Drug-induced acute liver failure and gastrointestinal complications

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The objective of this article is to describe adverse drug events related to the liver and gastrointestinal tract in critically ill patients. PubMed and other resources were used to identify information related to drug-induced acute liver failure, gastrointestinal hypomotility, constipation, diarrhea, gastrointestinal bleeding, and pancreatitis in critically ill patients. This information was reviewed, and data regarding pathophysiology, common drug causes, and guidelines for prevention and management were collected and summarized. In cases in which data in critically ill patients were unavailable, data were extrapolated from other patient populations. Drug-induced acute liver failure can be caused by many drugs routinely used in the intensive care unit and may be associated with significant morbidity and mortality. Drug-related hypomotility and constipation and drug-related diarrhea are reported with many drugs, and these are common adverse drug events in critically ill patients that can substantially complicate the care of these patients. Drug-induced gastrointestinal bleeding and drug-induced pancreatitis occur less frequently, can range in disease severity, and can be associated with morbidity and mortality. Many drugs used in critically ill patients are associated with adverse drug events related to the liver and gastrointestinal tract. Critical care clinicians should be aware of common drug causes of drug-induced acute liver failure, gastrointestinal hypomotility, constipation, diarrhea, gastrointestinal bleeding, and pancreatitis, and should be familiar with the prevention and management of these diverse conditions. (Crit Care Med 2010; 38[Suppl.]:S175–S187)

KEY WORDS: adverse drug events; critical illness; intensive care; liver failure; constipation; motility; diarrhea; gastrointestinal bleeding; pancreatitis

Adverse drug events related to the liver and gastrointestinal (GI) tract are associated with many drugs used in critically ill patients. To this end, drug toxicity is the leading cause of acute liver failure (ALF) in the United States, and drug-induced acute liver failure (DIALF) is an important consideration in the management of critically ill patients (1–3). Other drug-induced adverse drug events related to the GI tract that may be observed in critically ill patients include constipation/hypomotility, diarrhea, GI bleeding, and pancreatitis. These events can present significant challenges in the management of intensive care unit (ICU) patients because they are diverse, can have complex and multifactorial pathophysiology, can result in substantial morbidity and mortality, and in some cases, are extremely common in critically ill patients. This review presents an overview of the pathophysiology of these adverse drug events, lists commonly used medications in the critical care setting that contribute to these events, and reviews prevention and treatment strategies.

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DIALF

Pathophysiology

Currently, drug-induced liver disease (DILD) accounts for almost 10% of adverse events reported in the United States. Nearly 50% of cases of acute liver failure can be attributed to medications (4). Approximately 1000 medications have been implicated as a cause of DILD (5, 6). Establishing causality attributable to medications is difficult because of the complex nature of delivering critical care. Commonly encountered problems within critical care, such as polypharmacy, altered pharmacokinetics, and compromised perfusion, may make critically ill patients particularly susceptible to the development of DIALF.

The reported range of population-based DILD ranges from one to five in 1,000,000 to 13.9 cases per 100,000 (7, 8). Information regarding DILD is difficult to identify for a number of reasons. First, the voluntary nature of postmarketing reporting of adverse drug events as required by the U.S. Food and Drug Administration possibly leads to under-reporting. Second, the nature of toxicity is relatively rare. Third, diagnosing DILD is challenging. Drugs that have a high incidence of DILD will not be approved by the Food and Drug Administration. Therefore, drugs that make it to market have a comparatively lower incidence of DILD (9). Identifying hepatotoxicity attributable to medications requires astute observation by clinicians and direct reporting to the Food and Drug Administration. DIALF remains the leading reason for regulatory action (10). Epidemiologic studies of DIALF are even more difficult to characterize given the limitations in reporting. Currently, it is estimated that acute liver failure affects approximately 2000 individuals annually (10, 11). A review of the United Network for Organ Sharing Standard Transplant Analysis and Research files showed 661 patients who underwent liver transplantation for DIALF from 1987 to 2006 and found that the four drugs groups most responsible for liver transplantation were acetaminophen (40%), antituberculosis agents (8%), antiepileptics (7%), and antibiotics (6%) (12). One-year survival rates related to each drug class were 76% for acetaminophen, 82% for antituberculosis agents, 52% for antiepileptic agents, and 82% for antibiotics. The higher rate of DIALF-associated mortality for the antiepileptics was attributed to the higher rate of mortality in children.

Table 1. Commonly used medications in critical care causing drug-induced acute liver failure

Drugs	Hepatotoxic Reaction
Acetaminophen, ketoconazole, rifampin, isoniazid, phenytoin, valproic acid, carbamazepine, venlafaxine	Necrosis
Amoxicillin/clavulanate, chlorpromazine, angiotensin-converting enzyme inhibitors, erythromycin	Cholestasis
Didanosine, valproic acid	Acute steatosis
Phenytoin, sulfamethoxazole/trimethoprim, nitrofurantoin, cyclosporine	Mixed pattern
Methotrexate	Fibrosis/cirrhosis
Amiodarone, tamoxifen, chloroquine	Nonalcoholic steatohepatitis

It is important to recognize that drugs can induce the entire spectrum of liver disease, but acute hepatitis is the most common syndrome (5). In terms of critical care management, it is important to describe what acute liver failure is and what best utilizes critical care resources. Whereas there are no definitive guideline recommendations, there is consensus that ALF is a syndrome characterized by sudden hepatocyte dysfunction occurring in a previously healthy individual manifesting clinically with a coagulopathy (international normalized rate >1.5) and hepatic encephalopathy (13–18). The pathogenesis of DIALF is primarily attributable to the liver being the main site of drug metabolism, making it susceptible to acute toxicity. Hepatotoxicity can result from either the drug or its toxic metabolite. Toxicity attributable to the parent drug usually occurs in the setting of a combination of multiple drugs leading to drug–drug interactions and elevated serum drug concentrations. Drug metabolites are the main cause of DIALF. Drug metabolism producing toxic metabolites may overwhelm the liver's ability to adequately transform them into inert chemicals. Metabolites can be free radicals or electrophilic chemicals that can induce lipid peroxidation, disrupt fatty acid oxidation, covalently bind to lipids and proteins, or deplete glutathione. Subsequent cellular changes can lead to necrosis, apoptosis, or immune response. Hepatocyte death is the main cause of DIALF (2, 19, 20). Within critical care, the management of DIALF may include acute toxicity that resolves with simple discontinuation of the medication all the way to administration of an antidote, support of failing organs, and transplantation. DILD and DIALF are used throughout the course of this text. DIALF specifically refers to cases of drug-induced hepatotoxicity consistent with the definition of ALF.

The presentation of DIALF is similar to acute hepatitis or cholestatic disease. DIALF presenting as acute hepatitis is more serious and is associated with a higher mortality rate (15, 18). Acute hepatitis is accompanied by markedly elevated serum transaminase levels and an associated increase in alkaline phosphatase. Symptoms can include deep jaundice, hepatic encephalopathy, coma, coagulopathy, and ascites. DILD attributable to acute cholestasis is a result of reduced biliary flow. It is associated with an isolated increase in serum alkaline phosphatase and conjugated bilirubin. Clinically, these patients present with jaundice, pruritus, dark urine, and abdominal pain. The prognosis for drug-induced hepatotoxicity attributable to acute cholestasis is much better than that attributable to acute hepatocellular injury (16, 18).

The two most commonly used assessment tools for drug-induced liver disease are the Roussel Uclaf Causality Assessment Method and the Clinical Diagnostic Scale (21, 22). The Roussel Uclaf Causality Assessment Method was developed specifically for the evaluation of drug-induced liver injury and is the tool used by the Drug-Induced Liver Injury Network established by the National Institutes of Health. It has seven major criteria for assessment with a corresponding point-scoring system to determine to determine causality. The Clinical Diagnostic Scale is modified from the Roussel Uclaf Causality Assessment Method tool and is simpler to use. However, when the two assessment tools were compared, the Roussel Uclaf Causality Assessment Method provided a greater level of certainty of causality (23). The Clinical Diagnostic Scale can underestimate reactions not previously documented in the literature.

Common drug causes

There is an abundant list of medications that can cause DILD. However, a notable number of medications commonly used in critical care settings can contribute, exacerbate, or directly cause DIALF (Table 1). As mentioned previously, careful monitoring and observation may detect drug-induced hepatotoxicity that may otherwise go unrecognized. A brief discussion of medications commonly used or with a high prevalence of documented DIALF relevant to critical care follows.

Acetaminophen. Acetaminophen (APAP) is the most common cause of DIALF, accounting for 39% of all cases within the United States (4). Given the availability of APAP, and its inclusion in several combination narcotic medications, it is not surprising that APAP is the leading medication cause of DIALF. Cases of unintentional overdose represent a significant problem because of their late recognition and subsequent treatment. Either as a result of suicidal overdose or unintentional ingestion, APAP toxicity is dose-related and is primarily attributable to its active metabolite, *N*-acetyl-p-benzoquinone-imine (2, 5, 20). The depletion of glutathione results in the inability to detoxify the active metabolite of APAP, resulting in acute hepatocellular injury and necrosis. Drug–drug interactions can be a cause of acetaminophen toxicity within the ICU. Several commonly used ICU medications, such as phenobarbital, phenytoin, and isoniazid, can lead to induction of CYP2E1 (15, 24, 25). The induction of CYP2E1 can result in an overproduction of *N*-acetyl-p-benzoquinone-imine. Toxicity from the metabolite results is typically manifested with serum aminotransferase concentrations >200 IU/L. Fulminant liver failure is severe and includes the stigmata of acute liver failure, such as progressive hepatic encephalopathy, coagulopathy, and associated multiple organ failure.

Anticonvulsant agents. Phenytoin-induced DILD is idiosyncratic, can occur in days to weeks, and does not appear to be dose- or concentration-related (2). Phenytoin-induced DILD is typically characterized by an acute elevation in serum aminotransferase concentrations (typically more than five times the upper limit of normal). Associated clinical symptoms include fever, rash, and eosinophilia. The mechanism of toxicity is poorly understood (26). Carbamazepine hepatotoxicity is idiosyncratic and may result because of a hypersensitivity mechanism. The onset is usually within weeks to months, and the severity can vary from mild transaminases to ALF. Clinical symptoms are similar to those of pheny-

toin-induced DILD. Again, the mechanism of toxicity is poorly understood but is thought to result from a genetic predisposition to lower epoxide hydrolase metabolizing enzymes, leading to a toxic accumulation of the oxide metabolites and manifested as biliary injury (27, 28). All of the aromatic antiepileptic agents (phenytoin, phenobarbital, carbamazepine, oxcarbazepine, lamotrigine) are associated with anticonvulsant hypersensitivity syndrome (28). Anticonvulsant hypersensitivity syndrome is typically associated with the triad of symptoms of fever, rash, and organ-system involvement and can progress to hepatitis and DIALF (28). Additionally, there is a high incidence of cross-reactivity among the aromatic anticonvulsant agents that can trigger anticonvulsant hypersensitivity syndrome on initiation (28). Hepatotoxicity is self-limiting and usually resolves on drug discontinuation. Valproic acid can induce DILD by hepatocellular injury and steatosis (29). The onset can be days to weeks after initiation of therapy, and there does not appear to be a dose-related effect. Febrile illness immediately before DILD is specific to valproic acid. The mechanism of toxicity is thought to result from an accumulation of the toxic metabolite leading to mitochondrial dysfunction (30).

Amiodarone. Amiodarone DILD is characterized by hepatocellular injury. Interestingly, the acute toxicity attributable to intravenous amiodarone is thought to be caused by the cosolvent, polysorbate 80, and higher serum concentrations. Acute amiodarone DILD attributable to the intravenous formulation can occur immediately after the administration, resulting in an acute increase in serum aminotransferase concentrations (31). Chronic oral amiodarone use can result in increased concentrations of the metabolite desethylamiodarone. This form of hepatoxicity results in chronic steatosis (32). Given amiodarone's route of metabolism through CYP3A4, there are numerous significant drug–drug interactions that can cause acute elevations of the metabolite, resulting in acute DILD and ALF (33, 34).

Anesthetic agents. Halothane undergoes metabolism via the CYP 2E1 enzyme producing the toxic metabolite (35). The risk of DIALF with isoflurane, desflurane, and sevoflurane is thought to be much less, leading to these agents largely replacing halothane in clinical practice (36). Clinical symptoms can present days after exposure and can include fever, rash, arthralgia, and jaundice. Associated risk factors for DIALF attributable to volatile anesthetics include multiple exposures, female gender, and obesity (37). The mechanism of toxicity is largely attributable to hepatocellular necrosis.

Anti-infective agents. Numerous antibacterials have been associated with DILD, including erythromycin, trimethoprim/sulfamethoxazole, minocycline, doxycycline, and nitrofurantoin. Of the β-lactam antibiotics, amoxicillin-clavulanate is the leading cause of DIALF, although DIALF attributable to this class of antibacterials is relatively rare (38). The onset of DIALF after amoxicillin-clavulanate typically occurs within 4 wks of initiation and is characterized by clinical symptoms of cholestatic disease, including nausea, vomiting, fatigue, fever, and jaundice (39). The mechanism of injury is thought to be attributable to a variation in a human leukocyte gene, resulting in cholestatic DIALF (39). Significant hepatotoxicity has also been associated with antituberculosis agents, specifically isoniazid and rifampin (40, 41). In both cases, toxicity develops within the first several months of initiation and is characterized by elevated transaminases. Because of their varying effects on the CYP3A4 metabolic isoenzyme (isoniazid, CYP3A4 inhibitor; rifampin, CYP3A4 inducer), the addition of other CYP3A4 metabolized medications (e.g., amiodarone) may predispose the critically ill patient to DIALF. Liposomal amphotericin B and fluconazole have been associated with the development of DIALF, defined as serum aminotransferase concentrations greater than three times the upper limit of normal, independent of other variables (42). Itraconazole and ketoconazole are both widely recognized as hepatotoxic because of numerous case reports (43, 44). The mechanism of toxicity is hepatocellular necrosis resulting in DIALF.

Psychotropic agents. A retrospective study of selective serotonin reuptake inhibitors reported 158 cases of DILD (45). This encompassed all selective serotonin reuptake inhibitors, including paroxetine, fluoxetine, fluvoxamine, sertraline, and citalopram. The spectrum of DILD included the entire spectrum, with DIALF being the most common. Most cases of DILD occurred at therapeutic doses, suggesting an idiosyncratic reaction. Risk factors for DIALF included alcohol abuse, age older than 70 yrs, and concomitant hepatotoxic medications. Given the prevalence of selective serotonin reuptake inhibitor use in the United States, patients admitted to ICUs should be carefully watched for the development of DIALF, especially patients with a recent history of selective serotonin reuptake inhibitor use.

Recommendations for prevention and management. Once DIALF has developed, treatment is mostly supportive, and emergency transplantation provides the best chance of survival (3, 17, 18). Because management of ALF is complex and involves the management of numerous complications, it is beyond the scope of this review. This section primarily focuses on prevention and the administration of specific antidotes for DIALF.

Prompt recognition of DIALF is primary in preventing the progression to more severe forms of liver disease, such as multisystem organ failure and death. The understanding that it may be impossible to prevent the development of DIALF should raise sensitivity to the issue. In some cases, recognition of the possibility of severe drug–drug interactions can heighten awareness, and frequent monitoring may be enough to prevent the development of DILD and progression to DIALF. Within the hospital setting, medication safety systems should be developed to prevent the inadvertent administration of >4 grams per day of acetaminophen, including administration of acetaminophen-containing combination medications.

For patients with DIALF caused by APAP overdose, prompt administration of *N*-acetylcysteine (NAC) is essential, because NAC is the specific antidote to limit APAP overdose (15, 20). NAC is thought to limit further progression of hepatocellular injury by repleting glutathione stores and binding the toxic APAP metabolite, *N*-acetyl-*p*-benzoquinone-imine. Other proposed benefits to NAC include antioxidant activity, improved hemodynamic parameters, and increased oxygen delivery. In many cases, it is difficult to apply to the widely utilized Rumack-Mathew nomogram because of the uncertainties involving time of ingestion or with patients using enzyme-inducing medications. Because NAC is the only antidote to fulminant ALF, in cases of uncertainty, administration should not be withheld. Of note, given the complexity of the dosing regimen, there is documentation of medication errors with the administration of intravenous NAC (46).

Recently, the United States Acute Liver Failure Study Group completed a study comparing the administration of

intravenous NAC to placebo in patients with ALF not attributable to APAP toxicity (47). One hundred seventy-three patients were randomized *a priori* by grade of encephalopathy (mild to moderate [grade 1 or 2] vs. severe [grade 3 or 4]) to determine whether the administration of intravenous NAC would improve 21-day survival. There was no difference between groups in overall survival (70% vs. 67%; $p = .57$). Furthermore, spontaneous survival was not improved in patients with severe encephalopathy (9% vs. 22%; $p = .18$). When analyzing the subgroup of patients with mild-to-moderate encephalopathy for the secondary end point, there was a survival benefit to the administration of intravenous NAC (52% vs. 30%; $p = .02$). Because the primary benefit was noted for the secondary end point in less severely ill patients, the application of intravenous NAC for non-APAP–induced ALF remains uncertain in the critical care setting.

The administration of corticosteroids and ursodeoxycholic acid has been studied for the management of DIALF associated with hypersensitivity reactions. An uncontrolled trial of corticosteroid administration for DIALF found a potential benefit (48). However, two large, randomized, control trials have found no survival benefit to the administration of corticosteroids for non-APAP DIALF (49, 50). The role of corticosteroid administration remains unclear and is complicated by the recent literature for the treatment of relative adrenal insufficiency (51, 52).

Drug-induced GI hypomotility and constipation

Pathophysiology

Impaired GI motility is extremely common in the ICU, affecting up to 50% of mechanically ventilated patients (53). This can include alterations in esophageal, gastric, small bowel, and colonic function, alone or in combination (54). Alterations in upper GI motility can lead to regurgitation, reflux, aspiration, vomiting, high gastric residuals, gastroparesis, and delayed gastric emptying (55). In contrast, reductions in colonic motility tend to result in constipation, discussed separately in the following paragraph. Regulation of GI motility involves complex regulation of the enteric nervous system by a number of hormones, neuroendocrine peptides, and efferent/afferent neuronal influences (54–56). As such, motility impairment during critical illness is complex and multifactorial. Pathophysiologic alterations often involve abnormal propulsive motility, and specific pathologic alterations include disturbances in esophageal motility and reductions in lower esophageal sphincter pressure (leading to regurgitation and potential aspiration), antral hypomotility and abnormal gastric digestive patterns (leading to delayed gastric emptying), and disturbances in the digestive and interdigestive motility patterns (resulting in abnormal peristalsis) (55–57). Drugs frequently impair gastric motility via one or more of these mechanisms. For example, exogenous catecholamines reduce antral contractions, alter motility patterns, and decrease small bowel peristalsis (56, 58, 59). Opioids inhibit GI transit by inhibiting neurotransmitter release, changing neuronal excitability, and altering water and electrolyte absorption, resulting in dysregulated motility patterns, impaired gastric emptying, and hypomotility (also see discussion of opioid-induced constipation) (54, 56, 60). The precise mechanisms of drug-induced hypomotility are often unknown. Clinical consequences of hypomotility may include aspiration and inability to provide enteral nutrition, increased bacterial translocation, and patient discomfort (54).

The utility of standard definitions for constipation relying on subjective symptoms is limited in the ICU, and studies evaluating constipation in critically ill patients have often used the failure of the bowel to open for 3 to 4 consecutive days as a working definition (61–63). Using this definition, constipation is a frequent problem in critically ill patients, with a reported incidence ranging from 50% to 80% (62, 63). Drugs probably contribute substantially to constipation in the ICU, although the precise extent to which drugs contribute is difficult to define numerically. Most causes of drug-induced constipation involve increased colonic transit time related to changes in neuronal or motor function of the intestine (64). The opioids are the most common drug class implicated as a cause of constipation, particularly in the ICU. Opioid-induced constipation occurs through a combination of central effects (inhibition of acetylcholine release from the myenteric plexus) and peripheral effects (binding to opioid receptors in the intestine); collectively, this results in a decrease in intestinal motility and fluid secretion, and an increase in intestinal fluid absorption (61, 65). Unlike other opioid-related adverse effects, tolerance to the constipating effects of opioids does not usually occur (61). Drugs with anticholinergic effects can result in decreased intestinal tone and motility, and bulking agents can promote constipation in the absence of adequate oral fluid intake (66). Potential consequences of constipation include discomfort, abdominal distention, vomiting, restlessness, and, potentially, obstruction and perforation (62). Of note, in critically ill patients, constipation may be associated with delayed weaning from mechanical ventilation, prolonged ICU stay, and inability to provide enteral nutrition (62).

Common drug causes

A number of drugs have been associated with impaired gastric and small intestinal motility in critically ill patients. The use of opioid analgesics (morphine, fentanyl [although this is likely a class effect]) and sedatives (benzodiazepines and ketamine) are associated with impaired upper GI motility in critically ill patients (60, 67, 68). To this end, the use of midazolam and fentanyl for sedation/analgesia is an independent risk factor for elevated gastric aspirate volume during nasogastric feedings (68). Alpha-2 agonists (dexmedetomidine, clonidine) may also be associated with motility disturbances, although this is based on anecdotal and *in vitro* evidence and has not been evaluated in critically ill patients (69, 70). A sedation strategy using midazolam and morphine appears to impair gastric emptying to a greater extent than a strategy using propofol (71). Catecholamine vasopressors can also impair upper GI motility and they are also an independent risk factor for increased gastric aspirate volume during nasogastric feedings (58, 68). Other drugs that may impair upper GI motility are listed in Table 2. Unfortunately, the precise extent of the contribution of drugs to this problem is largely unknown.

Virtually any drug that decreases colonic motility can cause constipation. As indicated, the opioids are likely the most common cause of drug-induced constipation in critically ill patients. In noncancer patients, the reported incidence of opioid-related bowel dysfunction is as high as 40% (72). Although the specific incidence in critically ill patients is not known, opioid contribution to constipation is likely substantial because of the

Table 2. Common causes of drug-induced esophageal, gastric, and small intestinal hypomotility in critically ill patients[a]

Drug/Drug Class
β-2 agonists (dexmedetomidine, clonidine)[b] (69, 70, 139)
Anticholinergic drugs (56)
Benzodiazepines (68, 71)
Catecholamine vasopressors[c] (58, 59, 68)
Ketamine[d] (67)
Opioids[e] (54, 67, 68)

[a]This is an abbreviated list of drugs that may be associated with drug-induced upper gastrointestinal hypomotility in critically ill patients. Of note, the term *hypomotility* is applied in a broad sense. Although there are likely to be differences between different drug classes in terms of the pathophysiology (mechanisms and region of the upper gastrointestinal tract affected), these differences are often unknown because of challenges in assessing gastrointestinal motility in critically ill patients. Drugs were selected for inclusion based on incidence of motility disturbances and/or frequency of use in critically ill patients. Drugs associated with decreased colonic motility and/or constipation are shown separately in Table 3; [b]based on *in vitro* data suggesting alterations in gastric and small intestinal motility (dexmedetomidine, clonidine) and case reports of colonic pseudo-obstruction (clonidine) (69, 70, 139); [c]clinical data indicate dopamine likely impairs gastric emptying and gastroduodenal motility in critically ill patients; *ex vivo* animal data indicate several catecholamines may impair ileal peristalsis (epinephrine > norepinephrine > dopamine > dobutamine > dopexamine) (58, 59, 140); [d]may inhibit esophageal motility (67); [e]also impairs colonic motility (see Table 3).

Table 3. Common causes of drug-induced colonic hypomotility and constipation in critically ill patients[a]

Drug/Drug Class	Approximate Incidence, If Known[b]
Aluminum antacids	25% (141)
Anticholinergics	Up to 42% (142)
Anticonvulsants	6% (141)
Antihistamines (H1 antagonists)	27% (141)
Antipsychotics	10% (141)
Antispasmodics	21% (141)
β-adrenergic blockers[c]	16% (141)
Calcium channel blockers	
Diltiazem	25% (143)
Verapamil	25–40% (143)
Clonidine	1–10% (144)
Disopyramide	11% (145)
Diuretics	35% (141)
Mineral supplements	
Calcium supplements	2% (141)
Iron supplements	8–21% (141, 146)
Opoid analgesics	15–40% (up to 90%) (72, 141)
Fentanyl	4–27% (64)
Morphine sulfate	5–57% (64)
Oxycodone	6–23% (64)
Selective serotonin reuptake inhibitors	11% (147)
Sulcrafate	3% (148)
Tricyclic antidepressants	22% (147)

[a]This is an abbreviated list of drugs that may be associated with drug-induced colonic hypomotility in critically ill patients (drugs were selected for inclusion based on incidence of constipation and/or frequency of use in critically ill patients); given the vast number of drugs that may be associated with constipation, a list of all possible drug causes is beyond the scope of this review. Drugs associated with decreased upper GI motility are shown separately in Table 2; [b]in most cases incidence has been extrapolated from non-critically ill patient populations; [c]despite data suggesting potential association with constipation, other data suggests that β-adrenergic blockers may shorten the period of adynamic ileus following colonic surgery (141,149).

widespread use and aggressive dosing of opioid analgesics in the ICU. Opioid intake is inversely associated with the occurrence of a bowel movement in the first 96 hrs of ICU stay (63). Opioids also contribute to constipation associated with postoperative ileus (73). Drugs that may be associated with constipation in critically ill patients are presented in Table 3.

Recommendations for prevention and management

Most motility disorders in critically ill patients go unrecognized until they become symptomatic (e.g., when high gastric residuals or constipation occur). General preventive measures include correction of fluid and electrolyte imbalances, early enteral feeding, and judicious use of drugs known to contribute to alterations in motility (56). It is important to note that impaired upper GI motility is treated differently than impaired colonic GI motility (the latter is discussed below). Prokinetic drugs are frequently used to treat impaired esophageal, gastric, and small intestinal motility. Metoclopramide is a widely used dopamine-2 and 5-HT_3 antagonist, and 5-HT_4 agonist that increases gastric and small intestinal motility, with little action beyond the small bowel (55, 56). Intravenous metoclopramide increases GI transit, decreases gastric residuals, and improves feeding tolerance in critically ill patients (74–76). Erythromycin stimulates GI motility by activating motilin receptors on smooth muscle and enteric neurons of the stomach and small intestine (77). The prokinetic effects of erythromycin are dose-dependent and most studies have evaluated intravenous administration (56). Similar to metoclopramide, intravenous erythromycin accelerates gastric emptying, reduces gastric residual volume, and improves tolerance to enteral feeding, and some evidence indicates that erythromycin may be more effective than metoclopramide (74, 78). Tolerance to the prokinetic effects of erythromycin is possible with long-term use, and there is at least a theoretical risk of arrhythmogenesis and of promoting macrolide resistance associated with erythromycin use (77). In refractory patients, the combination of erythromycin and metoclopramide may be effective (78).

Efforts to prevent and treat drug-related colonic hypomotility and constipation in critically ill patients are poorly defined. Although the use of a "bowel regimen" (generally the use of either a stool softener and/or laxative) is frequently recommended, well-designed studies supporting the efficacy of such strategies in preventing constipation in the ICU are lacking (79). At a minimum, the establishment of a bowel protocol, including guidelines for prevention and management of ICU constipation, is likely to promote awareness and more structured monitoring of bowel function. General preventive strategies include avoiding drugs associated with constipation, use of nonopioid analgesia when possible, promoting enteral fluid intake, use of bulking agents (in conjunction with oral fluid intake), and promoting early ambulation when possible. In critically ill patients using high-dose opioids,

the use of stool softeners and/or laxatives has traditionally been used for the prevention and treatment of constipation. Stool softeners, such as docusate sodium, are generally well tolerated and often used in combination with osmotic or stimulant laxatives. Of note, studies evaluating the efficacy of docusate sodium monotherapy in alleviating opioid-induced constipation have yielded variable, if not disappointing, results (80, 81). Osmotic and stimulant laxatives, alone or in combination with a stool softener, may be used to treat drug-related constipation, including that caused by opioids (63, 82, 83). In general, the choice of agent is guided by clinician familiarity, and comparative studies are lacking (65, 82). Rectal formulations (suppositories/enemas) may be used in refractory constipation or when enteral administration is not an option. Neostigmine is a reversible acetylcholine esterase inhibitor that may increase colonic motility by stimulating parasympathetic and enteric neurons, although the clinical utility of neostigmine in treating motility disturbances in critically ill patients is unclear (55, 56). Neostigmine may be associated with adverse effects such as bradycardia and increased respiratory secretions (84). Prokinetic agents (metoclopramide, erythromycin) are generally considered ineffective in the management of drug-induced colonic hypomotility and constipation (85, 86).

The use of opioid receptor antagonists in the treatment of opioid-induced constipation and postoperative ileus is a topic of recent interest. Naloxone is a nonselective opioid receptor antagonist with limited oral bioavailability (approximately 3%) that may be effective in reversing opioid-induced bowel dysfunction (65). In a small, randomized, prospective study of critically ill patients receiving fentanyl, the use of oral naloxone (32 mg/day) reduced gastric reflux and the frequency of pneumonia without affecting the time to first defecation; fentanyl requirements were unaffected (87). Unfortunately, studies conducted using naloxone to treat opioid-related constipation in other settings have been disappointing. Of particular concern is the fact that, despite low bioavailability, naloxone readily crosses the blood–brain barrier and can precipitate withdrawal symptoms and inadequate analgesia (73). Therefore, insufficient data exist to recommend the routine use of naloxone in critically ill patients.

Methylnaltrexone and alvimopan are peripherally acting opioid receptor antagonists that do not cross the blood–brain barrier and therefore do not precipitate withdrawal or antagonize opioid analgesic effects (73). Methylnaltrexone is a μ-selective antagonist that partially attenuates the effects of opioids on intestinal motility, resulting in improved laxation and reduced time to defecation in patients experiencing opioid-related constipation (73, 88). Methylnaltrexone subcutaneous injection is approved by the Food and Drug Administration for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient (73, 89). Alvimopan is an orally administered opioid receptor antagonist with high μ-receptor affinity and low oral bioavailability (approximately 6%) that does not cross the blood–brain barrier (73).

Alvimopan appears to reverse opioid-induced GI effects and, in patients with postoperative ileus after bowel resection or total abdominal hysterectomy, it may decrease the time to tolerate solid food and/or time to first defecation or flatus (85). Of note, in a 12-month study of alvimopan in patients with chronic pain, a higher number of myocardial infarctions were reported in patients with alvimopan compared with placebo. Therefore, alvimopan should only be used for short-term use in hospitalized patients (85, 90). Alvimopan is approved for prevention/treatment of postoperative ileus after partial large or small bowel resection surgery with primary anastomosis (90).

Despite promising results with methylnaltrexone and alvimopan in other settings, few data exist regarding their use in critically ill patients, and their role in treating opioid-related constipation in this population remains to be determined. A multimodal approach to prevent opioid-induced constipation and postoperative ileus (early ambulation, early enteral intake, gum chewing, use of laparoscopy, restriction of intravenous fluids, early removal of nasogastric tubes, use of nonsteroidal anti-inflammatory drugs [NSAIDs], and use of thoracic epidural analgesia) in conjunction with pharmacologic therapy may offer benefit, although the success of each of these measures in critically ill patients is not fully known, and they may not be practical in some (91).

Drug-induced diarrhea

Pathophysiology

Diarrhea is a common complication of drug therapy, comprising up to 7% of all adverse drug events, and is reported with >700 drugs (92). As such, drug-induced diarrhea is a common adverse drug event in critically ill patients, although the precise incidence in this population is difficult to quantify. This is explained in part by the facts that diarrhea is extremely common in critically ill patients (with a reported incidence ranging from 2% to 95%), there are numerous potential causes for diarrhea in critically ill patients, and precise criteria for defining diarrhea in critically ill patients are rarely applied clinically (93). In general, diarrhea may be defined as frequent (≥3–5 times per day) and/or loose stools (200–300 grams/day or >250 mL/day) (93).

There are several potential mechanisms for drug-induced diarrhea, and many drugs cause diarrhea *via* multiple mechanisms. Although the classifications are somewhat arbitrary, common types of diarrhea based on mechanistic classification include osmotic, secretory, motor, exudative, malabsorptive, infectious/inflammatory, and others; each of these is briefly described (92–94).

Osmotic diarrhea is caused by the presence of poorly absorbed osmotically active solutes in the intestinal lumen, resulting in luminal fluid shifts, dilution, and poor mixing of bile and pancreatic juices (95). Examples of drugs that may cause osmotic diarrhea include magnesium salts, sodium phosphate preparations, poorly absorbed carbohydrates (e.g., mannitol, sorbitol, fructose present as sweeteners), and enteral nutritional products (94). The contribution of enteral nutrition to diarrhea is controversial and studies have not consistently identified enteral feeding as a risk factor for diarrhea in critically ill patients (93, 95–97). It may be more common with hypertonic formulations, aggressive infusion rates, and after prolonged bowel rest.

Secretory diarrhea is caused by an increase in intestinal ion secretion or inhibition of intestinal ion absorption, causing an excess of fluid and electrolytes in the intestinal lumen (94). Examples of drugs that can induce secretory diarrhea include digoxin, quinidine, propafenone, and theophylline (94). Accelerated intestinal motility can result in decreased intestinal contact time and altered absorp-

tive and secretory processes, resulting in diarrhea, and a number of drugs can induce diarrhea via this mechanism, including prokinetic agents and macrolide antibiotics (particularly erythromycin, via stimulation of intestinal motilin receptors) (64).

Drugs that result in changes in mucosal integrity and permeability can cause exudative diarrhea; this is a common mechanism of diarrhea induced by antineoplastic agents and can also be associated with NSAIDs (94, 98).

Drug-related malabsorption of fats, carbohydrates, and/or bile can also lead to diarrhea. Examples include octreotide (at high doses), highly active antiretroviral therapy, tetracycline, NSAIDs, and antineoplastic agents (64, 94).

Drug-induced infectious/inflammatory diarrhea is an arbitrary classification that includes microbial proliferation, pseudomembranous colitis, and histologic colitis. Microbial proliferation and/or pseudomembranous colitis attributable to antimicrobial agents are common causes of diarrhea in critically ill patients and most notably include *C. difficile*-associated diarrhea (*C. difficile*-associated diarrhea is not addressed in this review because it is addressed elsewhere in this supplement). Of note, a recent association between proton pump inhibitor therapy and *C. difficile*-associated diarrhea has been identified (99, 100). Diarrhea related to alterations in intestinal microflora in the absence of *C. difficile*-associated diarrhea is also common. Antibiotic-related diarrhea occurs, in part, because of changes in the intestinal microflora (resulting in secretory diarrhea because of alterations in carbohydrate metabolism) (92). In general, the risk of antibiotic associated diarrhea is higher with broad-spectrum agents (particularly those with antianaerobic activity and activity against Enterobacteriaceae), agents with high luminal concentrations (although oral/enteral administration is not necessarily a risk), longer duration of therapy, and use of multiple antibiotics (92). In studies of diarrhea in critically ill patients, antibiotics are frequently identified as a risk factor, and ceftriaxone therapy may be an independent risk factor for diarrhea (97). A number of other drugs can induce inflammatory diarrhea, pseudomembranous colitis, and histologic colitis (92, 94).

Clinical consequences of drug-induced diarrhea in critically ill patients can range from mild inconveniences to severe sequelae. Prolonged or severe diarrhea can result in malnutrition, hemodynamic instability, metabolic acidosis, and electrolyte disorders (93). Furthermore, in patients with fecal incontinence, diarrhea can result in wound contamination.

Common drug causes

A vast number of drugs can cause diarrhea, and a complete discussion of all of these is beyond the scope of this review. Table 4 lists drugs associated with diarrhea that are commonly used in the ICU and the potential mechanisms of diarrhea associated with them. As indicated, antibiotics likely are the most common cause of drug-induced diarrhea in critically ill patients. Antibiotic-related diarrhea accounts for up to 25% of all drug-induced diarrhea, and up to 40% of patients receiving antibiotics will experience diarrhea (92). The reported incidence of diarrhea associated with enteral feeding varies widely (ranging from 4% to up to 50%) (93, 95, 96).

Recommendations for prevention and management

In general, preventing drug-induced diarrhea involves limiting the use of drugs likely to cause diarrhea when possible. Although somewhat intuitive, avoiding unnecessary therapy with agents that may cause diarrhea can be an important preventive measure in the ICU (e.g., avoiding laxatives, stool softeners, and prokinetic agents when not required, avoiding liquid drug preparations with sweeteners [fructose, sorbitol, manni-

Table 4. Common causes of drug-induced diarrhea in critically ill patients[a]

Drug/Drug Class	Mechanism, If Known	Approximate Incidence, If Known[b]
Antibiotics (general)[c]	S, O,I	Variable, up to 50%
Ceftriaxone	I	Up to 50% (97, 150)
Clindamycin	S, I	15–30% (64, 151)
Fluoroquinolones	S, I	5–6% (152)
Macrolide antibiotics	M, I	>10% (64, 94)
Antineoplastics[d]	E, S	Regimen dependent (up to 90%) (153)
Artificial sweeteners (sorbitol, mannitol, fructose)	O	>10% (64)
Carbamazepine	S	– (94)
Cholinergic agents (neostigmine, physostigmine)	M	>10% (64)
Darbepoetin, erythropeotin	—	6–22% (154, 155)
Digoxin	S	8–30% (94)
Enteral feeding	O	4–50% (93, 95, 96)
Histamine-2 receptor antagonists	I	<2% (92)
Laxatives (osmotic, stimulant)	O, S	Frequent
Magnesium salts (antacids, etc.)	O	>10% (64)
Nonsteroidal anti-inflammatory drugs	S, E,I	3–9% (92, 98)
Octreotide	M	5–13% (92, 156)
Prokinetic drugs	M	10% (64)
Propranolol	—	– (157)
Proton pump inhibitors[e]	I	3–14% (64, 158)
Quinidine	I	8–30% (64, 92)
Selective serotonin reuptake inhibitors	M	16–19% (147, 159)
Theophylline	S	– (94,160)
Ticlopidine	S, I	>10% (92, 94)

O, osmotic; S, secretory; M, motor, E, exudative; I, infectious/inflammatory (including pseudomembraneous and histologic colitis).

[a]This is an abbreviated list of drugs that may be associated with drug-induced diarrhea in critically ill patients (drugs were selected for inclusion based on incidence of diarrhea and/or frequency of use in critically ill patients); given the vast number of drugs that may be associated with diarrhea, a list of all possible drug causes is beyond the scope of this review; [b]in most cases, incidence has been extrapolated from non-critically ill patient populations; [c]numerous antibiotics can cause diarrhea; in general the risk is greater with broad spectrum agents (particularly those with antianaerobic activity, and activity against enterobacteriacie), agents with high luminal concentrations (although oral/enteral administration is not necessarily a specific risk), longer duration of therapy, and use of multiple antibiotics. Antibiotics may also cause *Clostridium difficile* associated disease which is discussed elsewhere; [d]incidence varies substantially with individual agents/regimens (for a detailed overview of antineoplastic agent related diarrhea, see published guidelines on this topic) (161); [e]may also be associated with *C. difficile*-associated disease (99, 100, 162).

tol]). The primary means of preventing antibiotic-associated diarrhea is judicious use of antimicrobials, including avoiding unnecessary therapy, ensuring appropriate dose and duration of therapy, and using the most limited spectrum possible for a given infection (64). Considerable interest exists regarding the use of prebiotics and probiotics in the prevention of infectious complications and diarrhea (including antibiotic and enteral feeding-associated diarrhea) in critically ill patients (93, 101). Although some encouraging preliminary results suggest that probiotics may be of value in the prevention of antibiotic-induced diarrhea, further well-designed trials are warranted before this strategy should be routinely used (102, 103). Several strategies exist for the prevention of diarrhea related to enteral feeding. In general, use of isotonic formulations, gradual titration of infusion rates, and use of infusion pumps may decrease the incidence of diarrhea associated with enteral nutrition. Use of a formula containing fiber or supplementation with fiber (particularly water-soluble fiber) may also help prevent diarrhea related to enteral nutrition (104).

Management of drug-induced diarrhea in critically ill patients involves supportive care and, if possible, discontinuation of the causative agent. In many cases, diarrhea may be mild and self-limiting, so that minimal intervention is required (64). In the cases of severe or prolonged diarrhea, care should be taken to detect and avoid hypovolemia and electrolyte imbalances, and fluid/electrolyte losses should be replaced as necessary (95). Patients experiencing diarrhea while using antibiotics (particularly broad-spectrum antibiotics) should be evaluated for *C. difficile*-associated diarrhea (see drug-induced infectious complications section of this supplement). The use of prebiotics and probiotics has not been demonstrated consistently to effectively treat antibiotic-associated diarrhea (101, 105). In patients experiencing diarrhea thought to be related to enteral feeding, the formulation should be changed from a hypertonic to isotonic formula (if applicable), and the rate of feeding should be decreased (93). Antidiarrheal and antispasmodic agents (loperamide, diphenoxylate, atropine) should generally be reserved for patients in whom diarrhea is persistent or profuse. These agents should not be used in critically ill patients with *C. difficile*-associated diarrhea or other infectious forms of diarrhea (92).

Drug-induced GI bleeding

Pathophysiology

Drugs can contribute to GI bleeding in critically ill patients; however, the precise contribution of drugs to GI bleeding is difficult to discern, because many ICU patients have other risk factors for GI bleeding. Drug-related GI bleeding in critically ill patients is most often discussed in association with stress-related mucosal bleeding (SRMB). SRMB is a type of hemorrhagic gastritis, characterized by bleeding at multiple sites in the upper GI tract (particularly the corpus and fundus) (106, 107). The pathophysiology of SRMB is complex; it is thought to result from the interaction of a number of factors, including low-grade mucosal ischemia/hypoperfusion, reperfusion injury, gastric aggressive factors (acid and pepsin), decreased mucosal pH, and impaired mucosal integrity and protection (108–110). Endoscopic evidence of SRMB is present in up to 75% of patients within 24 hrs of ICU admission; however, the incidence of clinically important bleeding (i.e., SRMB that is considered life-threatening and/or associated with hemodynamic compromise or the need for transfusion) is thought to be far lower (approximately 6%, with a reported range of 0.1%–39%) (106, 111). The mortality associated with clinically important SRMB may be as high as 50% (112). The contribution of drugs to SRMB is controversial. The drug classes most frequently implicated as potentially contributing to SRMB are corticosteroids and anticoagulants. Corticosteroids may contribute to GI bleeding during critical illness by a combination of direct mucosal damage and impaired mucosal healing, may be related to corticosteroid-induced elevations in gastric acid and pepsin, and may reduce prostaglandin synthesis (113–116). The gastrointestinal tract is a common site for bleeding because of impaired homeostasis related to anticoagulation/antiplatelet effects of drugs and, as such, these agents may also contribute to GI bleeds in critically ill patients (117–119). Inhibition of cyclooxygenase, leading to inhibition of gastric prostaglandin synthesis, and impaired GI defense mechanisms represent additional mechanisms of drug-induced GI bleeding (120).

Common drug causes

Data are conflicting as to whether drugs are risk factors for SRMB. Some studies suggest that the use of high-dose corticosteroids (>200–250 mg/day hydrocortisone or equivalent) may be a risk for SRMB (111, 121). In contrast, in an evaluation of risk factors for clinically important SRMB in > 2200 critically ill patients conducted by Cook et al (112), only two risk factors (mechanical ventilation for at least 48 hrs and coagulopathy) were independently associated with SRMB, although high-dose corticosteroids were associated with SRMB in a univariate analysis. In a meta-analysis evaluating the use of corticosteroids for septic shock, there was no increase in GI bleeding associated with corticosteroid use (122). Thus, it is unclear to what extent high-dose corticosteroids may contribute to SRMB or other GI bleeding in critically ill patients, although they cannot be completely discounted as being without risk.

Similar to corticosteroids, anticoagulant therapy was associated with SRMB in the univariate analysis conducted in Cook's study, but it was not an independent risk in the multivariate analysis (112). Of note in this study, coagulopathy was independently associated with clinically important SRMB; however, the study did not indicate the extent to which coagulopathy may have been drug-related (112). Drotrecogin alfa (activated) may be associated with adverse bleeding events, including GI bleeding. In a large phase III study, the incidence of bleeding events in patients treated with drotrecogin alfa (activated) was 24.9%, compared to 17.7% in the placebo group; it was noted that the majority of the bleeding events were GI bleeds, although the precise number was not reported (123, 124). A detailed discussion of adverse events related to anticoagulants is found elsewhere in this supplement.

The contribution of NSAIDs, including aspirin (ASA), to GI bleeding in critically ill patients is not well-described, and these drugs have not been consistently implicated as causes of GI bleeding in critically ill patients (118, 125). Likewise, the exact contribution of antiplatelet agents to GI bleeding in critically ill patients is unknown. Despite the paucity of data implicating NSAIDs and antiplatelet agents as causes of GI bleeding in critically patients, this is a frequent complication related to the use of these drug classes in other settings, and problems related to platelet aggregation and bleeding are of concern in critically ill patients. Therefore, the potential for

NSAIDs and antiplatelet therapy (particularly dual antiplatelet therapy) to cause GI bleeding in critically ill patients should not be dismissed, and additional investigation is warranted.

Recommendations for prevention and management

There are no specific guidelines for prevention and management of drug-induced GI bleeding in critically ill patients. Histamine receptor-2 antagonists or proton pump inhibitors are appropriate prophylaxis against SRMB in patients with major risk factors (i.e., mechanical ventilation and coagulopathy), although they have not been specifically evaluated for the prevention of drug-induced GI bleeding in critically ill patients (118, 126, 127). Prevention of anticoagulant-related bleeding may be accomplished in part *via* appropriate dosing and monitoring to prevent over-anticoagulation, although patients may still experience bleeding during appropriate intensity anticoagulation. Guidelines have been published regarding prevention of GI bleeding related to NSAIDs and antiplatelet agents in noncritically ill patients (128, 129). In such patients, proton pump inhibitors are frequently used in the prevention of upper GI bleeding associated with NSAIDs and antiplatelet agents, although the value of this strategy in critically ill patients is not known. Of note, the use of proton pump inhibitors in patients receiving clopidogrel is controversial because of potential antagonism of the pharmacologic effects of clopidogrel (120, 128, 129). Management of drug-induced GI bleeding depends on the offending agent and the severity of the bleeding. In general, the offending agent should be discontinued whenever possible, particularly in severe bleeding. Management of drug-related GI bleeding in critically ill patients is similar to the management of GI bleeding of other etiologies and is beyond the scope of this review. Depending on the location and severity of the bleeding, treatment may include pharmacologic therapy (e.g., using enteral or intravenous proton pump inhibitors), endoscopic therapy, and/or surgical intervention, in addition to supportive care (130, 131). For some anticoagulant agents, reversal of anticoagulation may be warranted (reversal of anticoagulation is addressed elsewhere in this supplement).

Drug-induced acute pancreatitis

Pathophysiology

Drug-induced acute pancreatitis is a relatively uncommon cause of acute pancreatitis, representing approximately 0.1% to 2% of all cases of acute pancreatitis (although the incidence may be higher in specific populations; for example, children [approximately 15%] and HIV patients [up to 40%]) (132, 133). The actual incidence in critically ill patients is unknown but is probably low. Because of the uncommon nature of this adverse drug event, there is a paucity of data regarding specific mechanisms of drug-induced pancreatitis. Although highly speculative, potential mechanisms include pancreatic duct constriction, direct cytotoxic or metabolic effects, accumulation of a toxic metabolite or intermediate, hypersensitivity reactions, and arteriolar thrombosis (134, 135). Pharmacologic effects, including hypertriglyceridemia, hypercalcemia, local angioedema, immunosuppression, and hepatic involvement, may contribute (134, 135). In general, the pathophysiology of drug-induced acute pancreatitis is thought to be similar to that of other etiologies and involves inappropriate intrapancreatic conversion of trypsinogen to trypsin and subsequent autodigestion (132, 135); this results in the necrosis of pancreatic acini and islets, interstitial fatty necrosis, and necrotizing vasculitis (132). Release of pancreatic enzymes into the systemic circulation results in an inflammatory response; in severe cases, this may progress to the systemic inflammatory response syndrome and, ultimately, organ failure. The early stages of acute pancreatitis are characterized by inflammatory changes and fluid shifts, whereas later stages are characterized by infectious, septic, and necrotic complications (132, 135). Drug-induced pancreatitis is usually mild and self-limiting, although 5% to 15% of patients have a fulminant course that can be associated with significant morbidity and mortality (136). Diagnosis is typically based on presence of symptoms (abdominal pain, nausea, and vomiting) in the presence of elevated pancreatic enzymes (amalyase and lipase).

Common drug causes

Numerous drugs have been reported to cause acute pancreatitis, although many of these drugs are not routinely used in the ICU (133, 137, 138). Several classification systems have been devel-

Table 5. Potential causes of drug-induced acute pancreatitis in critically ill patients[a]

Drugs/drug classes with a likely association[b]			
Asparaginase	Azathioprine	Cimetidine	Corticosteroids
Corticotrophin	Cytarabine	Dapsone	Didanosine
Enalapril	Estrogens	Furosemide	Isoniazid
Mercaptopurine	Mesalamine	Methyldopa	Metronidazole
Omeprazole	Opiates	Pentamidine	Pravastatin
Salicylates	Simvastatin	Sulfasalazine	Sulfamethoxazole/trimethoprim
Sulindac	Tetracycline	Valproic acid	
Drugs/drug classes with a potential or questionable association[c]			
Acetaminophen	Amiodarone	Ampicillin	Benzapril
Carbamazepine	Captopril	Ceftriaxone	Clarithromycin
Cyclosporine	Diphenoxylate	Cisplatin	Endoscopic retrograde cholangiopancreatography media
Erythromycin	Fluvastatin	Gemfibrozil	Interferon/ribavirin
Interleukin-2	Ketoprofen	Lisinopril	Lovastatin
Metformin	Naproxen	Thiazide diuretics	Octreotide
Penicillin	Procainamide	Propofol	Propoxyphene
Ramipril	Ranitidine	Rifampin	

[a]This is an abbreviated list of drugs that may be associated with drug-induced acute pancreatitis in critically ill patients (drugs were selected for inclusion based on the likelihood of association with pancreatitis, and/or frequency of use in critically ill patients). Given the number of drugs that may be associated with drug-induced acute pancreatitis, a list of all possible drug causes is beyond the scope of this review. It should be noted that, in general, drug-induced acute pancreatitis is an uncommon event. Adapted from references 134, 136, 138, and 139; [b]arbitrary classification based on one or more of the following criteria: at least one case report with positive re-challenge and/or >10 reported cases and/or developed with exposure, disappeared after withdrawal, and recurred with re-challenge (135, 137, 138); [c]arbitrary classification based on suggestion of association with acute pancreatitis not meeting criteria for likely association.

oped to describe potential drug causes and their likelihood of association with pancreatitis (133, 137, 138). In general, most criteria define the likelihood of association based on the number of case reports, information regarding re-challenges, consistency of latency period, and exclusion of other causes (134, 137, 138). These classification systems should be viewed as a measure of strength of association rather than an indicator of the frequency of this event. Several drugs/drug classes commonly used in critically ill patients have been identified as having an association with pancreatitis, including valproic acid, opioids, corticosteroids, angiotensin-converting enzyme inhibitors, sulfamethoxazole/trimethoprim, furosemide, metronidazole, tetracycline, amiodarone, omeprazole, propofol, thiazide diuretics, and NSAIDs (134, 137, 138). A more extensive (but not comprehensive) list of drugs associated with drug-induced pancreatitis is presented in Table 5.

Recommendations for prevention and management

Given the idiosyncratic nature of drug-induced acute pancreatitis, preventive strategies do not apply. Drug-induced acute pancreatitis is managed in a similar manner to acute pancreatitis of other etiologies, and management is variable depending on disease severity. The suspected offending agent should be discontinued. A comprehensive overview of the management of acute pancreatitis is beyond the scope of this review. Briefly, management of mild acute pancreatitis primarily consists of supportive measurers, including fluid resuscitation, analgesia, antiemetics, and close monitoring to identify progression to organ dysfunction (132). Management of severe acute pancreatitis also involves general supportive care, including fluid resuscitation, analgesia, and nutrition support (132). Other interventions for severe acute pancreatitis include treatment of complications (e.g., treatment of infectious complications) and potential endoscopic and surgical interventions (132).

Summary

Numerous drugs used in critically ill patients cause adverse hepatic and GI complications. DIALF and other drug-induced GI complications, including GI hypomotility, constipation, diarrhea, GI bleeding, and pancreatitis, represent a diverse and challenging group of adverse drug-events encountered in the care of critically ill patients. Some of these events, including hypomotility, constipation, and diarrhea, occur frequently in critically ill patients and can substantially complicate the care of these patients. DIALF, drug-related GI bleeding, and drug-induced pancreatitis occur less frequently, can range in disease severity, and can be associated with substantial morbidity and mortality. Ultimately, critical care clinicians should be aware of common drug causes of DIALF, GI hypomotility, constipation, diarrhea, GI bleeding, and pancreatitis, and they should be familiar with the prevention and management of these conditions.

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