



State of the Art in Treatment of Mucosal Ulcerative Colitis

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Epidemiology

Mucosal ulcerative colitis (MUC) is an idiopathic chronic inflammatory disease affecting the rectum and extending proximally to affect a variable length of the colon. MUC is a superficial inflammation affecting the mucosa compared to Crohn's disease (CD) where the inflammation is transmural. It has a worldwide incidence but has a higher prevalence in the United States, United Kingdom, and northern Europe. In caucasians, the incidence fluctuates from 3-15 cases per 100,000 people/year, with a prevalence of 80-120 per 100,000¹. This pathology may affect all age groups, but predominates in young adults 20-40 years of age and ethnic groups such as Ashkenazi Jews are more susceptible².

Inheritance plays a role in the etiology of MUC in approximately 12–15% of cases. A

familial history has proven to be the strongest risk factor for developing MUC. The inheritance of MUC cannot be explained by the Mendelian model, which shows that several genes are engaged in determining disease susceptibility on chromosomes 2, 3, 6, 7 and 12². The factors responsible for variable expression of this potentially hereditary susceptibility are unknown. Evidence of minor variations in incidence has been found in urban areas, increasing the suspicion of a transmissible agent that may be responsible for disease expression or increased susceptibility. Some studies have shown that environmental factors may potentiate the onset and the course of MUC and include diet, smoking cessation, breast feeding, and oral contraceptive use^{3,4}.

Pathogenesis

The pathogenesis of MUC still remains unknown. Many theories have been presented including infection, vascular impairment, autoimmune mechanisms, and allergy to dietary components. One of those hypotheses states that the major triggers are microbial organisms. However, despite many attempts, no specific pathogen has been consistently isolated. Another hypothesis refers to the dietary antigens or

non-pathogen agent that triggers an abnormal immune response. One of the foods involved in the etiology of MUC is cow's milk, which is the most common allergen; a controlled therapeutic trial of a milk-free diet, showed that 20% of patients could benefit from this diet⁵.

A large group of studies have shown increased serum levels of antibodies to milk



proteins despite the fact that no IgE antibodies were demonstrated. Consequently, there is not enough evidence to support the theory that milk or any other foods play an important role in the etiology of MUC. The impact of environmental factors on the course of MUC is well supported; these factors include smoking

and the use of oral contraceptives. A meta-analysis by Calkins suggested a protective effect of smoking. These results are compelling because smoking increases the risk for CD. The mechanism is still unclear, but smoking probably acts as a protector of the colonic mucosa from developing MUC in predisposed individuals⁴.

Macroscopic Characteristics

The distribution of MUC is from distal to proximal and can be differentiated from CD based on the continuity of involvement. MUC extends proximally without sparing any section of the mucosa and initially begins in the form of proctitis. Macroscopic changes are generally most severe in the rectum. However, the differential diagnosis is often difficult and evidence has shown some rectal sparing and may be due to the use of topical corticosteroids or mesalamine⁶. This feature explains the efficacy of topical therapy administered per rectum. There are two circumstances described in patients with left-sided MUC that show skip lesions: appendiceal inflammation and areas of cecal inflammation⁷. With severe inflammation, the mucosa appears granular and more friable with spontaneous bleeding and more

pronounced ulceration extending deep into the lamina propria; pseudopolyps may be present as a result of regenerating epithelium. These changes are circumferential, extending beyond the sigmoid but not involving the colon in 30% to 40% of cases, and limited to the rectum and rectosigmoid in 40%-50% of the cases; approximately 20% have total colitis. In a study of 1116 patients, 46% had proctosigmoiditis evidenced by sigmoidoscopy; 17% had left-sided disease (to the splenic flexure) while 37% had pancolitis at the time of presentation⁸. Patients presenting with pancolitis were more likely to develop refractory symptoms, toxic megacolon, malignancy, extraintestinal manifestations, and required surgery.

Microscopic Characteristics

Microscopically, the inflammation is limited to the colonic mucosa showing a loss of the vascular pattern that varies from simple blunting to frank ulceration with hyperemia and edema. There is an inflammatory infiltrate of neutrophils, lymphocytes, plasma cells, and macrophages. The neutrophils invade the crypts, forming cryptitis and crypt abscess. Overall, an irregular surface is

present in approximately 60% of cases with MUC. Crypt alterations are more common and widespread and present in 57–100% of cases⁹. Several other features may help to establish a diagnosis of MUC or to evaluate the severity of the condition. These include mucosal ulcerations and erosions, mucin depletion, Paneth-cell metaplasia and diffuse thickening of the muscularis mucosa.

Clinical Presentation

The typical scenario includes diarrhea, rectal bleeding, abdominal pain, fever, passage of mucus, abdominal pain, and weight loss; the severity of symptoms usually correlate with

the severity of disease. It is very important to make the correct diagnosis for an accurate treatment. In order to do that, it is important to demonstrate the absence of any



infectious agent in the stool, as well as biopsies characteristic of chronic inflammatory changes.

Symptoms are usually present for at least a few weeks, if not longer.

Diagnosis

The diagnosis of MUC is based on a combination of clinical presentation, stool examination, endoscopic appearance, and biopsy. The clinical scenario is a patient suffering for several months with abnormal bowel habits with mucus, blood, and diffuse inflammation on sigmoidoscopy; it is very important to obtain a good medical history. The biggest diagnostic challenge in MUC is the differentiation from CD, because the surgical approach is substantially different. Consequently, the biopsy slides should be analyzed by a pathologist for confirmation of MUC. If the diagnosis is still questionable, a small bowel series should be performed to assess the remainder of the intestine for

lesions characteristic of CD. A double-contrast barium enema is the primary radiologic tool for confirming the diagnosis of MUC and for assessing the extent and severity of disease¹⁰. Approximately 15% to 20% of patients with severe MUC have an associated *backwash* ileitis, characterized by a fixed, patulous ileocecal valve and a dilated, granular terminal ileum on double-contrast barium studies. Another new diagnostic method is the measurement of anti-neutrophil antibodies (p-ANCA), showing 92% specificity for MUC; it is also known that the immunoglobulin titers correlate with the aggressiveness of MUC¹¹.

Differential Diagnosis

Mucosal ulcerative colitis can resemble CD, infectious colitis (entamoeba histolytica, campylobacter, etc), pseudomembranous colitis, ischemia, radiation colitis, and collagenous colitis. It is imperative to obtain a detailed medical history to support a correct diagnosis. The most important differential diagnosis is CD; the clinical differences rely on a history of perianal sepsis and, less frequently, rectal sparing is observed along with small bowel involvement (Table 1). Infective colitis is characterized by a sudden onset, with identifiable pathogens in the stool; edema and crypt abscesses may be seen on

histology. The hallmark of pseudomembranous colitis is the history of antibiotic use, the classical membrane may be seen on sigmoidoscopy, *C. difficile* is detected in the stool, and there is histologic confirmation of fibrinopurulent exudates. Ischemic colitis has a peculiar distinction, it is seen in older groups, has a sudden onset and is often painful, and rectal involvement is rare. Collagenous colitis is a new form of colitis which has been accepted as the possible cause of idiopathic diarrhea, bleeding is rare, and the colonoscopic appearance of the colon is normal.

Table 1. CLINICAL AND ENDOSCOPIC DIFFERENTIATION OF MUCOSAL ULCERATIVE COLITIS FROM CROHN'S DISEASE

Features	Mucosal Ulcerative Colitis	Crohn's Disease
Etiology	Idiopathic	Infectious
Distribution	Continuous	Segmental
Rectal Involvement	Uniform	Uncommon
Inflammation	Diffuse, with mucosal granularity, more friable	Focal, asymmetrical, cobblestone appearance, friability and granulation less common
Lumen	Narrow in chronic disease	Strictures
Ulcers	Small, deep into lamina propria	Mostly linear
Rectal Bleeding	Common-90%	Uncommon
Diarrhea	Frequent, in early disease	Less Frequent
Fever	Uncommon	Frequent
Palpable Mass	Uncommon	Frequent, right Lower Quadrant
Strictures	Uncommon	Frequent
Fistulas	Uncommon	Frequent
Recurrence after Resection	Uncommon	Frequent
Special Characteristics	None	Aphthoid ulcers, Granulomas, fissures

Extraintestinal Manifestations

Peripheral arthropathies are a very common form of extraintestinal manifestations. Joint involvement in enteropathic arthritis has been divided into two patterns: (1) peripheral arthritis, and (2) axial involvement, including sacroiliitis with or without spondylitis¹². A study performed by Orchard et. al. showed that 20% to 40% of all patients had more than one episode of arthritis. This type of peripheral arthropathy coexists with the underlying bowel disease activity and is associated with an increased incidence of erythema nodosum and uveitis¹³. Erythema nodosum is a classical dermatological manifestation manifesting as inflamed, red, and tender nodules, mainly in

the anterior portion of the lower legs. It has been reported that the prevalence of erythema nodosum in MUC is between 10%-20%¹⁴. Pyoderma gangrenosum is related to active colonic inflammation. The lesions begin as pustules and then ulcerate. This is a rare condition appearing in only 1%-2% of patients. Ophthalmologic manifestations of MUC are reported in 1.6% to 4.6%¹⁵. Episcleritis and uveitis are the two most common ocular manifestations associated with active colitis; uveitis presents as a painful eye with blurred vision, headache and photophobia while episcleritis presents only as a painful eye¹⁶.

Medical Therapy

Steroids are the “gold standard” for initiating remission of the disease, compared to any other method of therapy for moderate-to-severe MUC. No benefit has been seen with doses of prednisone greater than 40 mg and a once/day dose is as effective as a divided dosage²¹. Patients who fail oral Medical treatment has endured as the core in the management of MUC whereas surgery is postulated to be the cornerstone for treatment. Approximately 90% of all incident cases of UC are mild to moderate in severity¹⁷.

5-Aminosalicylates

Aminosalicylates are considered the mainstay therapy for mild-to-moderate MUC. The prototypic 5-aminosalicylate compounds (5-ASA) and sulfasalazine have been used for more than 40 years. There are three delivery methods for oral aminosalicylates and a number of topical compounds. One method may be accomplished via a controlled release coating of mesalamine, or azo bonding to an inert carrier (sulfasalazine, olsalazine, balsalazide). All azo-bonded compounds are subject to cleavage by colonic bacterial azoreductase with release of the 5-ASA portion in the colon. Another method is the pH-dependent mesalamine with various coatings (Salofalk, Asacol, and Claversal) and the time-pH release compound of mesalamine coated by ethylcellulose (Pentasa) which is capable of being released throughout the small bowel and colon. Several clinical studies have compared a 5-ASA compound with placebo for the prevention of a recurrence after surgery or a medical remission; most of these studies showed a one year reduction in the rate of relapse of 10%-20%¹⁸. All compounds have been compared to sulfasalazine in controlled studies without yielding any difference in efficacy if equal amounts of mesalamine are delivered to the colon^{18,19}. The main advantage of these compounds is safety and tolerability, especially at doses greater than 3g/day. The clinical response to aminosalicylates varies from 40% to 80%. A dose-response

effect has been proposed for sulfasalazine (1 g/day and 4 g/day) and mesalazine compounds (1.5 g/day and 4.8 g/day).

The incidence of adverse events is higher with sulfasalazine and is associated with the production of sulfapyridine. Reported data suggest that the risk of interstitial nephritis and pancreatitis is increased with mesalamine; conversely, the risk of blood dyscrasias, hepatitis, and skin reaction is higher with sulfasalazine²⁰. It has been shown that topical therapy is more effective than oral therapy in inducing and maintaining remission in cases of distal colitis. The best approach should be combined oral and topical therapy.

Corticosteroids

Prednisone need to be hospitalized and started on IV corticosteroids, hydrocortisone (300-400mg/day) or methylprednisolone (48-60mg/day), as either a bolus or as continuous infusion. The biggest disadvantage of this therapy are the side-effects which include infection, weight gain, cataract, hypertension, fluid retention, acne, myopathy and loss of bone density; the latter can be noted with chronic therapy in as much as 30%-60% of patients²².

Due to the potential for osteoporosis, prophylaxis with calcium and vitamin D should be given as soon as corticosteroid therapy is initiated. One study showed that of 34% of MUC patients required corticosteroid treatment, 16% failed to respond to steroids, and a strong link between corticosteroid-dependence and surgery were observed²³.

Cyclosporine

The efficacy of immunomodulators in severe MUC has been demonstrated by Lichtiger et. al in a randomized study which showed that in patients with severe MUC who fail IV corticosteroids, cyclosporine is an effective option. In this trial, nine of 11 patients treated with cyclosporine had a positive outcome in seven days, compared to none

of the nine patients who received placebo²⁴. corticosteroids have proven effective in 40% of patients with severe MUC who failed corticosteroid therapy²⁴. The standard maintenance dose is 4mg/kg/day in a continuous infusion. As with all steroid compounds, numerous serious adverse effects include renal insufficiency, infection, hypertension, gingival hyperplasia, and seizures. Furthermore, due to the risk of opportunistic infection with pneumocystis carinii, a regimen of thrice-weekly trimethoprim-sulfamethoxazole should be initiated concurrent with the cyclosporine. Cyclosporine should be avoided in cases of fulminant colitis or perforation.

Mercaptopurine/Azathioprine

These immunomodulators are indicated for long-term therapy in patients who are steroid-dependant or unresponsive to mesalamine or corticosteroid therapy. The recommended dosage for azathioprine is 2.0–2.5 and 1.5 mg/kg for 6-mercaptopurine. Side effects include bone marrow suppression, hepatitis, and pancreatitis. Its use has been recommended to start early in the therapeutic course. Evidence has shown that this agent is ineffective for acute MUC as it requires 4-6 month duration before any beneficial results are seen²⁵. Pearson *et al.* performed a systematic review and

Parenteral cyclosporines in combination with evaluated the results of 319 patients in 5 trials of AZA. The rate of maintenance of remission was 67% for active treatment versus 52% with placebo²⁶. The analysis proposed that higher doses of AZA were more beneficial compared to lower doses of 1 mg/kg. Two trials of AZA in chronic MUC patients yielded an important reduction in steroid dosage after 6 months of treatment at 1.5 mg/kg/day or 2.5 mg/kg/day, compared to a placebo group²⁷.

Colorectal Cancer in MUC

Appropriate strategies for preventing colorectal cancer in patients with MUC have been a topic of immense discussion. Endoscopic surveillance with biopsy of the colorectal mucosa has been established as a general consensus. A meta-analysis of 196 studies showed a prevalence of 3.7% (95% CI 3.2 to 4.2%) of patients with MUC to subsequently develop colorectal cancer. The prevalence in patients with total colitis was 5.4% (95% CI 4.4 to 6.5%). The cumulative risk was 2% by 10 years, 8% by 20 years and 18% by 30 years²⁸. These results show the need for more aggressive routine measurements such as prophylactic surgery in patients with long standing MUC²⁹.

Surgical Therapy

Emergent Surgery

Fulminant disease occurs as the initial presentation of MUC in up to 50% of cases^{30,31}. Patients with a severe attack of colitis require hospitalization with intravenous hydration, restriction of oral intake with possible nasogastric decompression, high-dose intravenous steroids, and broad-spectrum antibiotics. Intravenous hyperalimentation may also be used, depending on the patient's nutritional status and expected length of the hospital course³². Patients should be closely monitored with serial abdominal x-rays and leukocyte counts. Deterioration or lack of

improvement within 24 to 48 hours after induction of medical treatment warrants an urgent procedure, as the mortality is increased four-fold in patients with colonic perforation^{33,34}.

Up to 20% of patients will require urgent or emergent surgery for acute complications³⁵. Potentially fatal complications of MUC necessitating surgery include fulminant colitis, toxic megacolon, and massive hemorrhage. Toxic megacolon is a life-threatening variant of toxic colitis in which the dilation of the colon has progressed to

the point of imminent perforation. This decompensation results in a dilated, edematous, thin-walled colon. Although some patients with toxic megacolon have been successfully treated medically, a high rate of recurrence with subsequent urgent operation has been reported^{31,33,34}. In this situation, therefore, surgery is indicated without a trial of medical therapy. Aggressive preoperative stabilization is required, with volume resuscitation with crystalloid solutions to prevent dehydration secondary to third space fluid losses, stress-dose steroids for patients previously on steroid therapy, and broad-spectrum antibiotics.

Massive hemorrhage from MUC is a less common complication, occurring in up to 4.5% of cases³⁶, and approximately 10% of all emergent colectomies for patients with MUC are performed for massive hemorrhage³⁷. Again, these patients require medical stabilization prior to surgery, with blood transfusions, as needed.

Although the safety of a single-staged ileoanal reservoir in the acute setting has been reported³⁸, we believe that both proctectomy and anastomosis are generally contraindicated in the acutely ill patient with an unprepared bowel. Total proctocolectomy in the urgent setting carries a prohibitively high mortality rate^{31,39}, and the leak rate from a primary anastomosis is unacceptably high^{40,41}. Whereas the goal in elective surgery is to remove all the colonic or dysplastic mucosa, the aim in emergent surgery is to rescue the patient from a life-threatening situation. A total abdominal colectomy with ileostomy is therefore the preferred operation for these situations. This procedure can be expeditiously performed with relatively low

morbidity and mortality, and it is a non-committal procedure that serves the main purpose of removing the diseased colon while leaving the rectum intact.

The entire rectum, if not the distal sigmoid colon, must be preserved. This method minimizes the morbidity of a pelvic dissection in the acute setting and leaves the option of creating an ileoproctostomy in the future. Moreover, this is particularly important in patients in whom the diagnosis of MUC is unclear (indeterminate colitis) and a subsequent ileoanal reservoir may be contraindicated. In patients who will undergo restorative proctectomy, identification and preservation of the presacral sympathetic nerves is safer and technically easier in an undisturbed presacral plane.

Some controversy exists regarding management of the distal segment of bowel. The remaining rectum or rectosigmoid can be delivered as a mucous fistula, placed subcutaneously, or left closed as a Hartmann's pouch. Each management strategy has its proponents, but no randomized prospective trial has been performed to date that has shown superiority of any of these options.

The "blowhole" procedure was a popular procedure for the treatment of toxic megacolon prior to the availability of intensive care units and parenteral nutrition. This technique involved the creation of a loop ileostomy with an antimesenteric transverse colostomy⁴². This procedure limited handling of the bowel and thus the chance for fecal contamination during dissection, but was contraindicated in the presence of free perforation.

Elective Surgery

Approximately 70% of patients with MUC undergo surgery for chronic problems⁴³. Indications for elective surgery include intractable disease, complications of medical therapy, dysplasia, carcinoma, and occasionally for attempted improvement of

extraintestinal manifestations. Malnutrition and growth retardation may necessitate resection in pediatric and adolescent patients. Patients with intractable disease have persistent symptoms such as crampy abdominal pain, frequent bowel movements,

and stool urgency which may result in the deterioration of the patient's quality of life⁴⁴, which is markedly improved following surgery, regardless of the procedure performed^{45,46}. Complications of long-term steroid therapy, such as diabetes mellitus, avascular necrosis of the femoral head, cataracts, psychiatric problems, osteoporosis, and weight gain are a frequent indications for surgical resection, despite the fact the MUC may be under control.

The finding of carcinoma is an absolute indication for surgery, and it may occur in up to 75% of patients with pancolitis despite long-standing well-controlled disease after 40 years⁴⁷. The relative risk of colorectal carcinoma of 14.8% in patients with pancolitis makes surgery an option even in the absence of symptoms⁴⁸. Currently, the best marker for carcinoma is dysplasia, as the correlation between the two is well established. Patients with long-standing pancolitis should therefore undergo surveillance colonoscopy with biopsies taken from each segment of the colon and rectum. Patients who are found to have any dysplasia or carcinoma should be treated by colectomy^{29,49}.

A less common indication for elective surgery in MUC is for the treatment of debilitating extraintestinal manifestations of the disease. Pyoderma gangrenosum, erythema nodosum, peripheral arthritis, and uveitis should regress spontaneously postoperatively, however, sclerosing cholangitis and ankylosing spondylitis will not. Therefore, elective surgery should be considered in patients with colitis and significant extracolonic manifestations refractory to nonoperative measures⁵⁰.

Elective surgical options for MUC include total proctocolectomy with either an end ileostomy or continent reservoir (Kock pouch), total abdominal colectomy with an ileoproctostomy, or a restorative proctocolectomy with an ileoanal reservoir. Each procedure has its advantages and disadvantages, and selection of a specific operation must take into account the age and overall health of the patient, the presence of dysplasia and the risk of carcinoma, the status of the patient's anal continence, and the certainty of the diagnosis of MUC.

Total Proctocolectomy with End Ileostomy

Total proctocolectomy has the advantage of removing all possible diseased mucosa, thereby preventing further inflammation or the potential for progression to dysplasia or carcinoma. The major disadvantage of this procedure is the need for a permanent ileostomy. In addition, despite improvements in bowel preparation, antibiotics, and surgical technique, total proctocolectomy still has a fairly high morbidity rate.

Most of the morbidity is related to perineal wound healing, adhesions, the ileostomy, and complications of pelvic dissection. In a study from St. Marks Hospital in which 70 patients underwent elective total proctocolectomy, the complication rate was 39%⁵¹. Thirty-six percent of patients required readmission and 21% required reoperation. The most common

complications were problems related to the ileostomy in 13 patients (19%), small bowel obstruction in 10 patients (14%), and delayed perineal wound healing in six patients (9%). Perineal wound problems may be reduced if an intersphincteric proctectomy is performed. This approach involves a dissection between the internal and external sphincters, preserving the external sphincter and levator ani for a more secure perineal wound closure. Painter and Oakley reported a 93% complete wound healing at six months using this technique⁵².

Total proctocolectomy with end ileostomy was one of the earliest operations performed for MUC, and despite advances in sphincter-saving procedures continues to have a role. Elderly patients, those with poor sphincter function, and patients with carcinomas in the

lower rectum may be candidates for this

procedure.

Total Proctocolectomy with Continent Ileostomy

The continent ileostomy was introduced by Kock in 1969⁵³ and became very popular in the 1970s as it offered patients with an ileostomy control over evacuation. Its creation involves suturing several limbs of ileum together to create a reservoir. The pouch becomes continent by intussuscepting the outflow tract to create a valve. As the pouch distends, pressure over the valve causes it to close and retain stool, allowing patients to wear a simple bandage over a skin level stoma. Between two and four times per day, the patient introduces a tube through the valve to evacuate the pouch.

The major problem associated with the Kock pouch is the high reoperation rate, required in up to 50% of patients⁵⁴. The most common surgical procedure is revision of the nipple valve⁵⁵, typically when one side of the valve “slips,” or loses its prolapsed position within the pouch. This leads to either the inability of the pouch to remain continent or the inability to intubate the pouch, leading to spontaneous emptying of the pouch as it overflows. Techniques have been developed to reposition the valve to allow for pouch continence⁵⁶. Other complications include pouchitis in 15 to 30% of cases, fistula formation in 10%, and stoma stricture in 10% of patients^{57,58}.

The continent ileostomy is a technically demanding procedure associated with a steep learning curve. The experience from the Cleveland Clinic Florida showed that reoperation was necessary in 43% of

patients operated on in the first three years, but only 7% of patients by the ninth year⁵⁷. Even with the need for revisional surgery, however, a continence rate of greater than 90% was achieved. These results have been duplicated at other centers as well^{58,59}.

Despite the high complication rate, a role still exists for the continent ileostomy. The most frequent current indication is conversion of a failed ileoanal reservoir in a patient who refuses a Brooke ileostomy. Hulten, *et al.* reported five patients who underwent conversion from a failed ileoanal reservoir to a continent ileostomy⁶⁰. There were no perioperative complications and four of the five patients had well-functioning continent ileostomies. The remaining patient had recurrent nipple valve prolapse requiring pouch excision. In addition, Kock pouch may be an option in patients who have previously undergone a total proctocolectomy with a Brooke end ileostomy who wish to undergo a restorative procedure, as well as patients with weak anal sphincters who do not want a Brooke ileostomy. At present, however, the most common surgery related to continent ileostomies is revisional surgery.

The Kock procedure should not be performed in obese patients, debilitated patients, or any patient with physical or mental handicap that would not allow them to safely catheterize the stoma. In addition, a preoperative diagnosis of CD is an absolute contraindication to the procedure.

Total Abdominal Colectomy with Ileoproctostomy

A third alternative in the surgical management of MUC is total abdominal colectomy with ileoproctostomy. Many of the intrinsic complications of total proctocolectomy are not experienced with

this procedure because there is no mobilization of the rectum. Complications of pelvic nerve disruption including impotence, retrograde ejaculation, and bladder dysfunction, as well as presacral venous

bleeding are avoided as resection is halted at the rectosigmoid junction and the anastomosis is performed at the level of the sacral promontory. In females patients, intercourse, gravity, and parturition should be unimpeded and dyspareunia, an occasional complication of total proctocolectomy, has not been reported following ileoproctostomy. This procedure has been shown to be safe, with an anastomotic leak rate of less than 2% in several large series^{61,62}.

Functional results after ileoproctostomy are excellent. In a series collected by Jagelman

and coworkers⁶³, over 90% of patients had fewer bowel movements per day postoperatively than preoperatively, and 40% had three or fewer per day. Other authors have reported similar results, which are shown in Table 2. Parc *et al.*⁶⁴ demonstrated that postoperative function continued to improve for 12 to 18 months, but only rarely improved after two years. Because the rectum, sphincters, and their nerves are preserved, continence should not be affected in virtually all patients.

Series	Patients No.	Frequency Mean (Range)	Patients Requiring Antidiarrheal Medications (%)	Patients with Nocturnal Bowel Movement (%)
Khubchandani, <i>et al.</i> ⁶²	110	1.4	73	---
Newton and Baker ⁶⁵	92	4.5 (1.7-8.7)	50	4
Oakley, <i>et al.</i> ⁶⁶	92	4.3(1-10)	23	5
Parc, <i>et al.</i> ⁶⁷	197	4.5	50	35
Pastore, <i>et al.</i> ⁶⁸	48	6	53	---
Church, <i>et al.</i> ⁶⁹	51	3.6	---	22
Eu, <i>et al.</i> ⁷⁰	66	2.9	33	---
Ko, <i>et al.</i> ⁷¹	14	5.2	---	---
Elton, <i>et al.</i> ⁷²	215	3.0	37	---

Failure of ileoproctostomy is usually due to continued inflammation rather than the development of carcinoma. Failure rates, along with mortality and leakage rates are presented in Table 3. More recent long-term studies have reported failure rates in excess of 50%⁵⁵. Reports of failure of ileoproctostomy must be carefully interpreted, however, as the incidence of

severe postoperative inflammation is often related to the severity of the preoperative inflammation. This feature makes comparison of failure rates among studies impossible in terms of patient selection. In addition, newer 5-ASA enema preparations may have improved action against inflammation in the rectum.

Table 3. MORBIDITY AND MORTALITY OF ILEORECTAL ANASTOMOSIS

Series	Patients No.	Mortality	Anastomotic Leakage (%)	Failure Rate (%)	Developing Carcinoma in Rectum
Aylett ⁷³	300	6	12	5	---
Backer, <i>et al.</i> ⁷⁴	59	0	0	22	---
Baker, <i>et al.</i> ⁷⁵	384	---	---	---	22
Fazio, <i>et al.</i> ⁶¹	157	2	1	---	---
Grundfest, <i>et al.</i> ⁷⁶	89	---	---	---	4
Gruner, <i>et al.</i> ⁷⁷	57	7	10	---	---
Khubchandani, <i>et al.</i> ⁶²	110	0	2	10	---
Leijonmarck, <i>et al.</i> ⁷⁸	60	4	2	57	---
Oakley, <i>et al.</i> ⁷⁹	145	0	2	24	5
Parc, <i>et al.</i> ⁶⁷	197	---	---	25	---
Pastore, <i>et al.</i> ⁶⁸	48	0	2	17	4
Soravia, <i>et al.</i> ⁸⁰	60	0	3	---	---
Eu, <i>et al.</i> ⁷⁰	66	3.0	4.5	---	---
Elton, <i>et al.</i> ⁷²	215	0.9	6.5	11	---

One of the disadvantages of ileoproctostomy is the risk of subsequent rectal carcinoma. The risk of carcinoma varies with time and by reported series, but can reach as high as 6% at 20 years, 15% at 30 years, and 18% at 35 years⁷³. Early series reported tumors that were poorly differentiated or of advanced stages at the time of diagnosis. However with routine endoscopic evaluation of the rectum with random biopsies, early detection of dysplasia or rectal carcinoma should be possible. Several authors have reported that dysplasia or carcinoma in the resected colon correlates with subsequent rectal carcinoma. Grundfest, *et al.*⁷⁶ found that five of seven patients with cancer or severe dysplasia in the resected colon developed cancer or severe dysplasia in the retained rectum. In the series by Oakley, *et al.*,⁶⁶ of five patients with cancer in the rectal stump, two had cancer elsewhere in the colon and one had severe dysplasia. Patients with cancer or severe dysplasia in the resected colon are therefore not candidates for ileoproctostomy.

Despite the risk of carcinoma and the potential for persistent inflammation leading to failure, ileoproctostomy may be an attractive option, especially for older patients with MUC who have other significant medical problems. Although elderly patients may average up to six bowel movements per day in the immediate postoperative period, the average usually decreases to about three per day at late follow-up⁸¹. The risk of carcinoma in the retained rectum is of less concern in the elderly population. Preoperative proctoscopy (with a flexible fiberoptic sigmoidoscope, if preferred) should, however, verify relative lack of inflammation. In addition, preoperative assessment of incontinence should be undertaken using a scoring system in the evaluation of patients for this procedure⁸². Contraindications to ileoproctostomy include severe proctitis, perianal disease, fecal incontinence, and dysplasia in the rectum.

Ileoanal Reservoir

Restorative proctocolectomy with ileoanal reservoir has become the most common definitive procedure in the elective treatment of MUC. The procedure involves a near-total proctocolectomy with preservation of the anal sphincter complex. The mucosa of the distal anal canal can be stripped of the internal sphincter with the aim of preventing recurrence of symptoms or the potential of the development of cancer. A pouch is then fashioned using two, three, or four loops of small bowel (S, H, J, or W configuration) and is anastomosed to the anal canal⁸³⁻⁸⁶. The pouch and anastomosis were traditionally protected with a diverting loop ileostomy, however, there are some proponents of the single-stage procedure without diversion⁸⁷⁻⁹². In a series from the Cleveland Clinic Florida⁹³, 0 of 110 patients who underwent an ileoanal pouch had clinical leaks when a diverting ileostomy was used. Three of 26 patients who underwent single-stage procedures, however, had clinical leaks requiring subsequent diversion. Surgeons from other institutions, including the University of Minnesota, Cleveland Clinic Ohio, Mayo Clinic, University of Leeds, and St. Marks' Hospital have all cautioned against single-stage procedures⁹⁴⁻⁹⁷.

Regardless of the configuration of the pouch, functional results are similar among many reported series^{83-86,98}. A summary of functional results is shown in Table 4. The mean number of bowel movements in 129 patients with S-pouches at the University of Minnesota was 5.4 throughout the day and 1.5 at night⁹⁹. The Mayo Clinic evaluated 1193 patients with J-pouches and found that the mean number of bowel movements in a 24-hour period was five¹⁰⁰. Similarly, Fleshman, *et al.*¹⁰¹ reported a mean of 6.2 bowel movements per day in their series of patients. Schoetz *et al.*¹⁰² reported 7.0 bowel movements per day during the first three months following ileostomy closure and 5.1 per day following three months. Other authors have reported similar findings that improvement in function can be expected to decrease bowel movements

during the ensuing 3 to 24 months following reestablishment of continuity^{102,103}.

Because the ileal reservoir is anastomosed directly to the anal sphincter mechanism, continence can be affected. Nocturnal incontinence is a more significant problem than daytime incontinence. In the University of Minnesota series, 91% of patients had good control of both solid and liquid stool during the day⁹⁹. This number dropped to only 76% of patients during the night. Minor spotting occurred in a significant number of patients and almost two thirds wore protective pads. Pemberton, *et al.*¹⁰⁷ reported that almost half of patients had nocturnal leakage at 6 months, but at one year only 20% continued to have leakage at night. Other authors have shown similar improvements in continence with time^{101,102}.

The double stapling technique of ileoanal anastomosis was first described by Knight and Griffen¹¹⁴. This technique involves a lower rectal dissection with transection of the anus within the levator hiatus. The pouch is then secured to the anal transition zone, usually within 1 cm of the dentate line. Avoiding the traditional mucosectomy preserves the anal transition zone which contains nerve endings involved in differentiating liquid and solid stool from gas and helps in maintaining continence^{105,115-118}. Mechanisms involved include the retention of mucosal electrosensitivity and the preservation of the rectoanal inhibitory reflex^{119,120}. Physiologically, resting pressures have been shown to be higher and functional results improved with the double stapling technique^{110,119,121}. Sugarman, *et al.*⁹¹ compared results of pouches with stapled and handsewn anastomoses. There were fewer complications, better functional results including better continence, and decreased hospitalizations in patients who had a stapled anastomosis. Other authors have also shown similar benefits of the non-mucosectomy technique^{105,122-125}.

Table 4. FUNCTIONAL RESULTS OF ILEOANAL RESERVOIRS

Series	Patients No.	Bowel Movements (No. of Times)		Leakage (%)			Incontinence (%)		
		Day	Night	Day	24h	Night	Day	24h	Night
Becker and Raymond ¹⁰³	100	5.4	---	---	---	25	---	---	---
Fleshman, <i>et al.</i> ¹⁰¹	102	6.2	---	18	---	23	1	---	7
Fonkalsrud, <i>et al.</i> ¹⁰⁴	138	4.8	---	---	---	---	---	---	22
Kelly ¹⁰⁰	1193	4.5	0.5	---	25	---	---	---	---
Liljeqvist, <i>et al.</i> ¹⁰⁵	38	4.9	---	8	---	8	---	---	---
Michelassi, <i>et al.</i> ¹⁰⁶	391	6	1	---	16	---	0	---	12.5
Nicholls & Lubowski ⁸⁶	64	3.3	14	---	8	---	---	0	---
Pemberton, <i>et al.</i> ¹⁰⁷	389	6	1	22	---	52	---	---	---
Reissman, <i>et al.</i> ¹⁰⁸	140	5.4	1.2	0	---	0.6	5.4	---	8.1
Schoetz, <i>et al.</i> ¹⁰²	86	4.9	0.2	---	12	---	---	1	---
Sugarman & Newsome ¹⁰⁹	75	5.1	1.8	4	---	14	8	---	17
Tuckson, <i>et al.</i> ¹¹⁰	54	6	1	6	---	14	2	---	2
Wexner, <i>et al.</i> ⁹⁹	114	1.5	---	12	---	29	2	---	1
Blumberg, <i>et al.</i> ¹¹¹	145	4.5	---	---	---	15	0	---	---
Dayton, <i>et al.</i> ¹¹²	565	6	--	---	---	---	---	---	12
Delaney, <i>et al.</i> ¹¹³	1399	6	1	---	---	36	--	1	---

A concern of using the double stapling technique is the possibility of developing either recurrent disease or carcinoma in the retained rectal mucosa. It has been shown, however, that not all patients harbor rectal mucosa following this technique. Many patients have only squamous or transitional epithelium remaining^{126,127}. To date there have been no reports of carcinoma using the non-mucosectomy technique. Two cases of carcinoma, however, have been reported following mucosectomy^{128,129}. The non-mucosectomy technique allows for surveillance and biopsy of the remaining mucosa¹³⁰, whereas the mucosectomy technique may be hiding retained rectal mucosa in over 20% of patients¹³¹.

The major complications after ileoanal reservoir are listed in Table 5. A common complication is small bowel obstruction, occurring in up to 27% of patients. Bowel obstructions after ileoanal pouches tend to be severe and require surgery in almost

50% of cases¹⁰¹. The most significant complication is pelvic sepsis^{132,133}. Anastomotic and pouch suture line leaks are devastating complications that can lead to pelvic abscess and seriously threaten the quality and longevity of the pouch. Laparotomy in the treatment of pelvic sepsis can lead to pouch excision in up to 50% of patients¹³². Pelvic sepsis is related to whether or not a mucosectomy was performed, as well as the use of a diverting ileostomy^{105,122,132,134}. Treatment of pelvic sepsis secondary to pouch leaks is typically with a diverting ileostomy. Delayed ileostomy closure after healing of pouch-anal anastomotic complications has been shown to have no deleterious functional effects¹³⁵. A specific form of pelvic sepsis that is difficult to manage is a pouch-vaginal fistula, which can occur in up to 7% of women¹³⁶⁻¹³⁸. This type of fistula may often occur in patients with misdiagnosed CD and, despite numerous surgical alternatives, results in pouch excision in 18% of patients.

Series	Patients No.	Sepsis (%)	Bowel Obstruction (% Laparotomy)	Pouchitis (%)	Stricture (%)
Fleshman, <i>et al.</i> ¹⁰¹	102	17	19	23	8
Fonkalsrud ¹⁰⁴	138	4	(9)	29	---
Francois, <i>et al.</i> ¹³⁹	626	---	17 (7)	---	---
Kelly ¹⁰⁰	1193	5	15 (5)	---	---
McMullen, <i>et al.</i> ¹⁴⁰	73	5	16	15	---
Nicholls & Lubowski ⁸⁶	205	15	(14)	30	4
Orselund, <i>et al.</i> ¹³³	100	8	(14)	30	4
Reissman, <i>et al.</i> ¹⁰⁸	140	6	8 (5)	6	4
Schoetz, <i>et al.</i> ¹⁰²	86	8	27 (12)	10	---
Schoetz, <i>et al.</i> ¹⁴¹	165	7	---	---	8
Scott, <i>et al.</i> ¹³²	500	6	---	---	---
Wexner, <i>et al.</i> ¹⁴²	180	11	27 (15)	27	12
Barton, <i>et al.</i> ¹⁴³	86	4.6	11.6 (7)	---	---
Blumberg, <i>et al.</i> ¹¹¹	145	8.2	26	10.3	---
Dayton, <i>et al.</i> ¹¹²	565	5	(5.5)	25	4.8
Delaney, <i>et al.</i> ¹¹³	1399	5.6	---	---	---
Michelassi, <i>et al.</i> ¹⁰⁶	391	7.7	11	---	10.7

Another complication of the ileoanal reservoir is pouchitis, which occurs in 7% to 33% of patients^{107,133,141,144,145}. An accurate estimation of the incidence of pouchitis is difficult as some authors define pouchitis by clinical criteria which can be nonspecific and may be associated with other causes, while others require histologic evidence obtained by pouchoscopic biopsy to make the diagnosis. Pouchitis typically presents with increased frequency of stools which may be accompanied by fever, bleeding, cramps, and dehydration. The cause is unknown but may be related to bacterial overgrowth, mucosal ischemia, or other local factors^{146,147}. Episodes will usually respond to rehydration and oral metronidazole, but the diagnosis of CD must again be entertained.

In some cases, the preoperative distinction between CD and MUC can be difficult, and the pathologist may label the disease as "indeterminate" colitis. Crohn's disease is a contraindication to ileoanal reservoir, and published series have reported very poor

results^{148,149}. Pouchitis or ileitis will affect up to 100% of these cases and pouch-vaginal fistulas occur in 33% of females. Pouch failure leading to excision of the pouch occurs in more than half of these cases. Hyman, *et al.*¹⁵⁰ reported a series of patients who had undergone an ileoanal reservoir and ultimately were diagnosed with CD. In nine patients, a preoperative suspicion of CD based on clinical or endoscopic data was retrospectively present. On follow-up, only one of these patients had a functioning pouch. Fifteen of 16 patients with no preoperative suspicion of CD on rereview, however, maintained a functioning pouch.

Patients with indeterminate colitis who undergo ileoanal reservoir and do not develop CD have results that are more encouraging. Yu, *et al.*¹⁵¹ reported a series of 82 patients with indeterminate colitis who underwent ileoanal reservoir. In comparison with patients with MUC who underwent ileoanal reservoir, patients with the preoperative diagnosis of indeterminate

colitis had significantly more episodes of pelvic sepsis, pouch fistula, and pouch failure. Fifteen percent of these patients were found to have CD, however, and when these patients were removed from the analysis, the rate of complications for the remaining patients with indeterminate colitis

was identical to that of patients with chronic MUC. Similarly, in a series at the Cleveland Clinic Florida there was no difference in the rates of complications or the functional outcome in patients with indeterminate colitis and MUC who underwent double-stapled ileal pouch anal anastomosis¹⁵²

Laparoscopy

The use of laparoscopic surgery for diseases of the colon and rectum began in the early 1990s and has now become standard of care in some disease states. Peters¹⁵³ was the first to publish the results of laparoscopy in the treatment of inflammatory bowel disease, and it appears to be a versatile and effective modality in the surgical treatment of MUC in selected patients¹⁵⁴. The success of the procedure depends on the actual procedure performed, the patient's underlying condition, security of the diagnosis, and the skill of the laparoscopic surgeon. Although early reports noted increased morbidity¹⁵⁵, improved techniques and equipment have produced both early and later results that are comparable to those of standard laparotomy¹⁵⁶⁻¹⁶². Laparoscopy may afford the advantages of decreased intraoperative fluid loss, shorter postoperative ileus, less pain, and improved cosmesis¹⁶³⁻¹⁶⁵. Longer operative times and the increased need for blood transfusion may be higher with laparoscopy than with standard ileal pouch anal anastomosis^{155,166}.

Marcello, *et al.* compared 20 consecutive laparoscopic restorative proctocolectomies with 20 matched open cases¹⁶⁷. There were no intraoperative complications in either group, although the operative times were significantly longer in the laparoscopic procedures (median 330 minutes vs. 230 minutes). Bowel function returned quicker in the laparoscopic group and length of stay was decreased. Table 6 outlines the results of this and other laparoscopic total proctocolectomies.

Overall, laparoscopy can be selectively applied in patients with MUC. In the hands of skilled laparoscopic surgeons, laparoscopic total proctocolectomy with ileal pouch anal anastomosis is a safe and effective procedure despite having few, if any, real advantages. The surgeon to whom a patient is sent should be familiar with all the possible procedures available for MUC as well as an accomplished laparoscopist. In this setting, the appropriate use of laparoscopy can benefit the proper patients with improved cosmesis.

Series	Patients No.	Mean Operative Time	Morbidity (%)
Tucker, <i>et al.</i> ¹⁵⁸	4	5h, 27 min	---
Rhodes, <i>et al.</i> ¹⁶⁰	5	5h, 10 min	60
Liu, <i>et al.</i> ¹⁵⁹	5	8h	20
Hildebrandt, <i>et al.</i> ¹⁶³	5	6h	0
Santoro, <i>et al.</i> ¹⁶⁴	5	6h, 4 min	0
Marcello, <i>et al.</i> ¹⁶⁷	20	5h, 30 min	20
Pace, <i>et al.</i> ¹⁶⁸	13	4h, 25 min	46
Hasegava, <i>et al.</i> ¹⁶²	18	6h	33



Summary

Patients with MUC now have a variety of procedures to treat their disease. Surgical techniques have improved, complication rates have declined, and the functional results of ileoanal reservoir surgery are excellent in most patients. Despite the

advent of newer medications, one must balance poor function secondary to disease, cancer risk, and the side effects of medication against surgical morbidity and postoperative function.

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