Noninfectious Colitides: Collagenous Colitis, Lymphocytic Colitis, Diversion Colitis, and Chemically Induced Colitis

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ABSTRACT

Approximately 10% of patients with chronic diarrhea carry a diagnosis of microscopic colitis. The endoscopic appearance of both collagenous colitis and lymphocytic colitis may be normal; however, biopsies confirm the diagnosis. Available treatments include antidiarrheals, bismuth salicylate, and budesonide. Although most patients with fecal diversion may have endoscopic evidence of colitis, a much smaller percentage of patients are symptomatic. Some cases of diversion colitis respond to treatment with short-chain fatty acid enemas; however, return of the fecal stream is the most successful therapy. A variety of oral, intravenous, and per rectum chemicals may cause colitis; symptoms usually abate when chemical exposure is discontinued.

KEYWORDS: Collagenous colitis, lymphocytic colitis, microscopic colitis, diversion colitis

Objectives: On completion of this article, the reader should be able to summarize the diagnostic work-up and available treatments for microscopic colitis. The reader will also be familiarized with diversion colitis and chemically induced colitis.

A small percentage of patients with inflammatory bowel disease have no endoscopic evidence of inflammation, yet biopsies reveal abnormal histopathology. The term microscopic colitis is used to describe patients with histologic evidence of colitis with a normal colonoscopy. Microscopic colitis includes collagenous colitis and lymphocytic colitis, both of which arise with the symptom of watery diarrhea. These two colitides may represent two separate diseases or be variants of the same disease process; they are differentiated at present only by histology.

Other atypical forms of colitis may be caused by the absence of normal fecal matter or the addition of

colonic irritants. Diversion colitis and chemically induced colitis are discussed later in this article.

COLLAGENOUS COLITIS

Epidemiology

The incidence of collagenous colitis ranges from 1.0 to 4.9 per 100,000 people,^{1,2} and the prevalence in a Swedish study was observed to be 15.7 per 100,000.³ Approximately 10% of patients who are evaluated by colonoscopy for watery diarrhea have microscopic colitis.⁴ In a pathologic review of 2815 patients who had

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three to five biopsies of normal-appearing colon, the incidence of collagenous colitis was 0.4%, with a higher incidence of lymphocytic colitis of 0.9%. The same review noted a higher female-to-male ratio of 1.8 for collagenous colitis and 1.6 for lymphocytic colitis; the average male is diagnosed at least 5 years earlier than the mean female age of 55.⁵ Most epidemiologic studies⁶⁻⁸ have supported an even higher female prevalence; however, a review of cases reported in the literature⁹ noted no difference in gender distribution. Collagenous colitis has been diagnosed in pediatric patients.¹⁰ Although there is no known genetic abnormality linked with the condition, there are case reports of families with collagenous colitis with and without other forms of inflammatory bowel disease.^{11,12}

Clinical Presentation

Patients typically present with chronic watery, non-bloody diarrhea. A sudden onset of diarrhea has been noted in ~40% of patients, suggesting a possible infectious cause for the disease.¹³ Most patients experience 4 to 10 bowel movements daily, but some may pass up to 5 L of stool per day.¹⁴ Diarrhea can worsen after meals, and fasting can significantly reduce symptoms. Over 25% of patients experience nocturnal diarrhea. A retrospective chart review of 104 patients with microscopic colitis revealed that presenting symptoms included diarrhea (95%), weight loss (41%), abdominal pain (40%), fecal urgency (29%), and nocturnal stools (22%).⁷

Associated Conditions

Collagenous colitis may be immunologically mediated. Up to 40% of patients also have an autoimmune disease such as celiac sprue, thyroiditis, rheumatoid arthritis, or Sjögren's syndrome at the time of presentation.^{7,13,15} Celiac disease may be present in as much as 20% of patients.⁸ The use of nonsteroidal anti-inflammatory drugs (NSAIDs) is often reported in patients with collagenous colitis; however, an exact mechanism linking the medication to the inflammatory process has not been shown. In a review of 104 patients with collagenous (63%) and lymphocytic colitis by Chande et al, up to 35% of patients reported NSAID use, and 2% were using ticlopidine.⁷

Diagnostic Testing

Stool cultures should be performed, including testing for ova and parasites, *Clostridium difficile*, and *Giardia lamblia* antigen. Fecal leukocytes are nonspecific and may be seen in as many as 55% of patients.¹⁶ Stool analysis is otherwise compatible with a secretory diarrhea, although an osmotic component is associated with meals.¹⁷ A Swedish study revealed increased stool levels of eosino-

phil protein X, myeloperoxidase, and tryptase in collagenous colitis patients compared with patients with irritable bowel syndrome and normal control subjects.¹⁸

Lower endoscopy with biopsies is required to make a diagnosis of collagenous colitis. Although most patients have normal-appearing mucosa on colonoscopy, erythema, edema, or changes in mucosal vascularity may be seen in up to 30%.¹³ A small minority of patients have mucosal ulcerations, and over 75% of these patients have a history of NSAID use compared with 20% of patients without ulcerations.¹⁹ Several case reports document the presence of pseudomembranes in patients with collagenous colitis who did not have a concurrent *C. difficile* infection.^{20,21}

It is debated whether flexible sigmoidoscopy with biopsies is a sufficient examination or whether colonoscopy is required for all patients. Normal rectal and rectosigmoid biopsies may be seen in over 40% of patients.^{22,23} Thijs et al²⁴ biopsied each segment of the colon in 103 patients with a normal colonoscopy and nonbloody diarrhea. Biopsies confirmed microscopic colitis in 13 patients; in 3 patients (23%) the disease was limited to the right colon. Unless symptoms are suspicious for malignancy or Crohn's disease, flexible sigmoidoscopy with four biopsies every 10 cm may be the best initial test given the ease of preparation and lower cost. If left-sided biopsies are normal, complete colonoscopy should be pursued.²⁵

Patients may require repeated endoscopy with biopsies if symptoms persist without a diagnosis. In a review of 97 patients diagnosed with microscopic colitis, the diagnosis was missed in nearly a third on the initial histological evaluation.²⁶ Although this may in part be attributed to a lack of awareness, a recent study indicates that symptoms may often precede fully evolved histological features in 25% of collagenous colitis patients and 50% of lymphocytic colitis patients.²⁷ Confocal endomicroscopy and endoscopic ultrasonography have been reported to produce more productive biopsies in collagenous colitis; experience with both techniques is limited and not widely available.^{28,29}

Histopathology

The key histologic features required to make the diagnosis of collagenous colitis are thickening of the subepithelial collagen layer and an inflammatory infiltrate. Surface epithelial injury may be patchy or diffuse, with a lymphocytic infiltrate having variable amounts of eosinophils and neutrophils. Lymphocytes, plasma cells, and eosinophils create expansion of the lamina propria.³⁰ Immunostaining reveals that intraepithelial lymphocytes are CD8-positive cells.³¹

The subepithelial collagen band is composed of types I, III, IV, and VI collagen.³² This subepithelial collagen band must be at least 10 μ m thick to qualify for

the diagnosis, and cases with the most classical subjective appearance of collagenous colitis have a band of at least 30 μm . The characteristic collagen band may be difficult to measure on routine hematoxylin and eosin (H&E) staining; Masson trichrome staining reliably and easily emphasizes the band.³³ Used less frequently, autofluorescence may improve distinction of the collagen band in H&E-stained slides.^{34,35}

Cause and Pathogenesis

There are several theories regarding the etiology of collagenous colitis. Given its occurrence in older women and association with other diseases, it is speculated to be an autoimmune phenomenon. Also supporting this theory is clinical improvement with anti-inflammatories such as 5-aminosalicylic acid (5-ASA), steroids, and other immunomodulators. Although serum immunoglobulin M has been found to be elevated in patients, no predominant increase in other immune factors or auto-antibodies has been found.³⁶

A toxin present in the fecal stream may cause collagenous colitis. Supporting this hypothesis is documentation of complete histologic resolution of the disease with fecal diversion.³⁷ Clinical symptoms and histologic abnormalities return with restoration of the fecal stream. Use of nonsteroidal anti-inflammatories is frequently associated and may cause some cases of collagenous colitis, and case reports document an association with proton pump inhibitors and H₂ blockers.^{38,39} The abrupt onset of symptoms in some patients has suggested an infectious agent. *Yersinia* antibodies are found more frequently in colitis patients, yet this still cannot be linked to all patients.⁴⁰

Other research has focused on the mechanism of collagen deposition in the lamina propria. Mast cells are present in higher numbers in the upper part of the lamina propria compared with controls, and their distribution differs from that seen in Crohn's disease or ulcerative colitis.⁴¹ Histamine is significantly produced and metabolized in collagenous colitis patients, and this does not appear to be influenced by the allergenic potential of certain foods.⁴² Transforming growth factor (TGF)- β 1 is associated with collagen accumulation in tissues. Increased expression of this gene in eosinophils is seen in collagenous colitis compared with normal controls.⁴³ A fourfold increase in mucosal basic fibroblast growth factor (bFGF) secretion has been found in collagenous colitis patients; however, no difference in the intensity of bFGF staining in surface epithelium or lamina propria was noted between colitis patients and normal controls.⁴⁴ Compared with controls, strong immunostaining for vascular endothelial growth factor (VEGF) is seen in collagenous colitis. Staining for leukocyte-derived VEGF decreases and epithelial-derived VEGF persists after budesonide treatment.⁴⁵ In-

creased endoluminal nitric oxide is seen in collagenous colitis as well as other forms of inflammatory bowel disease, and its production may be independent of nitric oxide synthetase.⁴⁶

Treatment

The majority of therapies for collagenous colitis are based on case reports and small uncontrolled trials published in the literature (Table 1).^{13,47-49} In a 2005 Cochrane review, Chande et al⁵⁰ evaluated six randomized controlled trials of four medications (Table 2).^{51,52} They concluded that budesonide is the only medication for which strong evidence of benefit exists for clinical improvement in collagenous colitis. Given its safety, low cost, and favorable results in one trial, larger trials of bismuth subsalicylate are warranted.

Most studies focus on improvement in clinical symptoms; it is unclear what role medications have in treating recurrent disease or achieving and maintaining remission. Miehleke et al reported that over 60% patients experienced symptomatic relapse, usually within 3 months of cessation of budesonide treatment. Predictors of recurrent disease included younger age and active sigmoid colon inflammation after drug cessation. Sixty-five percent responded to retreatment with budesonide.⁵³

Prognosis

Collagenous colitis is a fairly benign disease, although occasionally disabling. Symptoms often resolve on their own or after a short course of medical therapy.⁵⁴ Although progression to other forms of inflammatory bowel disease and a synchronous colorectal cancer have been reported in the literature, these cases appear to be rare.⁵⁵⁻⁵⁷ At this time, no data exist to warrant increased screening for malignancy in collagenous colitis patients.

LYMPHOCYTIC COLITIS

Epidemiology

Although there is much less literature on lymphocytic colitis, it may be a more common cause of inflammatory colitis than collagenous colitis. In a Spanish population study, the annual incidence was 3.1 cases per 100,000, which was three times the incidence of collagenous colitis.²² Conversely, Swedish and Icelandic studies reported a mean annual incidence of 4.4 and 4.0 cases per 100,000, comparable to 4.9 and 5.2 per 100,000 cases of collagenous colitis per year.^{2,58} The mean age of diagnosis is between 55.4 to 68.7 years,⁸ and the female/male ratio varies widely from 1.25:1 to 5.75:1.⁵⁹ LaSala et al noted that the majority of patients experience the onset of symptoms in summer

Table 1 Various Treatments for Collagenous Colitis

Treatment	Dose	Comments
Discontinue possible offending medications	N/A	NSAIDs, H2 blockers, PPIs
Antidiarrheal medications—loperamide, diphenoxylate hydrochloride with atropine, bulk-forming agents, cholestyramine ⁴⁷	Various	May help control symptoms
5-ASA, ^{13,139} sulfasalazine ^{140,141}	2–6 g/day sulfasalazine or 2–4.8 g/day 5-ASA	
Antibiotics—metronidazole, erythromycin ^{13,142}	250 mg t.i.d. or q.i.d.	
Prednisolone ¹⁴³	Up to 50 mg	Systemic effects, no statistically significant improvement compared with placebo at 3 weeks
Budesonide	Usually 9 mg/day for 6–8 weeks	No significant adverse effects; only medication with strong evidence of successful treatment clinically and histologically compared with placebo; only medication with known QOL improvement
Bismuth subsalicylate ^{144–146}	Eight or nine 262-mg tablets in three divided doses/day for 8 weeks	Many uncontrolled studies reporting clinical improvement; only one small RCT revealing clinical and histological improvement; well tolerated
Azathioprine 6-Mercaptopurine ^{147,148}	Various	Limited data—failure of most other therapies
Methotrexate ¹⁴⁹		
Probiotic <i>E. coli</i> strain Nissle 1917 ¹⁵⁰	One to six capsules/day containing 2.5–25 × 10 ⁹ viable bacteria each × 4 weeks	Reduction in stool frequency in 64% of patients in noncontrolled study
<i>Boswellia serrata</i> ⁴⁹	Three 400-mg tablets daily for 6 weeks	One small RCT without significant improvement versus placebo; long-term efficacy and safety unknown
Fecal diversion ^{48,151}	N/A	Clinical symptoms and histological abnormalities can recur with restoration of fecal stream

5-ASA, 5-aminosalicylic acid; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; QOL, quality of life; RCT, randomized controlled trial; N/A, not applicable.

and fall, suggesting a possible infectious etiology to lymphocytic colitis.⁶⁰

Clinical Presentation

The clinical presentation of lymphocytic colitis is identical to that of collagenous colitis: chronic nonbloody, watery diarrhea. Diarrhea may be accompanied by bloating, rectal urgency, fecal incontinence, and weight loss.⁶¹ In a series of 199 patients, Olesen et al found that the most prevalent symptoms were diarrhea (96%), abdominal pain (47%), and weight loss (41%).⁶² Sixty-three percent of patients reported a single attack with an average duration of 6 (4 to 11) months; the remainder of patients had a more chronic or intermittent course. Over 10% of patients reported a family history of ulcerative colitis, Crohn's disease, collagenous colitis, or celiac disease in a first- or second-degree relative.⁶²

Associated Conditions

Concurrent autoimmune disease is less common in lymphocytic colitis than collagenous colitis (25.9% vs 53.3%), but the presence of celiac disease is fairly common in both (14.8% and 20%, respectively). Bronchial asthma, which is not associated with collagenous colitis, may be seen in over 25% of patients with lymphocytic colitis.⁸ Nonsteroidal anti-inflammatory use is also prevalent in patients with lymphocytic colitis, and several cases appear to be associated with flutamide treatment.⁵⁹

Diagnostic Testing

The work-up of lymphocytic colitis is identical to that of collagenous colitis. Stool cultures are usually negative and laboratory and radiologic studies normal. The endoscopic appearance of the colon is normal, and biopsies

Table 2 Randomized Control Trials Included in 2005 Cochrane Review

Medication	Dose	Clinical* Improvement	Histologic Improvement	Quality of Life
Bismuth subsalicylate ⁵¹	Nine 262-mg chewable tablets daily in three divided doses for 8 weeks	4/4 treated 0/5 placebo $p=0.003$	4/4 treated 0/5 placebo $p=0.003$	Not assessed
<i>Boswellia serrata</i> ⁴⁹	Three 400-mg tablets daily for 6 weeks	Active treatment compared: placebo 44%: 27% $p=0.32$	Currently being assessed	Not assessed
Prednisolone ¹⁵²	50 mg daily for 2 weeks, tapered to 37.5 mg daily in third week	5/8 treated 0/3 placebo $p=0.064$	Not assessed	Not assessed
Budesonide	3 mg t.i.d. for 6 weeks ¹⁵³ 9 mg/day for 4 weeks, 6 mg for 2 weeks and 3 mg for 2 weeks ¹⁵⁴ 9 mg/day for 8 weeks ¹⁵⁵	38/47 treated 8/47 placebo OR =12.32	54% versus 1% $p < 0.001$ ¹⁵³ 100% versus 30% $p=0.001$ ¹⁵⁴ 91% versus 33% $p < 0.001$ ¹⁵⁵	Significantly improved versus placebo ⁵²

*Usually defined as two or less bowel movements a day.

Pooled analysis in Chande N, McDonald JWD, MacDonald JK. Interventions for treating collagenous colitis. Cochrane Database Syst Rev 2005, Issue 4. Art. No: CD003575. DOI:10.1002/14651858.CD003575.pub3.

are required to make the diagnosis. Flexible sigmoidoscopy may be more successful in making the diagnosis of lymphocytic colitis: only 8% of lymphocytic colitis patients have negative rectal biopsies, compared with 43% of collagenous colitis patients.²² Because lamina propria inflammation is often present in the cecum due to fecal stasis, some authors argue against biopsying this area to prevent a false-positive diagnosis.⁶³

Histopathology

The histologic diagnosis of lymphocytic colitis is dependent on the presence of intraepithelial lymphocytes in the absence of thickening of the subepithelial collagen layer. A minimum of 20 intraepithelial lymphocytes per 100 epithelial cells must be present, compared with the normal ratio of 5 per 100. Surface epithelial damage and increased chronic inflammation in the lamina propria may be seen with a minimal amount of crypt distortion or active cryptitis.⁶⁴

Cause and Pathogenesis

Few theories exist regarding the possible etiology of lymphocytic colitis. Medication-induced lymphocytic colitis may be seen with NSAID use, ticlopidine, flutamide,⁵⁹ carbamazepine,⁶⁵ ranitidine,⁶⁶ and acarbose.⁶⁷ Symptoms often abate after drug cessation.

Human leukocyte antigen (HLA) typing suggests that lymphocytic colitis is a distinct form of inflammatory bowel disease compared with collagenous colitis, ulcerative colitis, and Crohn's disease. An increased frequency of HLA-A1 and a decreased frequency of HLA-A3 are found in lymphocytic colitis

patients compared with normal controls. Autoimmune-associated class I HLA antigens, B8, and DR3 antigens are not more commonly seen in lymphocytic colitis patients.⁶⁸

Given the disease's seasonal onset of symptoms, an infectious etiology has been postulated. In a preliminary study, Helal et al performed tissue cultures of biopsies performed in lymphocytic colitis patients and normal controls. Cultures grew out *Escherichia coli* in 70% of colitis patients compared with 20% of controls. Rod-shaped bacilli were seen on the majority of tissue slides in *E. coli*-positive colitis patients compared with none of the controls. Future serotyping and molecular studies will investigate what role *E. coli* plays in the pathogenesis of lymphocytic colitis.⁶⁹

Treatment

Lymphocytic colitis is presently treated similarly to collagenous colitis; however, there are fewer data available to support these interventions. Possible offending medications should be discontinued. Response to bile acid binders such as cholestyramine is seen in 46% to 75% of patients.^{70,71} Although well tolerated, more moderate success is seen with loperamide, diphenoxylate/atropine, and bismuth subsalicylate treatment.⁵⁵ Budesonide therapy has been reported to be successful in a patient who failed to respond to 5-ASA.⁷² Varghese et al reported on a patient who failed maximal medical therapy and had persistent histologic features of lymphocytic colitis despite 6 months of complete fecal diversion. This unusual case was treated successfully with total proctocolectomy and ileoanal J pouch reconstruction.⁷³

Prognosis

Lymphocytic colitis appears in most cases to be a fairly benign disease. Over 80% of patients experience resolution of symptoms and histologic changes within 38 months.⁷⁴ Spontaneous remission often occurs, and most patients do not require medications for an extended period of time.⁷⁵ Therefore, symptomatic treatment may be the best initial therapy prior to initiating medications with substantial side effects.

DIVERSION COLITIS

Epidemiology and Clinical Presentation

The term diversion colitis was first used by Glotzer et al⁷⁶ in 1981, although the presence of inflammatory changes in the diverted colon was noted by Morson and Dawson⁷⁷ nearly 10 years earlier. Endoscopic evidence of disuse colitis can be found in 70% to 91% of patients with fecal diversion.^{78–80} Findings may be mild to severe and include mucous plugs, friability, petechia, erythema, ulcers, exudate, and nodules or polyps.⁸¹ A much smaller percentage of patients experience symptoms such as rectal pain or discomfort, bleeding, and discharge. Not surprisingly, up to 87% of patients with ulcerative colitis have symptoms, compared with 30% of Crohn's patients and 28% of patients without inflammatory bowel disease.⁸²

Lymphoid follicular hyperplasia can be found on double-contrast barium enema in 30% of diverted patients. This often resolves after reanastomosis.⁸³ Colonic diversion may also cause anatomic changes in the diverted segment. Roe et al evaluated 12 patients who underwent a Hartmann procedure for cancer or complicated diverticulitis at 1 and 3 months after diversion. Although no changes in rectal sensation, rectal compliance, or anal manometry were found, proctorectogram revealed a 35% decrease in rectal volume.⁸⁴

Histopathology

A diffuse spectrum of pathologic features may be seen in diversion colitis. Histology appears not to depend on the length of diversion but instead is related to the condition of the colonic mucosa prior to diversion.⁸⁵ Endoscopic biopsies of previous normal colon may reveal diffuse mild acute and chronic inflammation with or without mild crypt architectural abnormalities, crypt abscesses, atrophy, or follicular lymphoid hyperplasia.^{86,87} Resected specimens reveal diffuse nodularity secondary to lymphoid hyperplasia; inflammation is limited to the mucosa with erosions, crypt abscesses, mucin granulomas, and aphthoid ulcers.⁸⁸ In patients who have undergone subtotal colectomy for ulcerative colitis, the rectal stump may also develop transmural inflammation, granulomas, fissures, and changes similar to those in ischemic or to

pseudomembranous colitis.⁸⁹ Given these findings, a change in diagnosis from ulcerative colitis to Crohn's disease should not be made on the basis of biopsies of diverted colonic segments.

Lymphoid follicular hyperplasia is described as a distinctive pathologic finding in patients with diversion colitis despite the prediverted condition of the colon.⁹⁰ Enlarged germinal centers of B-cell and T-cell lymphocytes are found consistently in pediatric patients but not in all adults with diversion colitis.⁸²

Cause and Pathogenesis

Diversion colitis is thought to be due to absence of a nutritional factor provided by the fecal stream or to an alteration in bacterial flora. In 1982, Roediger⁹¹ observed that butyrate is the preferred substrate of colonocytes. Butyrate and other short-chain fatty acids (SCFAs) are delivered to the distal colon after bacterial fermentation of starch and proteins. By disrupting the fecal stream, distal colonocytes are deprived of their primary substrate, resulting in inflammation or possibly a change in bacterial populations. Supporting this theory are several reports of successful treatment of diversion colitis using SFCA enemas.

No single predominant bacterial organism has been identified as the inciting agent of diversion proctitis. However, when rectal swab cultures are compared with controls, there appears to be a higher percentage of nitrate-reducing bacteria in diverted patients. Whether these bacteria are truly pathogenic to the colon remains unclear.⁹²

Treatment

Restoring the fecal stream cures diversion proctitis. When this is not possible, treatment with SCFAs may improve symptoms. Harig et al were the first to describe successful treatment of diversion colitis with SCFA irrigation (acetate 60 mM, propionate 30 mM, *n*-butyrate 40 mM) twice a day.⁹³ Others have not been able to duplicate this success.⁹⁴ Endoscopic and histologic resolution has been reported after treatment with 5-ASA (Rowasa) enemas.⁹⁵ The use of 5-ASA enemas and higher concentrations (100 mM) of butyrate may be particularly helpful in diverted ulcerative colitis patients.⁸²

CHEMICALLY INDUCED COLITIS

NSAID

Although better known for their effects on the upper gastrointestinal tract, NSAIDs may cause a diffuse spectrum of disease in the colon and rectum. NSAIDs can activate disease in inflammatory bowel disease,^{96–100}

can be a primary cause of collagenous and lymphocytic colitis, and can precipitate complications of diverticular disease.^{101–105} A nonspecific colitis associated with ulcerations may also be seen, and this may be ischemia mediated.^{106,107} Patients may present with bloody diarrhea, weight loss, iron deficiency anemia, or abdominal pain. Exposure to NSAIDs may be anywhere from 2 days to 12 years, with a median of 3 months, prior to the development of symptoms.^{108,109} Symptoms often resolve soon after the drug is discontinued.¹¹⁰

Strictures of the colon may also form with NSAID use. These tend to be short, diaphragm-like strictures in the right colon. They are often multiple and associated with sustained-release NSAIDs. Although they may cause obstruction and require surgical resection, successful treatment with balloon dilatation has been reported.¹¹¹

Disinfectants

Acute toxic injury to the distal colon and rectum may occur after contact with a variety of disinfectants and other rectally administered agents. Exposure may occur during routine radiologic or colonoscopic procedures or self-administered accidentally or intentionally by the patient. Chemically induced colitis may be caused by endoscopy cleaning solutions,^{112–114} radiologic contrast material,¹¹⁵ hydrogen peroxide,^{113,116,117} soaps,^{118–124} formalin,¹²⁵ hydrofluoric acid,¹²⁶ alcohol,^{127–130} ammonia, lye,¹³¹ hot water,¹³² and herbal substances.¹³³ Patients present with abdominal pain, hematochezia, and fever. A history of a recent procedure or self-administered enema is critical. Endoscopic findings are variable and nonspecific and can be severe enough to mimic ischemic or pseudomembranous colitis. Stool cultures should be performed. Patients often respond to supportive care and antibiotics. In 10% to 15% of patients, however, the injury may progress to a colonic stricture or perforation and require surgical intervention. Two deaths attributable to chemical colitis have been reported in the literature.¹²⁹

Antineoplastic Agents, Cyclosporine

Colitis resulting from antineoplastic agents is being reported more frequently in the literature. Patients may present with abdominal pain, severe watery diarrhea, or hematochezia. 5-Fluorouracil may cause inflammation and ulceration of the upper gastrointestinal tract as well as the colon.¹³⁴ Treatment includes bowel rest, intravenous hydration, and broad-spectrum antibiotics.^{135,136}

Two case reports in the literature describe colitis in juvenile rheumatoid arthritis patients treated with NSAIDs and cyclosporine. Although symptoms resolved with cessation of both drugs, recurrence of

disease was seen when cyclosporine therapy alone was reinitiated.^{137,138}

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