Drug-induced injury commonly affects the gastrointestinal and hepatobiliary systems because of the mechanisms of absorption and metabolism. In pill esophagitis, injury is frequently related to direct contact with the esophageal mucosa, resulting in small superficial ulcers in the mid esophagus. Nonsteroidal anti-inflammatory drugs can lead to gastrointestinal tract ulcers and small bowel mucosal diaphragms (thin weblike strictures). Injury to the pancreatic and hepatobiliary systems can manifest as pancreatitis, acute or chronic hepatitis, cholestasis, or steatosis and steatohepatitis (which may progress to cirrhosis). Various drugs may also insult the hepatic vasculature, resulting in Budd-Chiari and sinusoidal obstructive syndromes. Focal lesions such as hepatic adenomas may develop after use of oral contraceptives or anabolic steroids. Ultrasonography, computed tomography, and magnetic resonance imaging can aid in diagnosis of drug-induced injuries and often are necessary to exclude other causes.

Introduction

The growth of various medical therapies has led to an increased frequency of medication side effects (1,2). Traditionally, most drug-induced side effects were diagnosed clinically according to the patient’s presenting symptoms and signs and history of medication use. However, as imaging is used more and more commonly, many of these complications are initially diagnosed at imaging instead of at clinical presentation. Therefore, it is important for radiologists to recognize the imaging appearance of common drug-induced complications and to include drug-induced injury in the differential diagnosis.
Because of the route of administration of most medications (ie, oral) and the mechanisms of absorption and metabolism, the gastrointestinal, hepatobiliary, and pancreatic systems are highly susceptible to drug-induced injury.

- Esophageal injury is usually caustic and is due to a chemical reaction of the drug when in direct contact with the esophageal mucosa. Esophageal ulcers induced by medications are frequently small and discrete and often correspond to the direct site of contact with the pill.
- NSAIDs are one of those most frequently prescribed classes of medications worldwide and can result in injury to the gastrointestinal tract due to their inhibition of prostaglandin, which impairs gastrointestinal mucosal defense mechanisms. This injury commonly manifests as ulcers in the stomach and proximal duodenum and can cause mucosal diaphragms in the small bowel, especially the ileum.
- ACE inhibitor–induced bowel angioedema and antibiotic-associated pseudomembranous colitis from Clostridium difficile infection are two specific entities with well-known causes and imaging findings. When there is a known history of medication use, the diagnosis can be made with high accuracy.
- Drug-induced injury to the liver can be classified broadly as hepatocellular, cholestatic, or mixed injury. Steatosis, cholestasis, vascular injury, and development of hepatic neoplasms are among the most common drug-induced injury patterns.

Because of the route of administration of most medications (ie, oral) and the mechanisms of absorption and metabolism, the gastrointestinal, hepatobiliary, and pancreatic systems are highly susceptible to drug-induced injury. This review highlights common medication-induced complications seen at abdominal imaging. Their mechanisms of injury are described, and entities that may have a similar imaging appearance are discussed.

## Esophagus

Drug-induced injury in the esophagus most commonly manifests as esophagitis. Patients typically present with odynophagia, dysphagia, and retrosternal chest pain (1–3). Prolonged transit of the drug through the esophagus and increased contact with the mucosa allow the pill to begin to dissolve and undergo chemical change while still in the lumen.

Normally, there is mild extrinsic compression on the esophagus at the level of the aortic arch, left main-stem bronchus, and left atrium (2,4,5). Pill esophagitis is commonly midesophageal because of enlargement of the aorta or left atrium, which can increase esophageal compression and narrowing in this region and delay pill passage. Intrinsic esophageal pathologic conditions, such as strictures, can also result in delayed passage of medications. Other factors that can affect esophageal transit include a suboptimal volume of liquid intake with medications; recumbent positioning soon after pill ingestion; and pill size, shape, and type of coating (5,6).

## Ulcer or Esophagitis

**Mechanism.**—Esophageal injury is usually caustic and is due to a chemical reaction of the drug when in direct contact with the esophageal mucosa. For example, antibiotics such as doxycycline and tetracycline are acidic and can result in a chemical mucosal burn (3). Other drugs, such as ferrous sulfate and potassium chloride, cause injury from hyperosmolarity and changes in local blood flow (2,3).

Gastroesophageal reflux also affects the development of pill esophagitis. In addition to causing altered esophageal motility, which can result in delayed passage of pills through the esophagus, reflux of acidic gastric juices can lower the pH, altering the compound’s chemical properties. For example, the bisphosphonate alendronate is a common source of pill esophagitis. Although it is a monosodium salt in alkaline environments, in the acidic environment (pH <2) of reflux, it becomes a free acid, which is more damaging to the esophageal mucosa (4,6).

**Imaging Appearance.**—At imaging, esophageal ulcers induced by medications are frequently small and discrete and often correspond to the direct site of contact with the pill (Fig 1a). Histopathologic analysis shows inflammatory changes and granulation tissue, sometimes with foreign material and/or dyskeratotic cells indicative of apoptosis of squamous epithelial cells (6).

On double-contrast barium esophagrams, the ulcers are often shallow, with sharply delineated margins (Fig 1b) (1,3). The surrounding mucosa is commonly normal. En face, the ulcers appear as central punctate collections of barium surrounded by a radiolucent halo that corresponds to a mound of edema (3,7). They may be single or multiple. When viewed in profile, they may appear as elongated, flat, plaquelike filling defects (Fig 1c). Erosions, which by definition are limited to the mucosa and do not penetrate through the muscularis mucosae, can also be seen as linear or serpiginous collections of barium surrounded by a radiolucent halo of edema (Fig 1d) (1,7). However, pill esophagitis may not manifest with any imaging findings at computed tomography (CT).

**Differential Diagnosis.**—The differential diagnosis for small superficial erosions seen on a barium esophagram includes herpes esophagitis and Crohn esophagitis (3,7,8). Herpes esophagitis is predominately caused by herpes simplex virus type 1 and most commonly occurs in immunocom-
Figure 1. Pill esophagitis. (a) Image from esophagogastroduodenoscopy (EGD) in a 74-year-old woman taking oral iron supplements who presented with odynophagia shows pill fragments stuck along the mucosa and linear and superficial ulcers (arrows). Pathologic analysis revealed iron-positive material. (b) Double-contrast esophagram in a 26-year-old woman taking tetracycline who presented with dysphagia shows a radiolucent round filling defect with a thin rim of barium (arrow). The finding represents a superficial ulcer with surrounding edema. (c) Double-contrast esophagram (profile view) in a 59-year-old man taking clindamycin who presented with dysphagia shows an elongated, flat, plaquelike filling defect (arrow) consistent with an ulcer. (d) Barium esophagram in a 72-year-old woman taking alendronate who presented with dysphagia shows a cluster of linear erosions (arrows) in the mid esophagus.

promised patients, such as patients with human immunodeficiency virus (HIV), organ transplant recipients, and patients undergoing chemotherapy, but it can also occur in immunocompetent patients (8). The imaging appearance is similar to that of pill esophagitis: small punched-out ulcers with intervening normal tissue (7,8).

Crohn esophagitis can also manifest at imaging as discrete superficial ulcers with punctate collections of barium surrounded by a halo of edema, a finding known as aphthous ulcers (3,7). These are more frequently seen in the colon of patients with Crohn disease, but any portion of the gastrointestinal tract is a potential site of involvement. The esophagus is rarely the sole site of Crohn disease. Thus, a diagnosis of Crohn esophagitis should be considered in a patient with other gastrointestinal tract symptoms or a known diagnosis of Crohn disease.

Crohn esophageal erosions can sometimes have a less discrete and less benign appearance (7). An area of confluent erosions may mimic findings of malignancy, particularly superficial spreading esophageal carcinoma, of which there are several subtypes. The plaquelike and flat subtypes in particular can be difficult to differentiate from...
a cluster of benign ulcers (superficial erosions) (3,7,9). Therefore, endoscopy is the criterion standard for tissue diagnosis when an esophageal erosion or ulcer is identified at imaging.

Stomach

Ulcer

Mechanism.—Drug-induced gastropathy is most commonly caused by nonsteroidal anti-inflammatory medications (NSAIDs), as these are one of the most frequently prescribed classes of medications worldwide (10,11). The mechanism of injury is related to reduced prostaglandin synthesis. Prostaglandins play an important role in gastric epithelial defense by stimulating mucus and bicarbonate secretion and suppressing gastric acid secretion, thus helping to maintain epithelial cell reconstitution and mucosal blood flow (11–13). Most traditional NSAIDs inhibit the cyclooxygenase (COX) enzyme involved in prostaglandin synthesis. COX-1 is a constitutive enzyme important for basal mucosal blood flow and pH balance, and COX-2 is an inducible enzyme important in maintaining perfusion when mucosal integrity is challenged (12–14). Thus, prostaglandin inhibition weakens the mucosal defense mechanisms and leads to increased acid and pepsin, leaving the mucosa susceptible to injury (13–16). Selective COX-2 inhibitors have been shown to decrease gastric ulceration compared with traditional NSAIDs, although their use is limited by potential cardiovascular side effects (17,18).

Imaging Findings.—Pill-induced injury in the stomach generally occurs in the body and antrum and along the greater curvature and is mostly a function of gravity in these areas, given their dependent position. Similar to drug-induced injury in the esophagus, prolonged contact of the drug with the gastric mucosa can result in ulceration. On double-contrast barium studies, the ulcers have a discrete “punched-out” appearance because of the sharply defined smooth border typical of benign ulcers (7,19,20). They appear as central punctate collections of barium surrounded by radiolucent halos that correspond to mounds of edema (Fig 2a) (19–21). The ulcers may vary in size and can be single or multiple. Injury can also appear as linear and serpiginous barium collections (often thought to represent incomplete erosions) surrounded by halos of edema (Fig 2b).

Occasionally, gastric ulcers can be deep, penetrating through the muscularis mucosae and involving the submucosa. Although superficial erosions and shallow ulcers are not detectable at CT, deeper ulcers appear as mucosal defects and luminal outpouchings (Fig 3). The ulcer margin is typically well circumscribed, with a smooth flat margin and normal wall thickness (19).

Differential Diagnosis.—The likelihood of drug-induced gastric injury depends largely on the clinical scenario. The differential diagnosis includes malignancy, infection, and inflammatory conditions. “Malignant ulcers” manifest as ulcerated masses. They are more likely to be associated with focal wall thickening (>5 mm), perigastric tissue abnormalities, and lymphadenopathy (21,22).

Chemotherapy may cause gastric mucosal ulceration, hemorrhage, and perforation. This is particularly the case with cytotoxic agents that target rapidly dividing cells, such as those in the gas-
In some cases of primary gastric or mesenteric metastases, the tumor provides structural stability to the gastrointestinal tract. When targeted with chemotherapy, tumor necrosis can cause a breakdown in the mucosal integrity of the adjacent gastrointestinal tract (Fig 4) (23,24). Other causes of gastric ulceration include alcohol, severe stress (eg, burns), and Crohn disease (19).

**Small Bowel**

**Mucosal Diaphragms**

**Mechanism.**—As with the stomach, the proximal duodenum can be exposed to the corrosive effects of pepsin and hydrochloric acid when there is a breakdown in mucosal integrity, leading to ulceration (25). NSAIDs are thus a common offender in drug-induced duodenal ulceration.
wall thickening, and inflammation resulting in duodenitis (Fig 5), which can progress to frank perforation. However, the remainder of the small bowel is not exposed to gastric acid, and thus NSAID-induced gastrointestinal injury is likely multifactorial. NSAIDs are weakly acidic lipid-soluble compounds that disrupt the phospholipid membranes of enterocytes and cause uncoupling of mitochondrial phosphorylation, which leads to breakdown of the mucosal barrier (26–28). This exposes the epithelium to bile acids, pancreatic secretions, and intestinal bacteria, resulting in inflammation. Areas of inflammation can then hemorrhage, form granulation tissue, and eventually result in weblike mucosal strictures. NSAID-induced enteropathy results in thin (usually less than 3 mm) circumferential rings of mucosa that cause focal strictures referred to as mucosal diaphragms (27–29).

**Imaging Findings.**—Mucosal diaphragms can be occult at imaging because, unlike most strictures, the morphology of the outer bowel wall is typically not affected. There is a focal intraluminal web or stricture at the site of the diaphragm that can lead to marked luminal narrowing. The bowel in the immediate proximal and distal segments may be normal in caliber (Fig 6) (27,29), or there may be upstream dilatation in the setting of obstruction. Thus, in a patient with long-term NSAID use and unexplained small bowel obstruction, mucosal diaphragms should be considered in the differential diagnosis. Capsule endoscopy in this setting is controversial (27,30) because capsule retention may necessitate surgical removal. There is a relatively high risk for capsule retention, but complete obstruction is rare (30–32). In high-risk patients (ie, long-term NSAID users, patients with Crohn disease or surgical adhesive disease, and those who have undergone radiation therapy), a patency capsule, which is designed to dissolve after about 30 hours, is sometimes used to determine whether a videocapsule can safely be used (30).

**Differential Diagnosis.**—Although mucosal diaphragms were once regarded as pathognomonic, a study presented at the 2006 International Conference on Capsule Endoscopy showed a 20% rate of incorrect diagnosis by four experienced clinicians when reviewing cases of NSAID-induced enteropathy and Crohn disease (27,29,32). The differential diagnosis for NSAID-induced enteropathy is mainly Crohn disease. Crohn disease usually produces long, thick, inflammatory strictures, while NSAID-induced injury causes thin fibrotic diaphragms and sharply demarcated ulcers (29,32–34). Other entities that have been shown to induce mucosal diaphragms include celiac disease and radiation injury (29).

Although it is rare, cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) can also be considered in the differential diagnosis. In this disease, multiple small fibrous strictures and shallow ulcers form in the small bowel and often result in chronic or relapsing ileus or subileus (35). The gross findings of diaphragm disease are similar to those of CMUSE. The cause is unclear but is thought to be related to overstimulated production of fibrous tissue and is probably immune-mediated, given the response to treatment with glucocorticosteroids (35).
Angioedema

Mechanism.—Angiotensin-converting enzyme (ACE) inhibitors are used for treatment of hypertension (36,37). These medications inhibit the breakdown of bradykinin. Bradykinin activates the nitric oxide system, leading to increased vascular permeability and capillary leakage. Edema of the face, oropharynx, lips, and tongue is a known side effect; however, visceral edema can also occur, either in addition to these sites or in isolation (36–38). ACE inhibitor–induced bowel angioedema most frequently affects middle-aged women and commonly manifests as abrupt-onset abdominal pain and nausea, with vomiting and sometimes diarrhea (37–39). Symptoms usually occur within the first 7 days of initiating or altering ACE-inhibitor therapy, but onset has been reported as many as 10 years later (39).

Imaging Findings.—In the small bowel, the increased vascular permeability affects the vasa vasorum, causing bowel wall edema, bowel wall thickening, and straightening of the involved segment. At CT, there is decreased attenuation in the submucosal layer (36). This accentuates the higher attenuation of the mucosa and serosa, leading to mural stratification, which is even more pronounced at contrast-enhanced CT (Fig 7). At magnetic resonance (MR) imaging, T2-weighted images show increased signal intensity from edema in the submucosal layer of the involved bowel segment. The jejunum is the most frequent site of involvement (37). Ascites, mesenteric edema, and fluid retention in the small bowel lumen are frequent findings in patients who present with acute symptoms (36–38).

Differential Diagnosis.—Segmental small bowel mural stratification can be seen with small-vessel vasculitis, small-vessel ischemia, chemotherapy-induced enteritis, and radiation therapy. ACE inhibitor–induced angioedema should be considered if these conditions are excluded and there is an appropriate clinical history. ACE inhibitor–induced angioedema rarely manifests as bowel obstruction, usually has only mild adjacent inflammatory fat stranding, and follows a nonvascular distribution (36). Furthermore, ACE inhibitor–induced angioedema is reversible with cessation of the medication.

Figure 6. NSAID-related mucosal diaphragm disease. (a, b) Coronal (a) and axial (b) contrast-enhanced CT enterographic images in a 60-year-old woman who presented with bloating show short segments of circumferential wall thickening in the small bowel (arrow), with luminal narrowing and associated mucosal hyperenhancement. (c) Image from capsule endoscopy in the same patient shows a small bowel stricture with mucosal erosion. (d) Gross surgical specimen from small bowel resection in a patient with a history of small bowel obstruction from NSAID-related diaphragm disease. Surgical findings included palpable areas of stricturing 60–100 cm proximal to the ileocecal valve. Pathologic analysis showed more than 10 diaphragms in various phases of evolution in the wall of the small bowel.
Figure 7. ACE inhibitor–induced angioedema in a 50-year-old woman who developed crampy abdominal pain and vomiting 2 days after starting ACE-inhibitor therapy for hypertension. Axial contrast-enhanced CT image shows mural stratification in the duodenum and jejunum, with low-attenuating submucosal edema (black arrow) adjacent to hyperemic enhancing mucosal (white arrowhead) and serosal (white arrow) layers. A small amount of ascites (black arrowhead) is seen.

Pneumatosis Intestinalis

Mechanism.—Pneumatosis intestinalis is a condition in which gas is present in the wall of the small bowel or colon. The small bowel is most commonly involved (40). Multiple conditions that range from benign to life-threatening have been associated with pneumatosis.

One proposed mechanism of drug-induced pneumatosis is loss of mucosal integrity, which allows intraluminal gas to escape into the bowel wall. Several medications are well known to be associated with benign pneumatosis, including corticosteroids and chemotherapeutic agents (Table 1) (40–43). In the case of corticosteroids, it is thought that intramural lymphoid tissue is depleted, causing disruption in the mucosa and subsequent dissection of gas into the submucosa (41). Breakdown of the mucosal barrier may also allow gas-forming bacteria to enter the bowel wall (40–42). Intestinal ischemia can be a life-threatening cause of pneumatosis. Mechanisms of medication-induced intestinal ischemia include shunting of blood from mesenteric vessels, vasospasm, and thrombogenesis (42), which can result in pneumatosis intestinalis.

Imaging Findings.—Pneumatosis intestinalis and pneumatosis coli appear as gas within the bowel wall and can be separated from intraluminal gas by the mucosal and muscularis layers (41). The gas parallels the mucosa in the submucosal or subserosal (less commonly in the muscularis propria) layer and may be linear or cystic (Fig 8) (41,43,44). The distribution and extent are variable. In life-threatening causes, there may be additional imaging findings, such as bowel wall thickening and perienteric soft-tissue stranding in the setting of bowel ischemia. However, radiologic features are not reliable indicators of whether the pneumatosis is due to a life-threatening or a benign cause (41–44). Other secondary findings that may be seen in both life-threatening and benign causes include free fluid, free peritoneal air, and portal or mesenteric venous gas. Although these findings are nonspecific, their presence increases the likelihood that the pneumatosis can be attributed to a life-threatening condition (40,43).

Differential Diagnosis.—Pneumatosis in the small bowel or colon should be treated as an emergent finding until life-threatening causes such as bowel ischemia and impending perforation are excluded (42). Other conditions that can lead to bowel necrosis, such as arterial or venous thrombosis, obstruction, volvulus, and strangulation, should be considered (41,43). Infectious causes, such as neutropenic colitis, toxic megacolon, and generalized sepsis, may also lead to bowel compromise and subsequent intramural gas (41).

Table 1: Common Drugs Associated with Pneumatosis Intestinalis

<table>
<thead>
<tr>
<th>Drug Class and Common Agents</th>
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<tr>
<td>Corticosteroids</td>
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<tr>
<td>Chemotherapeutics</td>
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<tr>
<td>Cytotoxic agents: methotrexate, etoposide, daunorubicin, cytarabine, fluorouracil, paclitaxel</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors: imitinib</td>
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<tr>
<td>Immunosuppressants</td>
</tr>
<tr>
<td>α-glucosidase inhibitors: voglibose, acarbose, miglitol</td>
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<tr>
<td>Other: lactulose, sorbitol</td>
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</table>
In addition to medication, other nonemergent causes of pneumatosis intestinalis include pulmonary causes such as asthma, chronic obstructive pulmonary disease, mechanical ventilation with positive end-expiratory pressure, and cystic fibrosis (41,43). Inflammatory bowel disease and iatrogenic causes (eg, colonoscopy) are other known sources (44).

Finally, pneumatosis can be idiopathic. Cystic collections of gas in the bowel wall, known as pneumatosis cystoides intestinalis or coli, are a subgroup that appears as air-filled cysts in the submucosa or subserosa, and they are almost always benign (41,43). However, it is important to remember that life-threatening pneumatosis can have a cystic morphology.

### Colon

**Mechanism.**—Drug-induced injury to the colon most frequently presents as colitis. Although NSAID-induced injury is most common in the stomach and small bowel, enteric-coated preparations are thought to be responsible for shifting some of the injury farther downstream into the colon (Fig 9) (45,46).

Pseudomembranous colitis is a severe manifestation of superimposed infection, named for the characteristic pseudomembranes on the mucosa that are seen at endoscopy. It is frequently a complication of antibiotic therapy. The common offenders are broad-spectrum antibiotics such as cephalosporins, third-generation (extended-coverage) penicillins, and clindamycin; however, all antibiotics, including those used for treatment of this condition (metronidazole and vancomycin), have been implicated (42–44). These antibiotics alter the normal intestinal flora and allow *Clostridium difficile*, a gram-positive bacteria that forms heat-resistant spores, to colonize the intestine (47,48). Once in the colon, ingested spores convert to an active state and produce two exotoxins that are responsible for the colonic injury. These toxins, which are enterotoxic and cytotoxic, bind to intestinal receptors, disrupt mucosal integrity, and stimulate multiple inflammatory mediators (49,50). The resulting inflammation leads to increased capillary permeability, hemorrhage, and edema. As inflammation within the colon worsens, ulcerations form with associated necrotic debris, giving rise to so-called pseudomembranes, which appear grossly as elevated yellowish-white plaques on the colonic mucosa (Fig 10a) (47–49).

**Imaging Findings.**—Imaging findings vary, and more than 40% of cases may have normal abdominal radiographs (50). Abnormal radiographic findings include small bowel or colon ileus with segmental or diffuse dilatation, ascites, and nodular haustral thickening. Thickening of the colon wall from submucosal hemorrhage and edema results in the appearance of wide perpendicular bands, referred to as “thumbprinting,” that are commonly associated with pseudomembranous colitis (Fig 10b).
Figure 10. Pseudomembranous colitis. (a) Image from colonoscopy in a 52-year-old man who presented with profuse diarrhea shows superficial ulcerations with overlying yellow-white plaques that correspond to pseudomembranes. (b) Abdominal radiograph in a 59-year-old woman who presented with diarrhea shows diffuse thickening of the colon wall with thumbprinting (arrows). The patient was taking cephalosporin for a urinary tract infection. (c) Pathologic specimen from colon resection in a 44-year-old woman with toxemia shows colonic mucosa with diffuse active colitis and polypoid pseudomembranes. (d) Axial contrast-enhanced CT image in a 62-year-old woman with a history of pneumonia treated with clindamycin who presented with diarrhea shows pseudomembranous colitis with pancolitis. There is marked diffuse thickening of the colon wall with submucosal edema (white arrow) and diffuse mucosal hyperemia (black arrow).

10b) (47,49). Severe cases can progress to toxic megacolon, where there is dilatation of the colon more than 6 cm (48). On fluoroscopic studies with intraluminal contrast agent, thickened haustra are evident, the colon can have an irregular, shaggy margin, and there can be polypoid mucosal thickening or plaquelike filling defects. The latter two findings are manifestations of the yellowish plaques (pseudomembranes) that form on the mucosa (Fig 10c) (47). Fluoroscopic enemas should be avoided in a patient with pseudomembranous colitis because of the risk for perforation of the diseased colon (47).

CT findings of pseudomembranous colitis include marked wall thickening, which usually is greater than 4 mm and has been reported to reach more than 30 mm (Fig 10d) (47,48). The “target” sign describes alternating attenuation of the bowel wall, with decreased attenuation of the submucosa secondary to edema juxtaposed to enhancing mucosa. The “accordion” sign describes oral contrast material trapped between folds of the thickened edematous colon wall. There is usually relatively mild pericolonic stranding for the degree of colonic wall thickening, and ascites may be present, particularly with advanced disease (47,48).

Differential Diagnosis.—Entities other than pseudomembranous colitis that can manifest with similar radiographic findings include the acute stage of ulcerative colitis and Crohn colitis, infectious colitis (as can be seen with enterohemorrhagic Escherichia coli), radiation colitis, and ischemic colitis (48–51). Pseudomembranous colitis and Crohn colitis tend to produce the
greatest amount of wall thickening, which is more irregular and shaggy in pseudomembranous colitis compared with in Crohn colitis (48). Distortion in wall morphology, with polypoid mucosal projections, may help narrow the differential diagnosis. As with all drug-induced injury, patient history plays a major role in determining the causative factor. Although pseudomembranous colitis is most commonly a result of toxins produced by C difficile, alterations in normal bowel physiology can occur with chemotherapy and immunosuppressant therapy.

Liver

Medication-induced hepatic injury is a common phenomenon because most medications contain compounds that are metabolized by the liver. Drug-induced injury is the number-one cause of acute liver failure in the United States and the most common cause of postmarketing drug withdrawals and warnings (52,53). It accounts for approximately 10% of all cases of acute hepatitis (54). More than 900 drugs have been associated with hepatotoxicity, the most common being antibiotics and analgesic drugs (Table 2) (52,55). Drug-induced liver injury occurs because of the direct toxic effects of a drug or its metabolites on the hepatic parenchyma, and the array of inflammatory mediators that subsequently result. Liver injury is often categorized according to the predominant histopathologic and biochemical features and can be broadly grouped as hepatocellular, cholestatic, or mixed hepatocellular and cholestatic patterns of injury. Further classification is often made according to the clinical “phenotype” and course of injury and includes acute hepatitis, cholestatic hepatitis, biliary cholestasis, sinusoidal obstructive syndrome, and steatosis (nonalcoholic fatty liver) (56–58).

Table 2: Examples of Drugs That Can Be Associated with Cholestatic Liver Injury

<table>
<thead>
<tr>
<th>Drug Class and Common Agents</th>
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<tr>
<td>Antibiotics</td>
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<tr>
<td>Penicillins: amoxicillin-clavulanate</td>
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<tr>
<td>Sulfonamides: trimethoprim-sulfamethoxazole</td>
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<td>Marocloides: erythromycin</td>
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<tr>
<td>Tetracyclines: doxycycline</td>
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<tr>
<td>Antifungals: ketoconazole</td>
</tr>
<tr>
<td>Anti-inflammatories: diclofenac, ibuprofen</td>
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<tr>
<td>Psychotropes: chlorpromazine, tricyclic antidepressants</td>
</tr>
<tr>
<td>Immunosuppressives: cyclosporine, azathioprine</td>
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<tr>
<td>Other: oral contraceptives, estrogens, anabolic steroids</td>
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Steatosis

**Mechanism.**—Steatosis is a frequent finding in hepatic injury. Steatosis is the accumulation of lipids within hepatocytes. This can result from drug injury to mitochondrial structure or processes, such as β-oxidation, and energy depletion. Steatotic liver injury can lead to steatohepatitis, fibrosis, and cirrhosis (53,55,57). Common drug-induced causes include chemotherapeutic agents such as 5-fluorouracil (5-FU), irinotecan, and methotrexate. Amiodarone, tamoxifen, corticosteroids, and antipsychotics are also frequently associated with steatosis or steatohepatitis.

**Imaging Findings.**—At ultrasonography (US), the hepatic parenchyma shows increased echogenicity, with decreased visibility of the portal triads and dampening of the ultrasound wave, leading to poor visualization of the posterior liver. At CT, the liver shows low attenuation (at least 10 HU less than the spleen on nonenhanced images; liver attenuation of less than 40 HU on contrast-enhanced images). At MR imaging with in-phase and out-of-phase gradient-echo sequences, there is signal loss (dropout) on out-of-phase images when compared with in-phase images because of the properties of chemical shift (59). The pattern of fatty deposition may be diffuse, focal, diffuse with focal sparing, multifocal, perivascular, or subcapsular.

**Differential Diagnosis.**—Other causes of steatosis include alcohol, metabolic syndrome (eg, obesity, insulin resistance, hypertriglyceridemia), glycogen storage disease, Wilson disease, and total parenteral nutrition.

Cholestatic Injury

**Mechanism.**—In the cholestatic pattern of injury, the bile ducts are predominately affected. Often this is a result of compromised perfusion of the biliary system, whose blood supply is via the hepatic artery. Bile duct injury is not an uncommon complication associated with intra-arterial chemotherapy for treatment of malignancy (60). Chemotherapeutic agents have direct toxic effects on the bile ducts and indirect embolization effects from chemotherapy beads, resulting in diminutive ducts and, ultimately, ductopenia (60,61). More than 30 medications have been implicated in drug-induced ductopenia, most commonly the immunosuppressive cyclosporine, the antibiotic trimethoprim-sulfamethoxazole, and the antipsychotic chlorpromazine (62,63).

**Imaging Findings.**—Most commonly, cholestatic liver injury is not detectable at imaging. When...
present, imaging features of bile duct injury can be subtle. The most sensitive imaging modalities are endoscopic retrograde cholangiopancreatography or percutaneous cholangiography, in which the biliary tree is directly opacified with contrast material (64). MR imaging is the most sensitive noninvasive imaging modality, particularly when heavily T2-weighted MR cholangiopancreatographic images are obtained (64,65). One may see small ducts that are diminished in number. At CT and US, the ducts are frequently not visible. Nonspecific findings of liver injury can also be seen, including hepatomegaly and heterogeneously enhancing parenchyma (Fig 11). When injury is severe, features of fibrosis and cirrhosis can be seen.

**Differential Diagnosis.**—In a patient with cholestatic liver injury, imaging is important to exclude other causes of biliary obstruction such as cholelithiasis (54,56,59,61). Other extrahepatic causes of cholestasis include choledocholithiasis or bile duct tumor and pancreatitis or pancreatic tumor. Intrahepatic causes, such as primary sclerosing cholangitis and primary biliary cirrhosis, should also be excluded.

**Vascular Injury**

**Mechanism.**—Drugs may also insult the hepatic vasculature, resulting in Budd-Chiari syndrome. Budd-Chiari syndrome is obstruction of the hepatic venous outflow tracts, which leads to increased sinusoidal pressure, portal hypertension, venous stasis, and hepatic congestion. This can result in ischemic injury to the hepatocytes, leading to necrosis and fibrosis. Oral contraceptive pills have been linked to the development of Budd-Chiari syndrome (52–54,56,57). The mechanism is thought to be related to the relative hypercoagulable state from exogenous estrogen. Chemotherapeutic agents, particularly platinum compounds such as oxaliplatin and cisplatin, have also been linked to sinusoidal injury (57).

Sinusoidal obstruction syndrome (SOS), also known as venoocclusive disease, is blockage of the small hepatic venules and can be seen in stem cell or bone marrow recipients (54,56,57). Drug-induced damage to sinusoidal endothelial cells leads to necrosis and extrusion into the hepatic sinuses, resulting in obstruction and congestion. Patients present with abdominal pain, swelling, and weight gain, with or without elevation in serum enzyme levels. SOS is most commonly seen with myeloablative regimens (eg, busulfan plus cyclophosphamide and total body irradiation) in preparation for hematopoietic stem cell transplantation, although it is now much less common with current lower-dose regimens (66,67). Other chemotherapeutic agents, including dacarbazine and platinum compounds such as cisplatin, oxaliplatin, and carboplatin, can also cause SOS. Although there is overlap with the clinical and imaging features of Budd-Chiari syndrome, the large hepatic veins and intrahepatic inferior vena cava typically remain patent in SOS (21,56,67).

**Imaging Findings.**—Imaging often shows hepatomegaly and hepatic congestion. At nonenhanced CT, this may appear as heterogeneous hepatic attenuation. At contrast-enhanced CT, there may be heterogeneous enhancement owing to altered perfusion in areas of increased sinusoidal pressure from venous stasis. CT may also show dilated thrombosed hepatic veins in Budd-Chiari syndrome (Fig 12) (68). In contrast, the small obstructed hepatic venules in SOS are not visible at imaging (Fig 13). At MR imaging, findings are typically most remarkable on T2-weighted images, which show a heterogeneous liver with areas of increased signal intensity corresponding to edema (21).
Differential Diagnosis.—Other causes of liver failure, including graft versus host disease (particularly in the setting of hematopoietic stem cell transplantation), viral hepatitis, and sepsis, must be excluded.

Neoplasm

Mechanism.—Oral contraceptive pills and anabolic steroids have been associated with development of hepatocellular adenomas (HCAs) (69). HCAs, also known as hepatic adenomas, are epithelial neoplasms composed of normal hepatocytes that are arranged in sheets separated by compressed sinusoids. They can contain “free-floating” arteries and veins but have no central vein, portal tract, or connection with the biliary system. HCAs are classified into three distinct subtypes: (a) inflammatory HCAs (HCA-I), (b) hepatocyte nuclear factor 1α (HNF-1A)–mutated HCAs (HCA-H), and (c) β-catenin–mutated HCAs (HCA-B). A fourth subtype, “unclassified,” is also recognized and does not have any specific gene mutations. Inflammatory HCA is the most common subtype and manifests frequently in obese patients and in young women with a history of oral contraceptive use (70,71). These lesions harbor mutations in interleukin-6 (IL-6) (71–73). The mechanism of oral contraceptive pill–related development of these lesions may be related to increased IL-6 signaling pathways that may occur as a result of hormonal manipulation. Inflammatory adenomas have a greater risk of hemorrhage compared with other subtypes and a 10% risk of malignancy (70). HNF-1A–mutated subtypes are the second most common subtype and are also seen in women with a history of oral contraceptive use (70). Many women with HNF-1A–mutated subtypes have a background of hepatic steatosis. About 10–15% of all HCAs are β-catenin–mutated subtypes and are due to activating mutations of the β-catenin gene (70,71). These tumors are seen more commonly in men,
particularly if there is a history of anabolic steroid use or glycogen storage disease, and they have the highest rate of malignant transformation (70). Hepatic adenomas larger than 5 cm also have a greater risk for malignant transformation (70).

**Imaging Findings.**—Because these tumors can undergo degenerative changes and may have dilated sinusoids, blood-filled (pelioid) spaces, myxoid stroma, focal necrosis, infarction, and fatty change, their appearance at imaging can be heterogeneous. At MR imaging, inflammatory subtypes are hyperintense on T2-weighted images and isointense or mildly hyperintense on T1-weighted images, with minimal to no signal drop with chemical shift sequences. Inflammatory adenomas also demonstrate intense enhancement in the arterial phase, which persists in the portal venous and delayed phases in dynamic contrast-enhanced series. There may be persistent enhancement at the periphery in the hepatobiliary phase because of ductular reaction (Fig 14) (72,73). Lesions of the HNF-1A–mutated subtype typically contain intracellular fat, and thus they are isointense to hyperintense on T1-weighted images and show signal loss with chemical shift sequences (Fig 15) (72,73). There are no specific imaging features of β-catenin–mutated subtypes.

**Differential Diagnosis.**—The differential diagnosis for hepatic adenomas includes other hepatic neoplasms, particularly focal nodular hyperplasia, as there is overlap in the imaging features. Both types of lesions can show early intense contrast enhancement. MR imaging may be helpful in differentiating these two lesions, particularly when hepatocyte-specific contrast agents are used, because persistent enhancement in the hepatobiliary phase is more typical of focal nodular hyperplasia than hepatic adenomas. However, as previously mentioned, it has been shown that some inflammatory subtypes of adenoma can show uptake in the hepatobiliary phase with hepatocyte-specific agents (72,73). Particularly for lesions of the HNF-1A–mutated subtype, other fat-containing hepatic neoplasms should also be considered and include focal nodular hyperplasia, angiomyolipoma, and hepatocellular carcinoma.

**Pancreas**

**Pancreatitis**

**Mechanism.**—Drug-induced pancreatitis has been reported for more than 50 years and may account for 3%–5% of cases of acute pancreatitis; however,

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**Figure 14.** HCA in a 24-year-old woman taking oral contraceptive pills who presented for imaging follow up. Axial arterial phase (a), portal venous phase (b), and 1-hour delayed phase (c) MR images obtained with hepatocyte-specific gadolinium contrast agent show a liver lesion in the right lobe (arrow) with early arterial enhancement that persists in the portal venous phase. The late persistent enhancement seen at the periphery in c is due to a ductular reaction (proliferation of ductular structures from a large duct obstruction). Pathologic analysis of a surgical tissue sample showed HCA, inflammatory subtype.
the true incidence is unclear because it may still be underrecognized and underreported by clinicians (74,75). Pancreatitis results from insult to the exocrine function of the pancreas and inappropriate accumulation or activation of pancreatic digestive proenzymes. More than 100 medications have been associated with acute pancreatitis (Table 3) (75). Among the most common are chemotherapeutic agents (21,74–76), azathioprine (and its metabolite, 6-mercaptopurine), and 2′,3′-dideozyinosine (75). Statins, ACE inhibitors, oral contraceptives, antiretroviral therapy, and diuretics are also frequently associated with drug-induced pancreatic injury (74). Proposed general mechanisms include pancreatic duct constriction, toxic metabolites, and cytotoxic effects of the drug (74).

**Table 3: Examples of Medications That Can Cause Drug-induced Pancreatitis**

<table>
<thead>
<tr>
<th>Drug Class and Common Agents</th>
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<tbody>
<tr>
<td><strong>Chemotherapeutics:</strong> azathioprine, 2′,3′-dideozyinosine, l-asparaginase</td>
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<tr>
<td><strong>Diuretics:</strong> thiazides, furosemide</td>
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<tr>
<td><strong>Antibiotics:</strong> metronidazole, tetracyclines, sulfonamides</td>
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<tr>
<td><strong>Estrogens</strong></td>
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<tr>
<td><strong>Statins:</strong> simvastatin</td>
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<tr>
<td><strong>ACE inhibitors:</strong> captopril, lisinopril, enalapril</td>
</tr>
<tr>
<td><strong>Other:</strong> sulfasalazine, mesalamine, sodium valproate</td>
</tr>
</tbody>
</table>

**Imaging Findings.**—The imaging features of drug-induced pancreatitis are nonspecific and are identical to those seen with other causes of pancreatitis. Interstitial or necrotizing pancreatitis may result. At CT and MR imaging, interstitial pancreatitis manifests as focal or diffuse parenchymal edema, with indistinct margins and inflammatory stranding in the peripancreatic fat (Fig 16) (76). Contrast-enhanced images show homogeneous enhancement of the pancreatic parenchyma. An acute peripancreatic fluid collection with ill-defined margins may be seen early in the course of the disease (<4 weeks). Pseudocysts with a well-defined wall can develop as a late complication (>4 weeks). Necrotizing pancreatitis, on the other hand, shows areas of nonenhancing pancreatic tissue at contrast-enhanced CT or MR imaging. Intra- or extrapancreatic fluid collections are referred to as acute necrotic collections (with no fully definable wall) early in the disease course and as walled-off necrosis (with a definable wall) late in the course (1,21,25).
**Differential Diagnosis.**—Common causes of pancreatitis should be excluded, including gallstone and alcohol-induced pancreatitis. Other possible causes that should be considered include autoimmune pancreatitis, hypercalcemia, hypertriglyceridemia, trauma, and pancreatic malignancy.

**Conclusion**

Drug-induced complications frequently involve the gastrointestinal system and can cause varying degrees of injury. Pill esophagitis commonly affects the middle third of the esophagus and may manifest with imaging findings similar to those of herpes or Crohn esophagitis, appearing as superficial discrete ulcers with normal intervening mucosa. NSAIDs impair protection and maintenance of mucosal defense mechanisms mediated by the prostaglandin pathway. Imaging findings of NSAID-induced injury range from superficial aphthous ulcers to deeper penetrating ulcers in the stomach and duodenum, bowel wall thickening, and mucosal diaphragms. These diaphragms can be difficult to see at imaging in the absence of bowel obstruction.

Medication-induced injury in the bowel can manifest as ACE inhibitor–induced angioedema, antibiotic-associated pseudomembranous colitis, and pneumatosis intestinalis. In the liver, medication-induced injury can broadly result in hepato-cellular or cholestatic injury (or a combination). Imaging findings are nonspecific and generally include hepatomegaly, steatosis, and, in cases of severe injury, fibrosis and cirrhosis. Cellular injury is most prominent in the periportal regions. Oral contraceptive pills are associated with HCAs (inflammatory and HNF-1A subtypes) and vascular injury such as Budd–Chiari and sinusoidal obstructive syndromes. Finally, medications can cause pancreatitis, with imaging findings similar to those in other causes of pancreatitis.

Radiologists should maintain awareness for drug-induced injury, particularly after excluding other disease processes that can produce similar imaging findings. This may help avoid delayed diagnosis and prolonged exposure to the offending agent.

**References**

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