Medical and Surgical Management of Chronic Ulcerative Colitis

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 idiopathic inflammatory bowel disease is divided into 2 major disease processes, Crohn disease (CD) and chronic ulcerative colitis (CUC). Often, both diseases are characterized by intermittent exacerbation of symptoms and periods of remission that may occur spontaneously or in response to treatment. The etiology of these diseases is unknown but most likely represents an interaction between the environment and host genetic susceptibility. Both medical and surgical treatment are used in the treatment of CD and CUC. However, given the different distribution of disease activity along the intestinal tract and the nature of the inflammatory process, the role and scope of medical and surgical management for each specific disease are different. Crohn disease may arise anywhere along the length of the intestine. It is characterized by transmural inflammation of the bowel wall. Such inflammation leads to a unique set of complications, including abscess and fistula formation and intestinal stenosis. By its very nature, therefore, CD does not allow for a definitive surgical treatment of the disease, and surgery should be reserved to address complications.

Conversely, CUC is a mucosal inflammatory process limited to the rectum and the colon. It is characterized by contiguous inflammation beginning in the rectum and progressing for variable distances proximally. Medical therapy is directed at control of symptoms or at the underlying inflammatory process. Medications are not curative for the intestinal or the extraintestinal manifestation of CUC. However, surgical removal of the colon and rectum cures the intestinal manifestations of the disease and eliminates or markedly reduces the associated risk of malignancy in CUC. Given that medical and surgical treatment are important in the management of CUC, it is also important that there be a close and effective working relationship between the gastroenterologist and gastrointestinal surgeons who care for these patients. Equally important is that both groups of physicians understand the advantages and limitations of the therapies they can provide.

In the United States, there are approximately 250000 to 500000 people diagnosed as having CUC, with an incidence of 2:100000 to 11:100000 population per year. The disease has a significant impact on the use of US health care resources, accounting for more than 250000 physician office visits, 20000 hospitalizations, and an estimated cost of treatment and hospitalizations of nearly $500 million per year. Not included in these estimates is the cost to society due to lost workdays for the patient and caregivers. As these numbers indicate, the medical and societal impacts of CUC are significant. The intent of this review is to discuss the current state of medical and surgical treatment for the intestinal manifestations of CUC. Not included in this review are the evaluation and differential diagnosis in a patient who presents with bloody diarrhea, the extraintestinal manifestations of CUC or their treatment, or the management of CD.

Chronic ulcerative colitis is classically characterized by the frequent passage of
Truelove and Witts\(^3,4\) are the easiest to apply clinically to differentiate disease activity, the criteria described by lar markers and the endoscopic appearance of the colon. Although newer indexes include biochemical or molecular markers since originally proposed, it divided patients’ disease into mild, moderate, or severe activity (Table 1). Although newer indexes include biochemical or molecular markers and the endoscopic appearance of the colon to differentiate disease activity, the criteria described by Truelove and Witts\(^3,4\) are the easiest to apply clinically for guiding medical or surgical therapy. Also important in the management of CUC is determination of the extent of the disease. As noted previously, CUC begins in the rectum and progresses proximally in a contiguous fashion for a variable distance in the colon. For an individual patient, the disease may be limited to the rectum (proctitis), the rectum and sigmoid colon (proctosigmoiditis), or the left colon (left-sided colitis) or may involve most or all of the colon (pancolitis). Often, as the extent of the disease increases, the patient’s symptoms worsen. In addition, the disease may progress from one episode of disease activity to the next. Therefore, if a patient who has had stable proctitis presents with worsening symptoms, reevaluation of the colon must be undertaken to ensure that the extent of the disease has not increased. Determination of the extent of the disease is important because local medical therapy such as medicated enemas will only be effective in those patients with disease limited to the left colon and rectum.

The choice of medical therapy for CUC is based on the extent and severity of the disease. As will be discussed, surgical therapy is reserved for patients with medically refractory disease, fulminant disease or its complications, mucosal dysplasia, or malignancy. The standard medical therapies for CUC are broadly divided into the following 3 categories: aminosalicylates, corticosteroids, and immunosuppressants. Biologic agents will be only briefly discussed, as these are not current standard therapy for the treatment of CUC. In the first 2 categories, topical and systemic preparations are available for use.

### AMINOSALICYLATES

The 5-aminosalicylic acid (5-ASA) derivatives of sulphasalazine are currently the primary treatment agents for mild or moderately active CUC. In 1965, Misiewicz and colleagues\(^2\) reported the first randomized placebo-controlled trial demonstrating that sulphasalazine was useful in maintaining remission in patients with CUC. In their study, 73% of patients taking placebo had a relapse of their CUC in 1 year compared with 21% taking sulphasalazine. The initial thought behind using sulphasalazine was that it contained both antibacterial properties from the sulfapyridine component that was azo bound to a 5-ASA moiety that provided anti-inflammatory properties. Investigation over time has shown that most of the therapeutic benefit from this class of drugs is related to the 5-ASA component, whereas most of the adverse effects are attributed to the sulfapyridine component.\(^8,9\) Newer formulations of prodrugs and drugs make use of this difference and no longer contain the sulfapyridine component. The exact mechanism of the effectiveness of 5-ASA in CUC is unclear. However, it is not simply disruption of prostaglandin or prostacyclin synthesis, as other potent nonsteroidal anti-inflammatory agents have no therapeutic effect or may actually worsen symptoms in a patient with CUC.\(^7\)

Although modulation of the prostaglandin pathways may be a component of the 5-ASA effect, it is also known to inhibit production of potent inflammatory cytokines such as interleukin (IL) 1, tumor necrosis factor (TNF), and interferon-\(\gamma\) and to act as a cellular antioxidant and free radical scavenger.\(^8,9\) The 5-ASA compounds are rapidly absorbed from the proximal small bowel where they are metabolized in the intestinal epithelium and liver before being excreted in the urine. The therapeutic effect of 5-ASA compounds is due to the local concentration at the inflamed mucosal surface. To achieve high local concentrations, different 5-ASA preparations have been developed that use different mechanisms to prevent early absorption of the compound in the small intestine.

### Table 1. CUC Disease Severity Scale*

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Mild</th>
<th>Severe</th>
<th>Fulminant</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of bowel movements per day</td>
<td>&lt;4†</td>
<td>&gt;6</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>Infrequent</td>
<td>Frequent</td>
<td>Profuse</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td></td>
<td>&lt;75% of reference range</td>
<td>Profound anemia that may require transfusion</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>Reference range: Male, 13.5-17.5 g/dL</td>
<td>&gt;30 mm/h</td>
<td>&gt;30 mm/h</td>
</tr>
<tr>
<td>Body temperature</td>
<td>Normal</td>
<td>Normal to elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Reference range: 60-100 beats/min</td>
<td></td>
<td>Tachycardia</td>
</tr>
</tbody>
</table>

Abbreviation: CUC, chronic ulcerative colitis.

*Modified from Truelove and Witts.\(^4\)
†No reference range available. Fewer than 4 bowel movements per day represents normal to mild disease activity.
One of the limiting factors related to the use of sulfasalazine and 5-ASA compounds is their profile of adverse effects. A large number of patients using sulfasalazine will experience adverse reactions that are usually dose related. Those adverse effects include nausea, vomiting, headaches, folate-dependent anemia, and abnormal sperm production. Furthermore, there are significant hypersensitivity reactions to sulfasalazine such as anaphylaxis, fever, severe skin reactions, profound bone marrow suppression, and pancreatitis. Although most patients who experience an adverse reaction to the sulfasalazine can switch to other 5-ASA compounds without difficulty, approximately 10% to 20% of patients will have similar reactions to both agents. If a patient has a severe hypersensitivity reaction to sulfasalazine, then they should not be exposed to 5-ASA compounds. The 5-ASA compounds are associated with few dose-related adverse effects, of which nephrotoxicity is the most common. Like sulfasalazine, it has similar hypersensitivity reactions. Overall, 5-ASA compounds are very effective in the treatment of mild to moderately active CUC and should be considered first-line therapy alone or in combination with other agents, depending on the severity of the patient's symptoms.

**GLUCOCORTICOIDS**

Glucocorticoids, corticosteroids, have been used extensively in the treatment of CD and CUC during the past half century. Although often very effective in reducing symptoms, the severe adverse effects associated with prolonged administration of these drugs should ideally limit their use to short treatment courses. The mechanism of action for corticosteroids is their interaction with the intracellular glucocorticoid receptor. The corticosteroid-receptor complex then interacts with corticosteroid-responsive transcription regulation sites throughout the genome. For the immune system and immune-responsive cells, there is inhibition of transcription for the genes of the proinflammatory cytokines, tumor necrosis factor and IL-1, multiple chemokines including IL-8, inducible nitric oxide synthase, and numerous enzymes involved in the prostaglandin and prostacyclin pathways. The overall result is a broad suppression of immune function by inhibiting migration and activation of immune cells.

Standard oral corticosteroid preparations, prednisone being the most commonly used, are readily absorbed from the intestinal tract. Although cleared hepatically, reasonable systemic tissue levels can be achieved with relatively low oral doses. Even locally administered corticosteroid preparations such as enemas for rectal and distal colon disease result in enough systemic absorption to suppress adrenal function after prolonged use. Newer synthetic analogues such as budesonide have very high affinity for the glucocorticoid receptor and high first-pass hepatic metabolism, which increases their local intestinal effect and reduces the systemic toxic effects. Although the effectiveness of budesonide for the treatment of CD has been shown, its use in CUC has not been reported. The adverse effects of prolonged corticosteroid use are extensive: they affect nearly every organ system in the body. However, individual patients may be more prone to certain complications. It is hoped that the increasing use of immunosuppressants in the management of CUC will decrease long-term low-dose corticosteroid administration and thereby decrease the incidence of corticosteroid-induced complications.
IMMUNOSUPPRESSANTS

The agents in this class most commonly used for CUC are mercaptopurine and azathioprine. Azathioprine, acting as a prodrug, is converted intracellularly to mercaptopurine. Both are purine antimetabolite agents; however, the exact mechanism of their action is not known. One of their metabolites, thioguanine, is thought to accumulate and disrupt use of purine nucleotides, which impair DNA repair and synthesis, thereby inhibiting cell proliferation. However, this compound has recently been shown to induce T-lymphocyte apoptosis, which might be its primary mode of action. Both of these drugs require several weeks to achieve therapeutic levels of the active metabolite. This delayed onset of action limits their effectiveness in the treatment of acute disease activity. Before initiating therapy, some clinicians recommend that the serum enzyme activity level of thiopurine methyltransferase be measured. This enzyme converts mercaptopurine into an inactive metabolite. In the general population, there are 3 groups of patients, depending on their genotype. Most patients are homozygous for the normal gene, whereas a smaller number of people are heterozygous or homozygous for a defective allele of the gene. The people with intermediate or low thiopurine methyltransferase activity will produce more of the active metabolite, thioguanine, for any given dose of mercaptopurine. This can lead to a higher risk for severe hematologic adverse effects, primarily profound neutropenia, although the association is not a direct one. During therapy, it is important to monitor the patient's hematologic profile for evidence of significant bone marrow suppression and liver function tests for evidence of hepatotoxicity, which can occur infrequently.

These agents, similar to the aminosalicylates, have allergic and nonallergic adverse effects that can limit their use. The most common allergic reactions include pancreatitis, fever, skin reactions, and gastrointestinal tract disturbances. Approximately 5% to 10% of patients will experience some type of allergic reaction that prevents continued use. Often, if a patient has a reaction to 1 of the 2 drugs, he or she will have a similar reaction to the other. The nonallergic adverse effects are primarily related to bone marrow suppression. The leukopenia and thrombocytopenia can be profound, leading to opportunistic infections or bleeding. Although there are reports of an association with long-term use of these agents and an increased risk for malignancies, particularly lymphoma, this has not been demonstrated in larger reviews.

Another drug in this class of medications that is useful for CUC is cyclosporine. This polypeptide, produced by a soil fungus, is a calcineurin inhibitor. Calcineurin is a cytoplasmic protein whose activity is required for T-cell activation. Unlike mercaptopurine and azathioprine, cyclosporine can be used during acute exacerbations of CUC because therapeutic levels can be achieved after a few days of intravenous administration. Cyclosporine needs to be used selectively because it has significant adverse effects that require careful patient monitoring, including cyclosporine levels and renal function, during short- or long-term use. Important adverse effects include hypertension, renal insufficiency, opportunistic infections, and seizures. While patients take cyclosporine, they need to receive a double-strength combination of sulfamethoxazole and trimethoprim (Bactrim) as prophylaxis against Pneumocystis pneumonia.

BIOLOGIC AGENTS

During the past decade, a better understanding of the molecular signals involved in the regulation of the inflammatory and immune response has allowed development of highly specific therapeutic agents. In the treatment of inflammatory bowel disease, most of the emphasis has been placed on antibody therapy for blocking tumor necrosis factor, which is a key signaling molecule in the local and systemic inflammatory cascade. Infliximab is a mouse-human monoclonal antibody specific for tumor necrosis factor that has been very effective in the treatment of the different manifestations of CD. Recently, a number of studies have reported on the usefulness of this agent in the treatment of CUC. These small studies have met with variable success. The primary adverse effects of infliximab are infusion reactions, which can include anaphylaxis; the development of tolerance due to an immune reaction to the antibody; and profound immune compromise leading to serious and even fatal infections. Currently, infliximab should be used to treat CUC only in the setting of a clinical trial.

TREATMENT FOR SPECIFIC DISEASE ACTIVITY

As previously discussed, treatment for CUC is directed at the extent and severity of disease activity. Because of their route of administration, bioavailability, anti-inflammatory properties, or time course of activity, the different classes of medication will determine the clinical setting in which they should be used.

For patients who have mild to moderate distal disease such as proctitis or left-sided colitis, the aminosalicylates are the primary treatment agent. Oral and topical formulations are equally effective in achieving symptomatic control and inducing remission. However, topical agents tend to have an earlier onset of activity because of increased local concentrations. Depending on the type of formulation, the average dosage for effective oral therapy is somewhere between 2 and 6 g/d in divided doses, whereas topical agents such as suppositories or enemas are effective in the range from 1 to 4 g/d in divided doses. It often takes 2 to 4 weeks to achieve optimal effect.

In those patients with mild to moderate pancolitis, topical therapy is not an effective sole treatment modality, because enemas rarely pass the splenic flexure. Again, aminosalicylates are the cornerstone of medical therapy. In patients with active mild to moderate pancolitis, oral 5-ASA compounds at therapeutic doses, alone or combined with enema administration, will induce remission or symptomatic improvement in 60% of patients within 4 weeks. For those patients who do not achieve significant symptomatic improvement or who are intolerant of aminosalicylates, oral corticosteroids are very effective. Patients with active disease unresponsive to ami-
nosalicylates usually start by receiving prednisone (40-60 mg/d). It is important to start with high-dose rather than low-dose corticosteroid therapy to determine whether the patient will respond. This strategy overall will shorten treatment time and identify patients who will need more aggressive treatment. Once symptoms improve, the corticosteroid therapy can be tapered using disease activity as a marker for the course of the taper. Patients who are able to tolerate the aminosalicylates should continue use of those medications during the corticosteroid course. Patients in whom corticosteroid therapy cannot be completely tapered because of symptom recurrence should be offered therapy with mercaptopurine or azathioprine. The usual starting dosage for mercaptopurine is 1.0 to 1.5 mg/kg per day; for azathioprine, 1.5 to 2.5 mg/kg per day. It may take 3 to 6 months for these drugs to induce remission of symptoms, which means that the patient will often need corticosteroid coverage in addition to aminosalicylates for control of their symptoms. Ideally, long-term corticosteroid use should not be maintained in any patient, to avoid severe adverse effects. Most published series about the use of mercaptopurine and azathioprine demonstrate an induction of remission and maintenance ranging from 40% to 70% across 12 months.29

Patients who present with severe CUC, that is, with more than 6 bloody bowel movements a day and signs of systemic toxic effects or fulminant CUC (>10 bloody bowel movements per day), often need hospitalization. For patients who can be treated as outpatients, high-dose oral corticosteroid therapy, such as prednisone, 60 to 80 mg/d, can be started. If there is no improvement in symptoms or if the patient's clinical condition deteriorates, inpatient treatment is required. The goals of treatment in the setting of a fulminant flare of CUC are to stabilize the patient's condition, rule out other causes for the flare of disease activity, and initiate aggressive medical therapy. Ideally, the patient will be cared for at the onset by a team consisting of a gastroenterologist and a surgeon.

Medical therapy consists of fluid resuscitation and correction of electrolytic and hematologic abnormalities. Blood transfusions may be necessary. The patient should be given nothing by mouth. Nasogastric tube decompression may be required if colonic distention is a component of the presentation. Stool samples for Clostridium difficile toxin and cultures for enteric pathogens should be obtained. Plain upright and supine abdominal x-ray films should be obtained to rule out free air or to assess the degree of colonic distention. More commonly now, abdominal and pelvic computed tomographic scans are obtained, which provide more information about the extent and severity of colonic mucosa than do plain radiographs. The patient should undergo expeditious endoscopic evaluation of the colon. Colonic mucosal biopsy specimens should be obtained for histological evidence of cytomegalovirus superinfection. Viral cultures should also be sent. Urgent endoscopy is meant not to evaluate the entire colon but only to visualize the rectal and distal colonic mucosa to confirm the working diagnosis. If the patient is clinically stable, antibiotic therapy is not indicated. However, if the patient is very ill or has a fever or leukocytosis, appropriate broad-spectrum antibiotic therapy should be initiated after culture samples are obtained.

The primary treatment of either severe or fulminant CUC consists of intravenous corticosteroids. Truelove and Witts4 demonstrated the efficacy of high-dose corticosteroids for severe/fulminant CUC in 1955 by showing a reduction in mortality from as high as 60% to 3%. Subsequent modifications of their regimen showed that nearly three quarters of patients treated with intravenous corticosteroids will achieve remission of their symptoms within 5 days. The usual dosage depends on the intravenous corticosteroid preparation being administered. If the patient's condition improves, then they start a diet to determine whether their symptoms recur. Full-dose aminosalicylate therapy is also resumed. Eventually, the patient makes the transition to high-dose (40-60 mg/d) oral corticosteroid therapy. At this point, the patient may also begin mercaptopurine or azathioprine therapy.

If the patient does not clinically improve within 7 days while receiving intravenous corticosteroid therapy, it is highly unlikely that continued corticosteroid therapy will be of benefit, and surgical intervention should be considered. However, some institutions report a success rate of 80% for induction of remission by intravenous cyclosporine in corticosteroid-refractory severe/fulminant CUC.30 The recommended starting dosage is 4 mg/kg per day by means of continuous infusion, with the goal of a serum blood level of 200 to 400 ng/mL. Before starting therapy, the patient's cholesterol level should be higher than 100 mg/dL (2.59 mmol/L) to decrease the risk of seizure activity. If the patient responds to intravenous therapy, then he or she can switch to oral cyclosporine at a daily divided oral dose that is twice the amount given intravenously that induced remission within 24 hours. These patients should also begin mercaptopurine or azathioprine therapy, as cyclosporine monotherapy has a very high rate of relapse.30

Medical therapy for CUC covers a broad spectrum of disease activity. The choice of therapy must be individualized for each patient and depends on the extent of disease and the severity of their symptoms. The induction and maintenance of remission may require multiple medications of different classes. Optimal therapy requires frequent visits by the patient to the gastroenterologist to assess efficacy of the treatment regimen and to monitor for potential serious adverse effects of medication. A broad overview of the different medical agents and their indications for use is presented in Table 2.

**SURGERY FOR CUC**

The intestinal manifestations of CUC are cured with surgical therapy. However, surgical treatment of CUC is not without risks and can lead to significant changes in a patient's lifestyle. Thus, there are specific indications for surgical intervention in patients with CUC. The indications for surgery are divided into emergency and elective situations (Table 3). In the emergency setting, the goal of surgery is to treat the emergency situation and restore the patient to good health in such a way that a future restorative procedure can be performed.
In the elective setting, the 2 main operations for patients with CUC are total proctocolectomy with ileal pouch-anal anastomosis (IPAA) and total proctocolectomy with end ileostomy. Total abdominal colectomy with ileorectostomy is less commonly used today because of the risks associated with the IPAA. The main disadvantage is that IPAA leaves a fair amount of diseased tissue in continuity with the fecal stream that might result in persistent symptoms and the risk of future malignancy. However, the ileorectostomy should be considered an option in patients who refuse an ileostomy or for patients who have medical conditions in which a stoma is relatively contraindicated, such as portal hypertension or ascites. Recently, some authors have advocated performing an ileorectostomy in women of childbearing age because of reports showing the significant reduction in fecundity after IPAA. Previously, the continent ileostomy, Kock pouch, was used for patients with CUC. The relatively high reoperation rate to maintain the pouch and the success of the IPAA make this operation mainly of historical interest. A new type of continent ileostomy has been described; however, again, it will most likely find limited use. The choice of surgical procedure needs to be individualized to the patient on the basis of the underlying physical and medical conditions and the patient's social and psychological situations. For the purposes of this review, only the surgical outcomes related to the IPAA will be discussed in detail.

**EMERGENCY SURGERY**

As discussed previously, the patient who presents with severe/fulminant CUC can be extremely ill. At the time of presentation, he or she may have indications for immediate surgical exploration such as perforation or extreme toxic effects. During hospitalization, such a patient must be closely monitored by the surgeon to ensure that there is no change in his or her status that warrants early operation. If there is no clinical improvement within 5 to 10 days during maximal medical therapy, it is very unlikely that continued medical therapy will achieve remission, and an operation should be strongly recommended. It is essential during this period that the patient's nutritional status be closely monitored because malnutrition predisposes to postoperative complications.

A unique presentation of a patient with severe/fulminant colitis is toxic megacolon. This process may be the initial presentation of ulcerative colitis or may represent a flare in a patient with long-standing disease. The entire colon or an isolated segment of the colon (usually the transverse or the left colon) is involved. Toxic megacolon is a clinical diagnosis. However, the strict radiographic definition of toxic megacolon is dilatation of the transverse colon of greater than 5.5 cm on a supine abdominal x-ray film. The medical treatment of toxic megacolon is similar to that used for patients with fulminant colitis. Some physicians advocate rolling the patient from the supine to a prone position every hour to prevent the accumulation of air in the transverse colon. Emergency surgery is indicated if the patient's clinical or radiographic status worsens, if there is evidence of perforation, or if there is no improvement after 48 hours of medical therapy. Delaying surgery increases the risk of perforation, which raises the mortality from less than 5% to nearly 30%.

Rarely, severe colonic hemorrhage results in hemodynamic instability. Initial treatment should be aggressive fluid and blood-product resuscitation. Correction of any electrolyte or clotting deficiencies should be undertaken. Identification of another possible source of bleeding should be aggressively sought by means of endoscopy to exclude a possible gastric or duodenal ulcer as the bleeding source. The timing of the operation is determined by the clinical situation. If the patient is hemodynamically unstable even after effective resuscitation, then operation is indicated because medical therapy to decrease the mucosal inflammation responsible for the bleeding take days to be effective. If there is slow but continuing hemorrhage that does not cause hemodynamic instability or symptoms, a trial of high-dose corticosteroids may be instituted. If there is no improvement after 48 to 72 hours of medical therapy, the patient should proceed to surgery.

The only real option for the patient who requires emergency surgery for treatment of CUC is a total abdominal colectomy with a Hartmann pouch and an end ileostomy. This allows most of the diseased colon to be removed, thus improving the patient's clinical condition while tapering off any immunosuppressive medication therapy. The reason for not performing a proctectomy in an emergency case is that by leaving the rectum in place, a restorative operation can be performed in the future without disturbing the dissection planes in the pelvis. In addition, an emergency proctectomy is associated with a higher risk of bleeding and injury to the nerves of the pelvic floor, bladder, and genitalia. Usually the small amount of diseased tissue left behind does not present a clinical problem.

**ELECTIVE SURGERY**

**Indications**

In the adult patient with CUC, the most common indications for elective surgery are intractable symptoms, the treatment of dysplasia, or suspected or known malignancies. Intractability is a clinical definition that occurs in both the acute and chronic states of CUC. During an acute flare,
intractability refers to the inability to control a patient's symptoms with maximal medical therapy. Intractability in a patient with long-standing CUC refers to the inability to taper corticosteroid therapy to a reasonable maintenance dosage, ineffective symptom control with maximal medical therapy, or the development of severe drug-related adverse effects. The development of malignancy in the setting of CUC has been well described. The risk of colon cancer in a patient with CUC has been estimated to be anywhere from 2% to 20% after 20 years of disease. A patient's individual risk for colon cancer ranges from 0% to 20% after 20 years of disease. A patient's individual risk for colon cancer is likely increased if there is evidence of high-grade dysplasia on random colon biopsy specimens or if there is a dysplasia-associated lesion or mass or a colonic stricture. However, some preliminary reports indicate that the presence of any degree of dysplasia not associated with a mass lesion should be viewed with a high degree of suspicion, and surgery should be recommended. The type of surgical procedure offered depends on a number of patient-related factors, including age and overall medical condition.

Ileal Pouch–Anal Anastomosis

The IPAA is considered the standard elective surgical therapy for the treatment of CUC. Parks and Nichols first described the procedure in 1978. The decision to proceed with operations other than IPAA is based on individual patient circumstances or preexisting medical or physiological conditions that are contraindications for this type of restorative procedure. The IPAA procedure removes the entire diseased organ while preserving the normal anatomic route for defecation.

Since the introduction of IPAA in the early 1980s, the surgical technique continues to evolve with the application of new technologies such as laparoscopic surgery. The operation basically involves the following 4 phases: (1) removal of the intra-abdominal colon, (2) dissection and removal of the rectum with sparing of the pelvic nerves and anal sphincter mechanism, (3) construction of an ileal reservoir, and (4) anastomosis of the ileal reservoir to the anal canal (Figure). The technical details of the operation have been described in numerous reports and textbooks and will not be discussed herein. However, some of the current controversies regarding the technical aspect of the operation will be addressed.

CONTROVERSIES

Stapled or Hand-Sewn IPAA

The manner in which the IPAA is constructed is usually left to the operating surgeon's preference. The relative value of performing a mucosectomy or a double-stapled anastomosis continues to be debated. The purpose of the mucosectomy is to remove all of the diseased or at-risk mucosa. However, even after a complete mucosectomy, the risk that residual tissue might undergo malignant transformation is not entirely eliminated, as there have been reported cases of adenocarcinomas occurring at the anastomosis or in the transition zone. Even with complete mucosectomy, small islands of rectal mucosa can be found buried in the fibrous tissue between the rectal muscularis and the serosa of the ileal pouches that required excision for other reasons. Surgeons who advocate a double-stapled pouch–anal anastomosis at the level of the pelvic floor believe that the remaining 1.5 to 2.0 cm of anal mucosa proximal to the dentate line improves the functional result by improving anal canal sensation. In a randomized prospective trial performed at the Mayo Clinic in 41 patients with CUC, there was no significant difference in functional outcomes as measured by stool frequency or episodes of fecal incontinence at 6 months after ileostomy closure. However, there was a higher resting sphincter pressure as measured by manometry and a trend toward less nocturnal incontinence in those patients who had a double-stapled anastomosis. In a small subset of patients recently described by the University of Minnesota after 12 years of follow-up, the authors were unable to conclusively state that a significant change in function existed between the 2 groups.

Diverting Ileostomy

To address the concerns about complications associated with staged procedures, some surgeons advocate performing the IPAA without a temporary ileostomy. Traditionally, a protecting ileostomy is constructed to divert the fecal stream.
from the pouch while the pouch staple line and anastomosis heal.\textsuperscript{42,43} The idea is that this maneuver decreases the risk of pelvic sepsis, which will avoid the long-term detrimental functional consequences of a pouch leak. On the other hand, supporters of a 1-stage procedure believe that an IPAA can be performed without an increased risk of pelvic sepsis.\textsuperscript{54-46} Also, a 1-stage procedure avoids an ileostomy and a second hospitalization and operation. In the large single-institution study reported by Sugerman et al,\textsuperscript{44} 201 patients, most of whom had CUC and were receiving corticosteroids, underwent a stapled IPAA in which 196 were performed without a diverting ileostomy. In that series, anastomotic leaks developed in 23 patients (12%), but only 9 required a return to the operating room for diversion. There was no difference in the long-term functional results and late complications compared with other published series of IPAA. In the only randomized controlled trial addressing this issue, 43 patients were intraoperatively randomized at the end of the IPAA to have a 1- or a 2-stage procedure.\textsuperscript{47} There were 2 anastomotic leaks, 1 in each group. Short-term follow-up showed no difference in functional outcomes. Although some authors believe that a 1-stage operation may be performed with comparable complication rates, one study suggested that the severity of complications was greater in those patients without a protecting ileostomy.\textsuperscript{48} For some patients who have uncomplicated procedures performed by experienced surgeons, a 1-stage IPAA might be appropriate. However, the surgeon and patient care team must be vigilant to the early signs of pelvic sepsis and aggressively investigate the possibility of a pouch or an anastomotic leak.

Age

Most patients with CUC are young and, unless there are unusual circumstances, they should be offered an IPAA. However, CUC is known to have a bimodal age distribution, and older patients are being referred for surgical evaluation. Although many institutions have reported their long-term results with IPAA, few have regularly performed IPAA in elderly patients. In the Mayo Clinic survey of 1386 patient who underwent IPAA, only 16% were older than 45 years, and none were older than 65 years.\textsuperscript{42} The functional outcomes as noted by nocturnal stool frequency, daytime and nocturnal incontinence, and need for constipating medications were all significantly higher in patients who were older than 45 years at the time of the IPAA. However, Tan and colleagues\textsuperscript{49} have evaluated their experience with patients undergoing IPAA from the age of 50 years to older than 70 years. When the elderly patients were compared with younger patients, there were no significant differences between the groups for the major complications of pelvic sepsis, pouch-related fistula, or anastomotic leak or functional outcomes. Pouch–anal stenosis was, however, significantly more common in the older patient group. Overall, it appears that advanced age itself should not be an absolute contraindication to IPAA.

Fertility

Although earlier studies looked at the course of pregnancies and complications that arose after IPAA, the specific issue of fecundity, the ability to conceive, after IPAA has not been thoroughly investigated.\textsuperscript{50,51} In a recent analysis of the rate of pregnancy after IPAA, there was shown to be a significant reduction in postoperative fertility.\textsuperscript{52} The birth rate in a cohort of Swedish women with CUC was compared with the expected pregnancy and birth rate for age-matched women in Sweden. There was no difference in the expected birth rate in women from the onset of CUC to the time of colectomy. However, there was a significant reduction in births after IPAA. More important, in the post-IPAA patients who became pregnant, 29% of pregnancies occurred after in vitro fertilization compared with the expected 1% of all births in Sweden. A follow-up study by the same authors looked at fecundity in patients with familial adenomatous polyposis who underwent an ileorectostomy compared with an IPAA.\textsuperscript{53} Those undergoing ileorectostomy had no reduction in their fecundity, whereas those undergoing IPAA had a nearly 50% reduction. The cause of this decreased fertility is unknown, but the authors believe that anatomic changes in the pelvis may contribute to the problem. Until further studies are performed to confirm and clarify these findings, women who consider undergoing IPAA should be informed of the possibility of decreased fecundity.

Laparoscopic IPAA

Although patient satisfaction with the IPAA procedure is high, application of newer technologies such as laparoscopic surgery might further improve patient satisfaction and decrease the morbidity of the surgery. This might then lead to earlier acceptance of surgery, faster resumption of normal activity, and possibly decreased cost. As surgeons have become more comfortable with laparoscopic colon surgery and as the instrumentation has improved, an increasing number of institutions have reported their results with laparoscopic IPAA.\textsuperscript{54-56} The series reported to date have shown that the short- and long-term complications, functional results, and quality of life are similar between open and laparoscopic IPAA. The only real benefit documented for laparoscopic IPAA is an improvement in cosmesis. However, continued refinement in the techniques and prospective evaluation are needed to better define the possible benefits of laparoscopic IPAA.

COMPLICATIONS AFTER IPAA

Total proctocolectomy with IPAA is a technically difficult operation and is associated with significant morbidity.\textsuperscript{57-59} The patient commonly has to endure 2 and sometimes 3 operations. A number of short- and long-term complications are associated with the IPAA procedure that can influence the function of the pouch and eventually could result in loss of the pouch (Table 4). The most commonly encountered short-term complications are small-bowel obstruction, anastomotic stricture, pouch leak, and pelvic abscess. Long-term complications include small-bowel obstruction, pouch fistulas, and pouchitis. Chronic pouch dysfunction, fistulas, and chronic pouchitis contribute to pouch failure that may require pouch revision or excision.
anastomosis was performed. Principles of management of the anastomosis, and are not dependent on how the some for CD. Most fistulas are low, originate at the level period or years later. Early pouch fistulas are most likely require operation. Anastomotic stricture is another common complication associated with IPAA. In patients who require any reoperative treatment after an IPAA, approximately one third will be for treatment of an anastomotic stricture. Fortunately, these strictures can often be dilated in the operating room under anesthesia or in the office. After the initial dilation, the patient can be taught how to self-dilate. Pouch leak and the associated pelvic sepsis rate in large series have been reported to range from 5% to 14%. Most patients with a pouch leak require operative intervention, with the remainder able to be treated with intravenous antibiotics or drainage guided by computed tomography.

Late Complications

The late complications associated with IPAA include small-bowel obstruction, fistula, and pouchitis. MacLean and colleagues reviewed the literature on the incidence of late small-bowel resection after IPAA and found a reported incidence of 12% to 35% with variable length of follow-up from many studies. In their institution, the 1-year incidence of small-bowel obstruction was 18%, and the cumulative risk increased to 27% at 5 years and 31% at 10 years. Most of the patients responded to conservative management, but the rate of operative treatment increased from 2.7% at 1 year to 7.5% at 10 years. The most common sites of obstruction were pelvic adhesions, followed by obstruction at the ileostomy closure site.

Fistulas after IPAA are difficult postoperative complications to treat. Pouch-vaginal fistulas and, rarely, pouch-perineal fistulas can occur in the perioperative period or years later. Early pouch fistulas are most likely the result of a technical error or the complication of a pouch leak or pelvic abscess. The appearance of a fistula years after an IPAA has been performed is very worrisome for CD. Most fistulas are low, originate at the level of the anastomosis, and are not dependent on how the anastomosis was performed. Principles of management include local control of any septic process and repair of the fistula by the interposition of healthy tissue between the pouch and the vagina or perineal opening. Trans-anal, transvaginal, transperineal, and transabdominal approaches to pouch-vaginal fistulas have been described, with rates of successful closure ranging from 10% to 78%. However, simple interventions such as the use of seton fistulotomy can sometimes be used to manage pouch-perineal or pouch-vaginal fistulas successfully. The most important consideration in managing a post-pouch fistula is to rule out CD.

Pouchitis

Another late complication of IPAA is pouchitis. Pouchitis is an acute inflammatory process of the pouch with no clear etiology. In a minority of patients, it can become a chronic process. Since it rarely occurs in patients with familial adenomatous polyposis and an IPAA, pouchitis may represent an element of immune dysfunction unique to patients with CUC. The exact incidence of pouchitis is difficult to measure. Most series report an incidence of pouchitis ranging from 12% to 50%. No specific factor predicts which patients will develop pouchitis. It should be suspected in any patient who experiences abdominal cramps, increased stool frequency, watery or bloody diarrhea, and flulike symptoms. Although many patients are treated on clinical grounds alone, accurate diagnosis requires endoscopic visualization of the pouch and histological evaluation.

Although the exact cause of pouchitis is unclear, the successful use of antibiotics, particularly metronidazole hydrochloride, in the treatment of acute and chronic pouchitis lends support to a theory that an interaction between pouch bacteria levels and the patient's mucosal immune system is important. After the diagnosis of pouchitis is made, most patients respond to a short course of antibiotics. The primary antibiotic used is metronidazole for a 7- to 10-day course. If the patient cannot tolerate metronidazole, then other broad-spectrum antibiotics such as ciprofloxacin hydrochloride, a combination of amoxicillin and clavulanate potassium (Augmentin), erythromycin estolate, or tetracycline hydrochloride may be used. If antibiotic treatment fails to resolve the pouchitis, then evaluation of the pouch and small bowel should be performed to rule out other causes of diarrhea, namely CD. Other agents that may be used to treat pouchitis include those medications used to treat the colitis, originally including corticosteroids in oral and enema formulations and oral immunosuppressive agents. Chronic pouchitis will eventually develop in less than 8% of patients who have an IPAA, with nearly half of those patients eventually requiring pouch excision.

Pouch Failure

Fortunately, pouch failure that requires proximal diversion or pouch removal is an uncommon occurrence. Early technical complications or later severe pouch dysfunction due to CD or chronic pouchitis may lead to failure rates reportedly ranging from 1% to approximately 20%. Pouch failure may be treated with a proximal
diverting ileostomy, pouch excision and end ileostomy, or pouch revision. The most common cause of pouch failure within the first 2 years after IPAA was chronic sepsis manifested as recurrent pelvic abscesses, with or without fistulas. Poor functional results as noted by increased stool frequency with incontinence and perineal irritation was the next most common cause. A few centers with a large experience in pouch surgery have reported good results in salvage surgery for pouch dysfunction due to mechanical causes or due to prior episodes of pelvic sepsis. In the Mayo Clinic experience, for those patients who had poor pouch function and required pouch reconstruction, post-reconstruction functional results were reported as satisfactory in 60% of patients. However, pouch excision with permanent ileostomy was required in 20% of patients.

FUNCTIONAL RESULTS OF IPAA

Although a large number of different surgeons and institutions have reported their experience with IPAA, the functional results are quite similar. Most patients report good to excellent function with their ileal pouch. The markers of function that are most often recorded are the number of bowel movements during the day and the night, episodes of soiling, and use of medications to control bowel activity. Normal function is 5 to 7 bowel movements per day and 1 to 2 at night. Most patients report complete daytime continence. In those patients who had their ileal pouch for longer than 10 years, stool frequency and continence are remarkably stable over time. However, episodes of incontinence, particularly nocturnal incontinence, increase slightly over time. Even with the slight decline in function over time, most patients report a high degree of satisfaction with their ileal pouch function and quality of life.

Although IPAA has become the procedure of choice for most patients with CUC, some authors have shown that quality of life improves no matter what procedure is performed and is probably due mostly to improvement in the patients’ general health after eradication of the disease. These findings suggest that existing quality-of-life measurement tools may not completely address all of the important variables influenced by these procedures.

CONCLUSIONS

Successful treatment of the patient with CUC requires close collaboration between the gastroenterologist and surgeon. Depending on the extent and severity of the patient’s disease, a number of effective medical therapies exist, including aminosalicylates, corticosteroids, and immunomodulators. Surgery should be considered for patients with symptoms refractory to therapy or severe adverse effects related to therapy, or for dysplasia or suspected or known colonic malignancy. The goal of emergency surgery is to restore the patient to good health by removing the bulk of the diseased colon without preventing a future restorative procedure. The most commonly performed operation in appropriate candidates is the total proctocolectomy with IPAA. This procedure removes essentially all of the colon and rectum but maintains a normal route of defecation through a reservoir constructed from the terminal ileum. The functional results of this operation are very stable over time, and patients report a high degree of satisfaction with the operation.

Accepted for Publication: October 25, 2004.

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