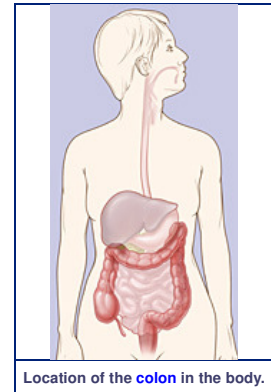


Collagenous & Lymphocytic Colitis: Introduction

Researchers (Read, et al.) used the term "microscopic colitis" in 1980 to describe the entity of **chronic**, watery diarrhea in patients with only microscopic evidence of inflammation. The term is currently used to include collagenous and lymphocytic colitis.



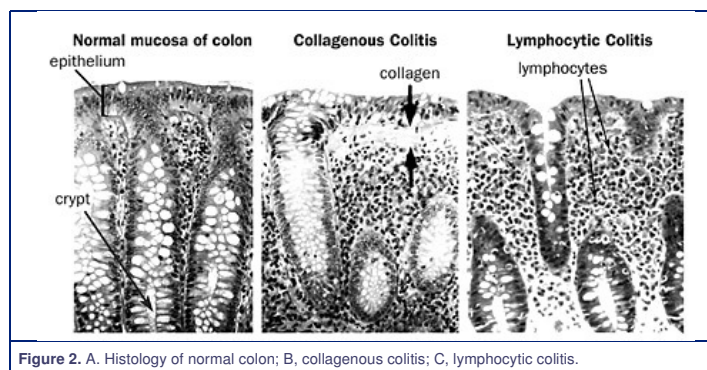
What are Collagenous and Lymphocytic Colitis?

Collagenous and lymphocytic colitis are clinical and pathologic syndromes representing forms of microscopic colitis that affect the large intestine. Both disorders usually present in middle-aged patients in the fifth or sixth decade of life. Collagenous colitis primarily affects women. The predominance in the female to male population is 8:2. Lymphocytic colitis is found in both men and women with an equal male-to-female gender distribution. Those affected by lymphocytic colitis are slightly younger; the mean age of onset is 53 years. In both disorders, most patients present with complaints of chronic, watery, noninfectious diarrhea, and abdominal pain. Clinical and histology differences do exist between lymphocytic colitis and collagenous colitis. These disorders rarely affect children.

Lindstrom first described collagenous colitis in 1976 as having a distinctive colorectal histopathology that included a subepithelial collagen band beneath the epithelium surface in colorectal mucosa. This disorder has two main histological components: 1) increased collagen deposition and 2) colitis. It is a chronic inflammatory process of unknown etiology and a relatively new entity in the realm of inflammatory bowel diseases. The incidence of this disorder is approximately 1.8 cases per 100,000 population. In the presence of chronic diarrhea, the frequency of collagenous colitis ranges from 0.3–5.0%.

Histopathology of ...	
Collagenous Colitis	Lymphocytic Colitis
Lymphocyte infiltration of epithelium without neutrophils	Lymphocyte infiltration of epithelium without neutrophils
Distinct pattern of fibrosis	
Localized subepithelial collagen banding in right and transverse colon	No collagenous thickening
Lack of crypt distortion	Minimal to no crypt distortion
Chronic inflammation in lamina propria	Chronic inflammation in lamina propria

Table 1.



The histopathology of lymphocytic colitis is similar to that of collagenous colitis except there is no collagenous thickening. Because of the clinical and histological similarities of these two disorders, they are commonly considered as a single category of inflammatory bowel disease for the purpose of treatment.

Symptoms

The main symptom in collagenous colitis, as well as lymphocytic colitis, is chronic, watery diarrhea. Sixty percent of these patients are unable to pinpoint the exact onset of their symptoms, although some relate preceding gastroenteritis. Patients describe 5–10 watery bowel movements per day persisting for an average of five years, but as long as 20 years. Diarrhea is usually accompanied by cramps and diffuse abdominal pain, which rarely occurs at night. These patients are frequently misdiagnosed as having irritable bowel syndrome.

Enteropathic arthritis may be a manifestation of collagenous colitis and is seen in approximately 7% of cases. This form of arthritis, seronegative for rheumatoid factor, is nondestructive and may involve one or several joints. Treatment of the underlying colitis aids in the resolution of these symptoms. Seventeen to 40% of patients with collagenous colitis present with a variety of other immune-related disorders, including Sjögren's syndrome, giant cell arteritis, recurrent iritis, celiac disease, rheumatoid arthritis, thyroiditis, and myasthenia gravis.

Collagenous & Lymphocytic Colitis: Anatomy

The colon may be divided into the cecum, the ascending colon, the transverse colon, the descending colon, the sigmoid colon and the rectum. The large intestine (colorectum) begins at the cecum, a pouch approximately 2–3 inches long. Ileal contents empty into the cecum through the ileocecal valve. The appendix extends from the base of the cecum. The ascending colon rises from the cecum along the right posterior wall of the abdomen to the undersurface of the liver. At this point it turns toward the midline (hepatic flexure), becoming the transverse colon. The transverse portion crosses the abdominal cavity toward the spleen and turns downward at the splenic flexure. Continuing along the left side of the abdominal wall to the rim of the pelvis, the descending colon turns medially and inferiorly to form the S-shaped sigmoid colon. The rectum extends from the sigmoid colon to the pelvic floor muscles where it continues as the anal canal, terminating at the anus (Figure 3).

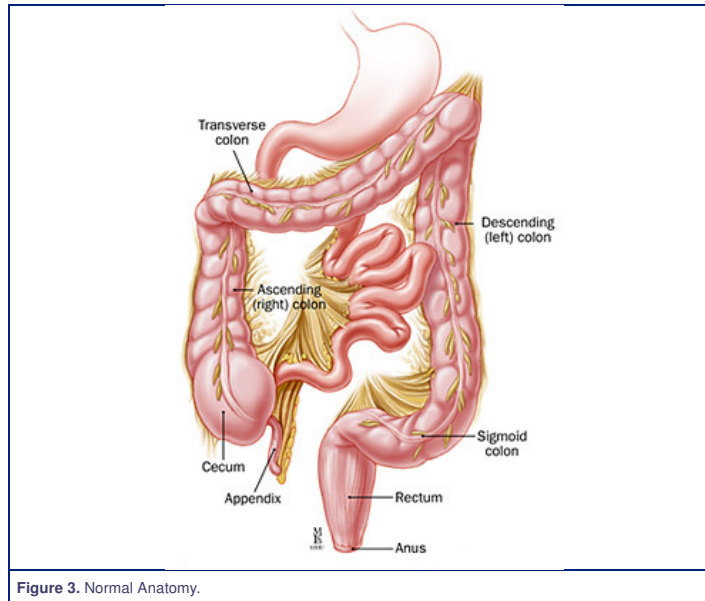


Figure 3. Normal Anatomy.

The large intestine is approximately 7–8 feet long and 2 1/2 inches in diameter. It is the site of water absorption. Glands secrete large quantities of alkaline mucus that lubricate the intestinal contents and neutralize acids formed by bacteria in the intestine. These bacteria aid in decomposition of undigested food residue, unabsorbed amino acids, cell debris, and dead bacteria through the process of putrefaction. Maintenance of potassium balance is also assigned to the colon, where the epithelium absorbs and secretes potassium and bicarbonate.

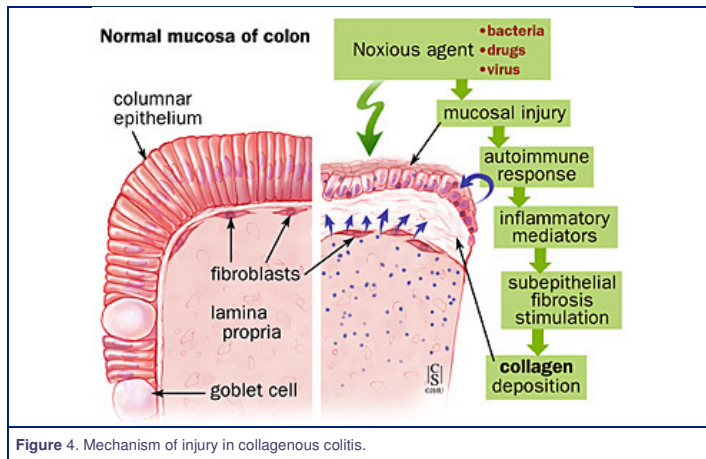
Collagenous & Lymphocytic Colitis: Causes

Overview

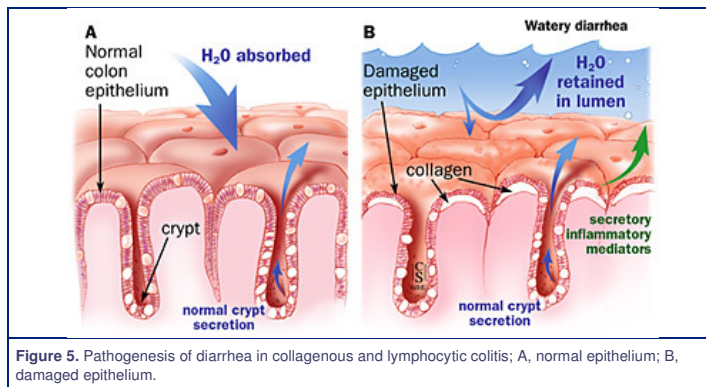
The cause of collagenous and lymphocytic colitis is unknown. No definitive causative agent has been identified, although an association with ingestion of nonsteroidal antiinflammatory (NSAIDs) has been suggested. This link requires further investigation.

Pathogenesis

Hypotheses concerning the pathogenesis of this disorder have included immune dysregulation leading to inflammation of the colon, collagen synthesis abnormalities, bacterial agents or toxins, mast cell abnormalities, and plasmatic vasculosis. It has also been suggested that a foreign luminal agent, perhaps a bacterial organism, may initiate colorectal mucosal inflammation. This may lead to an immunological cross-reactivity with an endogenous antigen produced by surface enterocytes (Figure 4).



The pathogenesis of chronic diarrhea in lymphocytic and collagenous colitis is multifactorial. Diarrhea may result from net fluid secretion in the colon from decreased absorption due to epithelial surface damage and deposition of collagen along with a normal rate of fluid secretion into the lumen from intact crypts. Small-bowel dysfunction has been noted in some patients, in addition to bile salt wasting, fatty acid malabsorption, small-bowel net secretion, and in rare circumstances, villous atrophy. Diarrhea may be exacerbated by these additional abnormalities (Figure 5). The physician must consider thyroid disease as a possible element in the diarrheal diathesis.



Collagenous & Lymphocytic Colitis: Diagnosis

Laboratory Tests

Routine blood studies are generally normal in these patients, but Westergren sedimentation rate elevation and eosinophil count abnormalities are not uncommon. In addition, abnormalities in complement levels and serum immunoglobulins (G [IgG], C3, or C4) may be found. Antineutrophilic cytoplasmic antibodies have been found in cases of collagenous colitis. No elevations of procollagen III, cytokines, or serum secretagogues have been reported. In collagenous and lymphocytic colitis, stool specimens are negative for occult blood, ova, parasites, bacterial pathogens and *Clostridium difficile* toxin. As many as 55% of collagenous colitis patients have leukocytes (white blood cells) on stool smears. These patients may also present with mild steatorrhea, elevated fecal clearance of alpha-antitrypsin, and protein-losing enteropathy. Bile salt breath testing with C-glycocholate is typically abnormal, indicating bile salt deconjugation or malabsorption.

Physicians should suspect collagenous and lymphocytic colitis in middle-aged patients presenting with chronic, watery, noninfectious diarrhea. Often mistaken for irritable bowel syndrome, there are key differences. Collagenous/lymphocytic colitis patients present at an older age and without long-term history of alternating constipation and diarrhea.

Radiological Diagnosis

Gastrointestinal radiographic studies are not diagnostic in collagenous and lymphocytic colitis. Usually upper and lower gastrointestinal barium studies are normal, but colonic mucosal irregularities and adenomatous polyps are occasionally noted.

Endoscopic Diagnosis

Lower endoscopy with colonic biopsy is the standard of diagnosis. Colonoscopy is the primary method for examination of the colon with extremely low complication rates (0.1–0.3%). The procedure allows the physician to visualize and biopsy the lower gastrointestinal tract with a high-resolution color view of the mucosa through wide-angle optics. The endoscope or colonoscope has a flexible shaft to accommodate colonic bends and air insufflation capabilities are incorporated with water wash to improve visibility. Colonoscopes have a full range of endoscopic accessories including biopsy forceps, electrocoagulating hot biopsy forceps, cytology brushes, washing and spraying catheters, sclerotherapy needles, a wide range of dilatory balloons and bougies, as well as snares for polypectomy and retrieval devices (Figure 6). Colonoscopy permits visualization of the anus, rectum, sigmoid, descending, transverse, and ascending colon, and the terminal ileum.

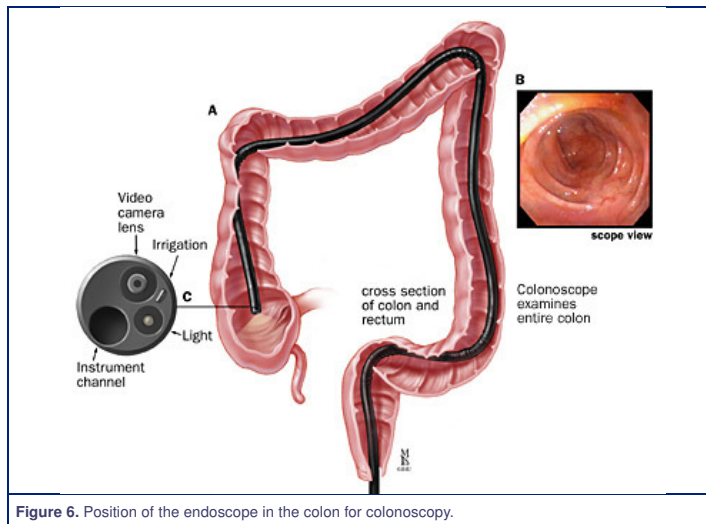


Figure 6. Position of the endoscope in the colon for colonoscopy.

Preparation for this procedure requires that the patient have nothing by mouth for eight hours (except for essential medications) prior to the procedure. Patients are also advised to avoid aspirin for at least seven days before the procedure to minimize the risk of bleeding with biopsy. A safe and successful colonoscopy requires that the patient have a clean colon. This may be achieved with two types of bowel preparations. Both are effective and safe. Oral lavage solutions, either buffered sodium phosphate or polyethylene glycol products, are widely used.

The patient is given a sedative before the procedure and placed in the left lateral position. The colonoscope is introduced through the rectum and advanced through the narrower extraperitoneal portion of the sigmoid colon, the descending colon, passing the splenic flexure into the transverse colon, ascending colon and to the cecum (Figure 7).

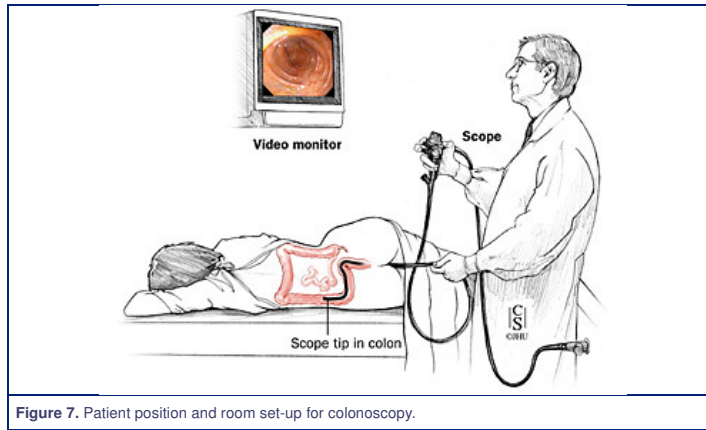


Figure 7. Patient position and room set-up for colonoscopy.

The colonic mucosa appears essentially normal on endoscopic evaluation, although nonspecific findings such as erythema, paleness, and edema have been noted in approximately one-third of cases. Colorectal biopsy can definitively establish a diagnosis of collagenous or lymphocytic colitis. Although the mucosa usually appears normal, procurement of colorectal biopsy specimens is essential to make a definitive diagnosis (Figure 8). Multiple biopsy specimens should be taken proximal to the rectosigmoid because collagenous thickening can be patchy and is usually (73% of cases) not found in rectal specimens.

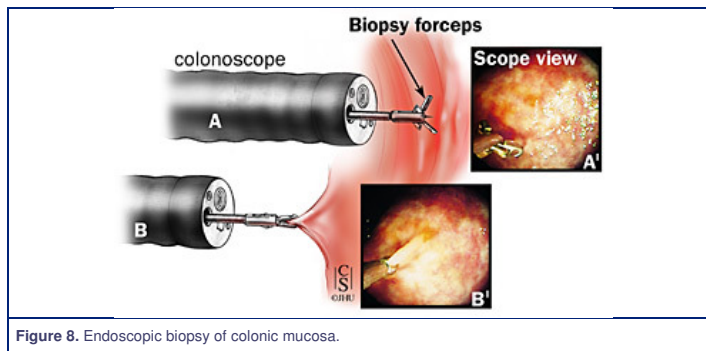


Figure 8. Endoscopic biopsy of colonic mucosa.

Collagenous & Lymphocytic Colitis: Therapy

Overview

The experience in the treatment of collagenous and lymphocytic colitis is limited. No randomized trials currently exist from which to draw firm conclusions regarding treatment efficacy. Additionally, the variability of the clinical course of these patients makes interpretation difficult. However, review of the literature suggests concepts to guide therapy.

Collagenous and lymphocytic colitis respond to the use of anti-inflammatory medications. Prompt improvement in diarrhea is noted in the majority of patients along with resolution of collagen banding in some. The literature also reports dramatic clinicopathological response with remission to antibacterial agents such as bismuth subsalicylate (Pepto-Bismol).

Because experience is limited, the danger of leaving collagenous and lymphocytic colitis untreated is not known. It is unknown whether colonic inflammation of this type may predispose patients to future complications, such as neoplasms. One study found no increased risk for colorectal cancer in patients with collagenous colitis. On one hand, spontaneous remission has been documented in some patients; however, exacerbation after discontinuation of anti-inflammatory medications has been noted in others. The appropriate duration of therapy is difficult to define. Biopsies from the right or transverse colon appear to be more reliable indicators of the degree of inflammation and collagen banding than rectal biopsy.

Further evaluation in the form of a double-blind randomized trial, which utilizes both clinical and histopathological data, should allow the assessment of a reasonable course of therapy.

Symptomatic Therapy

Dietary secretagogues, such as caffeine- or lactose-containing foods, should be eliminated. A low-fat diet should be instituted in cases where steatorrhea is documented. Cholestyramine has been useful in patients presenting with bile salt malabsorption. Some patients are helped by antidiarrheal medications such as Loperamide, or hydrochloride (Imodium) or codeine.

Antibacterial Agents

Investigators have treated collagenous colitis patients using antibacterial agents with remarkable results. In an open-label trial, investigators reported a trial of bismuth subsalicylate (eight chewable 262 mg tablets per day for eight weeks) in 12 patients, including those with collagenous and lymphocytic colitis. Eleven patients had resolution of diarrhea and histopathological changes with no recurrence 7–28 months after treatment. No side effects were reported. Response rates of 60% have been seen with metronidazole (250 mg 3–4 times a day) and erythromycin antibiotics.

Sulfasalazine

Sulfasalazine has been shown to be effective in idiopathic colonic inflammatory bowel disease with comparatively few side effects. The usual dosage is 2–4 g/day by mouth, in divided doses with meals and at bedtime. Full dosage should be achieved slowly, beginning with 0.5 g daily and adding 1 tablet per day until the desired dosage is reached. Gradually reaching the desired dosage may help to avoid such side effects as nausea and headaches. Fifty percent of patients respond to this therapy with abatement of diarrheal symptoms within 1–2 weeks. Patients may remain on this therapy for three months and then the dosage should be tapered to a maintenance dose of 1 g twice a day. Hematological status should be monitored during therapy. This therapy may interfere with dietary folate absorption, and routine folate replacement is suggested. Serious idiosyncratic reactions such as hepatitis, pancreatitis, alveolitis, and serum sickness are rare. Sulfasalazine should be discontinued if the patient experiences major side effects such as allergic skin reaction, hemolysis, neutropenia, or milder allergic reactions with rash and fever. The literature reports responses to 5-aminosalicylic acid in the oral form in patients with collagenous colitis.

Adrenocorticoids

Adrenocorticoid medication may be used if sulfasalazine fails to show clinical improvement after 2–4 weeks or if it is not well tolerated. Most patients are treated with prednisone with dramatic resolution of diarrhea in 80–90% of cases within 5 days. Histological improvement has been noted in patients with lymphocytic colitis and with collagenous colitis.

Most patients have responded to a morning dose of 20–30 mg of prednisone. Patients with greater than 2 liters of stool/day may benefit from hospitalization and treatment with intravenous prednisolone (60 mg/day) or hydrocortisone. After control of diarrhea, patients have been maintained on 20–30 mg of prednisone for three months. Recurrence of diarrhea may occur with discontinuation of therapy. In these patients, 10–15 mg of prednisone daily or alternate-day steroids may be successful in controlling symptoms. Budesonide, a steroid agent with greater first-pass metabolism, has also been effective. Antidiarrheal agents may minimize prednisone dosage and accompanying adverse effects.

Other Therapeutic Agents

There have been reports of improvement with Pepto-Bismol, mepacrine hydrochloride (an inhibitor of arachidonic acid metabolism), and steroid enemas. Metronidazole has also been used as an anti-inflammatory agent for a steroid-sparing effect or alone. In a case series of patients treated with Pepto-Bismol (eight tablets/day for eight weeks), dramatic clinical improvement was noted. Colectomy in a handful of patients resulted in diarrhea and one case of enteropathic colitis. Surgical bypass ileostomy resolved symptoms and histological findings.

Although these therapeutic approaches have demonstrated symptomatic improvement, there have been few patients with total histological reversal. Questions still remain regarding the duration of therapy and the utility of histological appearance as a treatment guide. Physicians should also consider the risk-benefit ratio when treating mildly symptomatic patients with corticosteroids.

Complications

Villous Atrophy

Villous atrophy of the small bowel has been documented in some cases of both collagenous and lymphocytic colitis. This may represent another disease entity rather than concomitant celiac disease. Patients have experimented with gluten-free diets without consistent improvement in collagenous and lymphocytic colitis. Attention to the role of the small bowel as a fluid source seems reasonable in unresponsive patients with lymphocytic or collagenous colitis. Conversely, collagenous or lymphocytic colitis should be considered in patients with refractory malabsorption and/or diarrhea and small-bowel villous atrophy.