OTHER DISORDERS

More common cardiopulmonary manifestations include endocarditis, myocarditis, pleuropericarditis, and interstitial lung disease. A secondary or reactive amyloidosis can occur in patients with long-standing IBD, especially in patients with CD. Amyloid material is deposited systemically and can cause diarrhea, constipation, and renal failure. The renal disease can be successfully treated with colchicine. Pancreatitis is a rare extraintestinal manifestation of IBD and results from duodenal fistulas; ampullary CD; gallstones; PSC; drugs such as 6-mercaptopurine, azathioprine, or, very rarely, 5-ASA agents; autoimmune pancreatitis; and primary CD of the pancreas.

TREATMENT INFLAMMATORY BOWEL DISEASE TREATMENT

5-ASA AGENTS

The mainstay of therapy for mild to moderate UC is sulfasalazine and the other 5-ASA agents. These agents are effective at inducing and maintaining remission in UC. They may have a limited role in inducing remission in CD but no clear role in maintenance of CD. Newer sulfa-free aminosalicylate preparations deliver increased amounts of the pharmacologically active ingredient of sulfasalazine (5-ASA, mesalamine) to the site of active bowel disease while limiting systemic toxicity. Peroxisome proliferator activated receptor γ (PPAR-γ) may mediate 5-ASA therapeutic action by decreasing nuclear localization of NF-κB. Sulfa-free aminosalicylate formulations include alternative azo-bonded carriers, 5-ASA dimers, and delayed-release and controlled-release preparations. Each has the same efficacy as sulfasalazine when equimolar concentrations are used.

Sulfasalazine was originally developed to deliver both antibacterial (sulfapyridine) and anti-inflammatory (5-ASA) therapy into the connective tissues of joints and the colonic mucosa. The molecular structure provides a convenient delivery system to the colon by allowing the intact molecule to pass through the small intestine after only partial absorption and to be broken down in the colon by bacterial azo reductases that cleave the azo bond linking the sulfa and 5-ASA moieties. Sulfasalazine is effective treatment for mild to moderate UC and is occasionally used in Crohn's colitis, but its high rate of side effects limits its use. Although sulfasalazine is more effective at higher doses, at 6 or 8 g/d up to 30% of patients experience allergic reactions or intolerable side effects such as headache, anorexia, nausea, and vomiting that are attributable to the sulfapyridine moiety. Hypersensitivity reactions, independent of sulfapyridine levels, include rash, fever, hepatitis, agranulocytosis, hypersensitivity pneumonitis, pancreatitis, worsening of colitis, and reversible sperm abnormalities. Sulfasalazine can also impair folate absorption, and patients should be given folic acid supplements.

Balsalazide contains an azo bond binding mesalamine to the carrier molecule 4-aminobenzoyl-β-alanine; it is effective in the colon.

Olsalazine is composed of two 5-ASA radicals linked by an azo bond, which is split in the colon by bacterial reduction, and two 5-ASA molecules are released. Olsalazine is similar in effectiveness to sulfasalazine in treating UC, but up to 17% of patients experience nonbloody diarrhea caused by increased secretion of fluid in the small bowel.

Delzicol and Asacol HD (high dose) are enteric-coated forms of mesalamine with the 5-ASA being released at pH >7. They disintegrate with complete breakup of the tablet occurring in many different parts of the gut ranging from the small intestine to the splenic flexure; they have increased gastric residence when taken with a meal. Asacol has recently been discontinued and replaced with Delzicol, which lacks dibutyl phthalate (DBP), an inactive ingredient in Asacol's enteric coating. DBP has been associated with adverse effects on the male reproductive system in animals at very high doses. Asacol HD with the same chemical in its coating is still on the market, but the human doses of DBP are within acceptable limits of toxicity.

Lialda is a once-a-day formulation of mesalamine (Multi-Matrix System [MMX]) designed to release mesalamine in the colon. The MMX technology incorporates mesalamine into a lipophilic matrix within a hydrophilic matrix encapsulated in a polymer resistant to degradation at a low pH (<7) to delay release throughout the colon. The safety profile appears to be comparable to other 5-ASA formulations.

Apriso is a formulation containing encapsulated mesalamine granules that delivers mesalamine to the terminal ileum and colon via a proprietary extended-release mechanism (Intellicor). The outer coating (Eudragit L) dissolves at a pH >6. In addition, there is a polymer matrix core that aids in sustained release throughout the colon. Because Lialda and Apriso are given once daily, an anticipated benefit is improved compliance compared with two to four daily doses required for other mesalamine preparations.

Pentasa is another mesalamine formulation that uses an ethylcellulose coating to allow water absorption into small beads containing the mesalamine. Water dissolves the 5-ASA, which then diffuses out of the bead into the lumen. Disintegration of the capsule occurs in the stomach. The microspheres then disperse throughout the entire GI tract from the small intestine through the distal colon in both fasted and fed conditions.

Salofalk® Granu-Stix, an unencapsulated version of mesalamine, has been in use in Europe for induction and maintenance of remission for several years.

Appropriate doses of the 5-ASA compounds are shown in Table 351-7. Some 50–75% of patients with mild to moderate UC improve when treated with 5-ASA doses equivalent to 2 g/d of

TABLE 351-7 ORAL 5-ASA PREPARATIONS

Preparation	Formulation	Delivery	Dosing Per Day
Azo-Bond			
Sulfasalazine (500 mg) (Azulfidine)	Sulfapyridine-5-ASA	Colon	3–6 g (acute) 2–4 g (maintenance)
Olsalazine (250 mg) (Dipentum)	5-ASA–5-ASA	Colon	1–3 g
Balsalazide (750 mg) (Colazal)	Aminobenzoyl-alanine–5-ASA	Colon	6.75–9 g
Delayed-Release			
Mesalamine (400, 800 mg) (Delzicol, Asacol HD)	Eudragit S (pH 7)	Distal ileum-colon	2.4–4.8 g (acute) 1.6–4.8 g (maintenance)
Mesalamine (1.2 g) (Lialda)	MMX mesalamine (SPD476)	Ileum-colon	2.4–4.8 g
Controlled-Release			
Mesalamine (250, 500, 1000 mg) (Pentasa)	Ethylcellulose microgranules	Stomach-colon	2–4 g (acute) 1.5–4 g (maintenance)
Delayed- and Extended-Release			
Mesalamine (0.375 g) (Apriso)	Intellicor extended-release mechanism	Ileum-colon	1.5 g (maintenance)