PCP prophylaxis with cotrimoxazole or inhaled pentamidine (15,16). CsA should be avoided during pregnancy and is contraindicated during breast feeding. In elderly patients, the CsA dosage should be reduced to decrease the risk of opportunistic infections.

Infliximab can also be considered for hospitalized patients with acute, severe steroid refractory UC (Figure 3). In a randomized study, the need for colectomy was markedly reduced in hospitalized patients with acute moderate or severe UC who received infliximab compared to those who received placebo (18). The best response to infliximab was seen in hospitalized patients with acute, moderately severe ulcerative colitis, with none requiring colectomy (18).

For patients with acute, severe ulcerative colitis, emergency colectomy is the only potential cure and can be lifesaving for patients with toxic megacolon, patients with massive hemorrhage, or patients non-responsive to therapy (19). Colectomy removes both the severely diseased colon and its associated risks and also allows the discontinuation of powerful immunosuppressive medications, thereby avoiding the risk of opportunistic infections and other medication induced side effects (19). The most common surgical procedure for ulcerative colitis has become colectomy with Ileal Pouch-Anal Anastamosis (IPAA). When performed by experienced surgeons, colectomy with IPAA has demonstrated excellent efficacy and patient acceptance (20–24).

Complications following colectomy with IPAA can occur (20–24). Therefore, the patient needs to understand that it may require time and effort to adjust to the IPAA as well as effectively deal with any complications. External anal sphincter function is well maintained following IPAA, but it may take up to six-to-12 months to recover internal sphincter function. Bacterial overgrowth in the pouch may lead to vitamin B_{12} deficiency. Rapid pouch filling and impaired evacuation may result in increased stool frequency and fecal incontinence.

There is a 20%–50% incidence of pouchitis, which can lead to decreased post-operative quality of life (24). Pouchitis presents with symptoms of increased diarrhea, abdominal cramping, urgency, tenesmus, incontinence, fever, and very often rectal bleeding (24). "Cuffitis" has been noted to occur in the columnar cuff of IPAA patients and, similar to pouchitis, can lead to pouch dysfunction (24). Crohn's disease involving the IPAA has been recognized with increasing frequency. In patients with these symptoms, the evaluation begins by obtaining stool cultures for enteric pathogens and *Clostridium difficile* (24). Flexible sigmoidoscopy (pouchoscopy) should be performed, looking for friability, edema, granularity, and ulcerations (24). When infectious pathogens have been ruled out, initial therapy is instituted with antibiotics such as metronidazole, ciprofloxacin, tinidazole, tetracycline, erythromycin (24). If antibiotic therapy is not successful, rectal 5-ASA or steroid products, oral 5-ASA products, or Entocort (controlled ileal release budesonide) can often prove helpful (24). If the patient has refractory pouchitis, prednisone, 6-MP or azathioprine, or infliximab can be used for select situations (24). Sexual dysfunction can occur postoperatively in men

and women (25). Increased rates of infertility have been documented in women following IPAA (26). This has led to the recommendation that consideration be given to the storage of eggs for later in-vitro fertilization by women undergoing IPAA, who plan to have children in the future. Although the potential complications and side effects colectomy with IPAA need to be discussed with the patient, the significantly improved QOL has lead to the widespread use of colectomy with IPAA in those patients who fail medical therapy.

CONCLUSION

After determining the extent and severity of the UC and excluding other causes of bloody diarrhea, patients with mild-to-moderate UC are treated initially with oral 5-ASA medications combined with 5-ASA or steroid suppositories plus 5-ASA enema or steroid foam preparations (Figure 1). The oral 5-ASA agents should then be continued for maintenance of remission. For patients with moderate-to-severe UC, oral steroids are used initially, followed by 6-MP or azathioprine for maintenance in the traditional step-up therapeutic strategy (Figure 1, 2). For patients with severe UC, infliximab is effective using a top-down strategy in order to more rapidly achieve response and remission and can be considered as an alternative to IV steroids (Figure 1, 2). For the patient with acute, severe UC, who has not responded to IV steroids for five-to-seven days, treatment choices are either IV cyclosporine or IV infliximab or colectomy (Figure 3). Table 2 provides a general overview of the clinical applications and efficacy of the medications used to treat UC. For UC patients who have not responded adequately to medications, colectomy with IPAA is appropriate because the diseased colon is removed and the medications with their potential side effects are avoided. ■

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