Chapter 5
Gastrointestinal Complications

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Abstract Gastrointestinal (GI) complications in the critically ill population are important to recognize and manage because of their implications not only on nutrition but also the endocrine and immunomodulatory functions of the GI system. An understanding of the anatomy and physiology of the peritoneal and retroperitoneal components of the GI tract is essential to appreciating their impact on morbidity and mortality for critical care patients. Addressing these issues often requires a multidisciplinary approach which includes nursing, pharmacy, nutrition and physician input in order to prevent, recognize and actively manage complications including malnutrition, infection and bleeding. Gastrointestinal physiology is sensitive to the hemodynamic shifts which are common in the critically ill patient. The following discussion will address the alterations in gastrointestinal physiology in the critically ill patient, followed by a review of GI complications in the intensive care unit using an anatomic-based approach. The pathophysiology, diagnosis and management of these complications will be discussed using an evidence-based approach.

Keywords Abdominal compartment syndrome • GI bleeding • Reflux • Feeding intolerance • Liver dysfunction • Diarrhea • Pneumoperitoneum

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Gastrointestinal (GI) complications in the critically ill population are important to recognize and manage because of their implications not only on nutrition, but also the endocrine and immunomodulatory functions of the GI system. The following discussion will address the alterations in gastrointestinal physiology in the critically ill patient, followed by a review of GI complications in the intensive care unit (ICU) using an anatomic approach. The pathophysiology, diagnosis and management of these complications will be discussed using an evidence-based approach.

Peritoneal-Based Complications

Intra-Abdominal Hypertension and Abdominal Compartment Syndrome

Intra-abdominal hypertension (IAH) is defined as a sustained intra-abdominal pressure greater than or equal to 12 mmHg, as measured by a trans-bladder measurement. Isolated clinical examination of the abdomen has been shown to be unreliable in diagnosing IAH and so serial objective measurement with a standardized trans-bladder approach is recommended in all patients with known risk factors for IAH (Table 5.1) [1]. There are several accepted techniques for measurement of trans-bladder pressure, with excellent inter-rater reliability when a single, standardized protocol is implemented within an institution [2] (see Fig. 5.1).

Diagnosis and management of IAH is important in preventing its progression to abdominal compartment syndrome (ACS) which is defined as a sustained intra-abdominal pressure greater than or equal to 20 mmHg with evidence of new end-organ dysfunction. The latter is thought to be a consequence of decreased abdominal perfusion pressure for delivery of blood flow to intra-abdominal organs. The incidence of ACS in the combined medical and surgical critically ill population is estimated at approximately 5–12 %, with a reported associated mortality of 40–100 % [2–4].

ACS is classified as primary or secondary. Primary ACS is a result of an injury or disease process that originates in the abdomen (e.g., abdominopelvic trauma, pancreatitis) whereas secondary ACS occurs when the inciting condition is not in the abdomen or pelvis (e.g., aggressive fluid resuscitation in sepsis and burns). Regardless of the classification, ACS has important physiologic consequences for not only the GI system, but the central nervous, cardiac, pulmonary and renal systems as well. Clinically, ACS often manifests as abdominal distension with worsening hemodynamic instability resulting from decreasing venous return and cardiac output, difficulty with ventilation secondary to decreasing respiratory system compliance (i.e., increasing peak airway pressures), and decreasing urine output. Management of ACS has been addressed comprehensively by the World Society for the ACS in their 2013 practice guidelines [1]. These recommendations can be categorized as noninvasive and invasive. Included in the noninvasive category is the use of sedation and analgesia, and if required as a temporizing measure, a trial of neuromuscular blockade with the objective of increasing abdominal wall compliance. Recommendations also include the use of nasogastric and rectal tubes for luminal decompression.

Table 5.1 Risk factors for intra-abdominal hypertension

Decreased abdominal wall compliance
Major burns
Abdominal surgery
Prone positioning
Increased abdominal volume
Intraluminal
Gastroparesis
Ileus
Bowel obstruction
Extraluminal
Pneumoperitoneum
Hemoperitoneum
Intra-abdominal fluid collections or abscess
Ascites
Tumor/mass
Pregnancy
Capillary leak and fluid resuscitation
Pancreatitis
Sepsis
Burns
Trauma
Hemorrhage and coagulopathy
Other
Obesity
Mechanical ventilation
PEEP > 10

Adapted from Kirkpatrick A, Roberts DJ, De Waele J, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med 2013; 39:1190

As discussed later in this chapter, in patients with an established diagnosis of colonic pseudo-obstruction (where mechanical obstruction has been ruled out), consideration may be given to the use of neostigmine to affect colonic decompression. Targeting a negative fluid balance is an important feature in the management of IAH/ACS, but this can be challenging in the setting of end-organ dysfunction that often includes renal failure. The impact of diuretics versus renal replacement therapy on outcome in this population has not been clearly established. Indeed, goal-directed fluid resuscitation, with the objective of minimizing excessive fluid administration, should be carried out. The benefit of colloid over crystalloid resuscitation in limiting progression of IAH to ACS has only been demonstrated in burn patients thus far [5].

Invasive interventions for ACS include percutaneous drainage of ascitic fluid, and the more definitive decompressive laparotomy. Drainage of ascitic fluid should be undertaken if technically feasible. Early surgical consultation should be considered even as the less invasive therapies are being instituted. This is particularly important in the setting of primary ACS as there may be underlying intra-abdominal pathology (e.g., intraperitoneal hemorrhage) that may need to be addressed surgically. Surgical intervention in this patient population involves substantial risks, with mortality for patients with ACS requiring surgical decompression reported as high as 50 % [6].

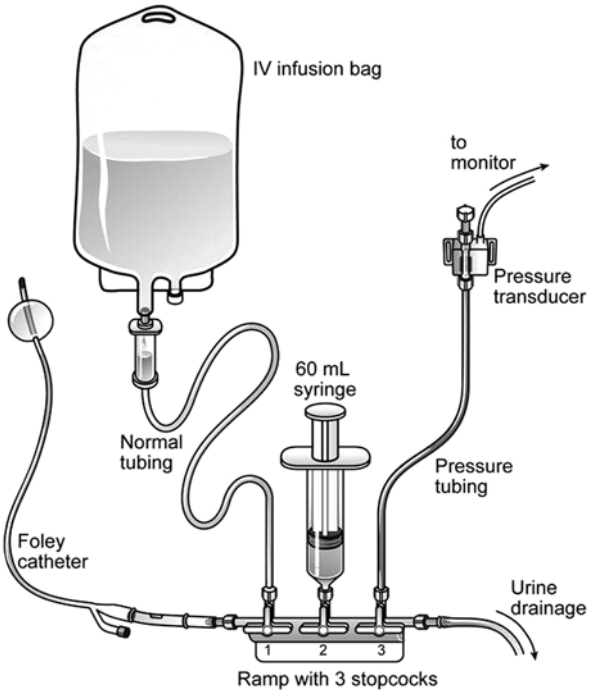

Fig. 5.1 Trans-bladder measurement of intra-abdominal pressure. Key features of trans-bladder pressure measurement: 1. Supine positioning, 2. Transducer placement, zeroed at the mid-axillary line, level of iliac crest, 3. Foley drainage tube clamped, with 25 mL sterile saline instilled into bladder. Measurement at end expiration, in absence of abdominal contractions. Reprinted from Desie N, Willems A, Da Iaet I, et al. Intra-abdominal pressure measurement using the FoleyManometer does not increase the risk for urinary tract infection in critically ill patients. Ann Intensive Care 2012; 2(Suppl 1):S10

Intra-abdominal pressure should be measured serially even after surgical decompression as patients can develop recurrent IAH even in the setting of an open abdomen. Other important considerations include careful management of fluid balance: a negative fluid balance facilitates subsequent abdominal closure, but this goal needs to be weighed against the ongoing fluid losses and redistribution (e.g., third space) that occur in the setting of an open abdomen. Other morbidity related to the open abdomen includes increased risk of infection, loss of abdominal domain, and the potential to develop enteric fistulae. Current recommendations target same-admission fascial closure when possible, as inability to complete primary closure is associated with increased morbidity and decreased quality of life in the post-ICU period [1].

Pneumoperitoneum

Pneumoperitoneum refers to extraluminal air within the peritoneal cavity. The most common cause of pneumoperitoneum is a perforated viscous, which is the case in almost 90 % of patients [7]. However, this radiological finding should be

interpreted in clinical context, which may be challenging in ICU patients as clinical parameters and physical examination are confounded by medications and underlying disease. Establishing a timely diagnosis for the etiology of pneumoperitoneum is essential, because if perforated viscous is suspected, surgical intervention must be prompt.

Thoracic causes of pneumoperitoneum in the ICU include mechanical ventilation causing rupture of alveoli with dissection of air along peribronchial and perivascular tissues of the lung into the mediastinum. It is felt that mediastinal air travels into the peritoneum via microdefects in the diaphragm, or into the retroperitoneum along the esophageal or aortic hiatus. From the retroperitoneum, air travels into the peritoneum along the planes of the intestinal mesentery or perinephric vasculature. Most case reports describe peak inspiratory pressures averaging around 40 cm H_2O, with most positive end expiratory pressures of 10 cm H_2O or less, but it is felt that respiratory system compliance is the more important determinant of who develops this unusual complication of mechanical ventilation [7].

Another described phenomenon is post-cardiopulmonary resuscitation pneumoperitoneum. This can be related to difficult intubation (e.g., aggressive bag-mask with a mechanism similar to that of mechanical ventilation), rib fracture with pneumothorax tracking into the abdomen, or esophageal and gastric perforation as a result of either difficult intubation or chest compressions. In this setting, decisions regarding further management are complex and establishing whether pneumoperitoneum is truly benign is difficult: the patient is often unstable from the underlying cause of arrest and transport of the patient for further imaging studies may be precarious. Determining whether pneumoperitoneum is contributing to patient instability is of utmost importance, because this may prompt surgical exploration without attempts to obtain imaging first.

An X-ray demonstrating pneumoperitoneum in the critically ill is most often a postoperative finding. Free air is seen on an erect chest X-ray more commonly with open procedures, but can also be seen following laparoscopic procedures. This finding should resolve over the course of 2–5 days [8]. If there is any concern regarding the clinical exam at any point in a postoperative course, surgical review should be requested regardless of imaging findings.

Intra-abdominal causes of pneumoperitoneum also include endoscopic interventions such as percutaneous endoscopic gastrostomy (PEG) tube placement. A small amount of post-procedural free air may be encountered, and is related to insufflation of air during endoscopy as the tube is placed percutaneously through the anterior gastric wall. If clinical examination of the abdomen and hemodynamic parameters are stable with these imaging findings, intervention is not required. Serial exam and repeat X-ray can be considered. One of the complications of PEG placement is inadvertent injury to small bowel or colon, and any clinical concern should prompt imaging in the form of CT abdomen with water soluble contrast administered via the PEG. Progressive symptoms on clinical exam or suspicion of injury to other viscera on imaging should prompt surgical consultation.

Esophagus

Esophagitis

Esophageal mucosal injury in the ICU patient has important clinical implications, namely bleeding and infection. The mechanism of injury in this population is generally either mechanical or reflux-induced, with a small subset caused by infectious precipitants. Nasogastric tubes can cause mucosal injury via direct irritation, and perhaps more importantly, by the mechanical interference with normal motility and lower esophageal function. This results in increased rates of gastroesophageal reflux (GER).

Infectious etiology of esophagitis is a consideration in the ICU patient, who may be immunocompromised on the basis of underlying medical conditions or secondary to the relative immunosuppression from critical illness. Infectious esophagitis is a rare cause of symptomatic esophagitis and is usually seen in immunocompromised hosts, such as patients with human immunodeficiency virus (HIV) infection, hematologic malignancy, chemotherapy, or organ transplant. Risk factors for infectious esophagitis in the immunocompetent host include underlying conditions such as diabetes, adrenal insufficiency and alcohol abuse. The broad categories of infectious organisms include fungal (*Candida*, *Aspergillus*), viral (herpes simplex virus [HSV], cytolomegavirus [CMV]), and less commonly bacterial (*Staphylococcous*, *Streptococcus* species). Although some organisms have a typical appearance on endoscopy, histopathologic diagnosis is ideal for directing further management. The most commonly implicated infectious agent is fungal, specifically *Candida albicans* [9]. Systemic treatment is required for this condition, and usually consists of an azole for 14–21 days. Echinocandins and amphoterecin B are alternative treatment options if the patient fails to respond to treatment with an azole. Diagnosis of other fungal infections such as *Aspergillus* or *Blastomycoces* should prompt consideration of a primary mediastinal or pulmonary infectious source [9].

Independent of nasogastric tube placement, GER and the related duodenogastroesophageal reflux (DGER) (i.e., bile reflux) are important risk factors for the development of esophagitis in the critically ill population. These disorders are described in further detail in the sections below.

The diagnosis of esophagitis in the ICU is often made at the time of endoscopy, usually precipitated by bleeding complications. This is one of the most common findings at the time of upper endoscopy performed for upper gastrointestinal bleeding in the ICU [10, 11]. Treatment of esophagitis is generally supportive, with the majority of bleeding episodes being self-limited. More specific therapy is instituted only if the precipitant of esophagitis is apparent on direct visualization. If the precipitant is determined to be nasogastric tube placement, the tube is removed. Brushings or biopsies may be taken to rule out or demonstrate suspected infectious etiology based on appearance (e.g., candidiasis, CMV). Further treatment may be directed by histopathological findings. If no mechanical or obvious infectious precipitant is demonstrated at the time of endoscopy, patients are generally treated for reflux esophagitis including acid suppression and promotility agents. Tissue manipulation for diagnostic purposes

is avoided in the setting of active bleeding. In general, severe hemorrhagic esophagitis is not amenable to endoscopic treatment because it tends to be diffuse. If, however, areas of focal, active hemorrhage are identified at the time of endoscopy they may be treated with epinephrine injection or topical ablative therapy.

Gastroesophageal Reflux

Retrograde movement of gastric secretions into the esophagus is a well-described problem in the critically ill, with important consequences including esophagitis and pulmonary aspiration. The mechanisms of GER all center on anatomic and physiologic lower esophageal sphincter (LES) dysfunction. Important pathophysiologic features include:

1. Transient Lower Esophageal Sphincter Relaxations (TLERs)
   TLERs are the most common cause of reflux in both normal subjects and GER patients with normal LES tone. LES relaxation occurs in two general scenarios: those in coordination with swallowing and peristalsis, and TLERs which are independent of swallowing and esophageal peristalsis but associated with relaxation of the diaphragm, an important part of the normal anti-reflux mechanism. TLERs are most frequent in the post-prandial period and are thought to be stimulated by gastric distension. Obesity is also associated with increased TLER frequency. The problem may be potentiated by the diaphragmatic dysfunction associated with these more frequent TLERs.
2. Diaphragmatic Hiatus Dysfunction
   Contraction of the diaphragm during inspiration increases LES tone by acting as an "external sphincter" at the level of the esophageal hiatus, and is therefore a component of the body's normal anti-reflux mechanism. This external sphincter relaxes in the setting of esophageal distension and both swallow-induced and transient LES relaxations. This mechanism is pathologically disrupted by the misalignment of crus and LES in the setting of hiatal hernia.
3. LES Hypotension
   While TLERs are the most frequent mechanism for reflux in the average patient population, in the critically ill impaired LES tone is the most important factor [12]. The normal LES is tonically contracted smooth muscle. Relative hypotension of the LES results in GER by both stress and free reflux. Stress reflux occurs when a sudden increase in intra-abdominal pressure overcomes the resting tone of the LES. In patients with lower resting tone of the LES, episodes of stress reflux become increasingly frequent. Therefore, episodes of increased abdominal pressure, (e.g., coughing during suctioning of the intubated patient), are more likely to result in GER. In contrast, free reflux is defined as a drop in esophageal pH without any detected change in LES resting tone, but occurs only in the setting of LES pressures less than half of normal (0–4 versus 10–30 mmHg) [12]. In addition to being common in critically ill patients, LES hypotension is found with increased frequency in diabetes, scleroderma, and pregnancy. Medications, many of which are used in the ICU, also can contribute to decreased LES tone, including beta-agonists, morphine, diazepam, and calcium channel blockers.

There is a substantial body of work that establishes the damage to esophageal mucosa that results from sustained exposure to an acidic milieu (e.g., pH < 4.0). At the cellular level, hydrogen ion diffusion into the mucosal cells and the subsequent acidity results in cell necrosis. This effect is potentiated by pepsin, secreted by the gastric chief cells as a zymogen which causes direct damage to the mucosal barrier, making it even more permeable to hydrogen ions. The mainstay of management of esophagitis secondary to esophageal reflux is acid suppression with proton pump inhibitors (PPIs). PPIs have been demonstrated to be more effective in healing esophagitis than H2 receptor antagonists [11, 13]. The role of prokinetic agents such as metoclopramide in this setting, however, remains unclear.

Duodenogastroesophageal Reflux

The term bile reflux has been used interchangeably with DGER in the past, but this is a misnomer because in addition to bile, duodenal secretions include hormones (e.g., secretin, cholecystokinin) as well as bicarbonate and digestive enzymes secreted by the pancreas. DGER is seen most frequently in the post-gastric resection population, where the mechanical barrier of the gastric pylorus is removed en bloc with the surgical specimen. However, there is some evidence to suggest that DGER occurs in the non-operative population as well, but a pure alkaline reflux is rare [12, 14]. In the last two decades the concept of DGER causing an "alkaline esophagitis" has been modified to suggest that combination acidic/alkaline reflux may result in higher rates of severe erosive esophagitis, strictures, and Barrett's esophagus. From a critical care perspective, the details of potential bile acid-mediated esophageal injury are less relevant in terms of acute reflux complications such as esophagitis: acid suppression therapy is the mainstay of treatment, because it is the acidic pH that causes most of the *acute* mucosal injury. The role of prokinetics for DGER in critically ill patients remains unclear, but there is some evidence to suggest prokinetics may have a role in patients who have previously undergone gastric resection [15]. However, the use of prokinetic agents in this setting needs to be weighed against the potential for adverse drug interactions and complications.

Stomach

Stress Ulcers

Most critically ill patients (75–100 %) have endoscopically detectable mucosal erosions within 24 h of ICU admission [10]. Stress ulcers fall into a broader category of what is referred to as stress-related mucosal disease (SRMD). This set of conditions represents an acute erosive gastritis ranging from superficial erosions to deep

ulcerations penetrating the submucosa. Anatomically, most SRMD is found in the fundus and body of the stomach, although it can also be seen in the distal esophagus and duodenum. The two most important risk factors for this disease are mechanical ventilation greater than 48 h and coagulopathy [16]. The most significant implications are perforation (a rare event, occurring in less than 1 % of SRMD in ICU patients), and most commonly, bleeding. A recurring concept in the literature discussing this topic is the term "clinically-important bleeding", which has been defined as bleeding causing hemodynamic instability or requiring transfusion. Clinically-important bleeding is associated with increased morbidity, mortality, and length of ICU stay [17]. However, it is important to note that while there is a strong association between clinically-significant bleeding in SRMD and subsequent mortality, it is more a marker for severity of illness, with patients dying from their underlying disease, and not from GI bleeding per se [11, 17].

The pathophysiology of SRMD is related to an interaction between the acidic pH of gastric contents and impaired gastric barrier function secondary to mucosal ischemia and direct toxic insults from factors such as pepsin [18]. Most ICU patients with SRMD have normal gastric pH of around 2. Although gastric acid is part of the pathophysiology of SRMD, the only critical care populations that have demonstrated acid hypersecretion are patients with head trauma, traumatic spinal cord injury, or burns. The normal barrier function of gastric mucosa to hydrogen ions is affected by the glycoprotein layer which traps bicarbonate and allows for neutralization of intraluminal acid. This barrier is disrupted by two main mechanisms: mucosal ischemia likely secondary to splanchnic hypoperfusion, and direct toxins such as bile acids and pepsin, each of which compromises the ability of the mucosa to neutralize acid resulting in enhanced tissue necrosis.

The mainstay of treatment of SRMD is prophylaxis in the form of acid suppression. Guidelines from the American Society of Health-System Pharmacists were last published in 1998, with an update to be published in 2014 [19]. These guidelines were based on studies comparing rates of SRMD in patients with prophylaxis versus no prophylaxis, using clinically-important GI bleeding as an endpoint. Patients who warrant stress ulcer prophylaxis include the following:

1. Mechanical ventilation >48 h
2. Coagulopathy (platelets <50, INR >1.5)
3. History of ulcers or bleeding in the past 12 months
4. Patients at risk for hyperacidity (burn, traumatic brain injury, spinal cord injury)
5. Patients with two or more of the following "minor" risk factors: sepsis, ICU stay >1 week, steroid therapy, occult GI bleeding for at least 6 days

The main classes of medications used for stress ulcer prophylaxis in ICU patients include histamine-2 receptor antagonists (H2RAs) and PPIs. H2RAs inhibit histamine-stimulated acid secretion by blocking receptors on the parietal cells of the stomach. Considerations in the use of H2RAs include potential for tolerance after short duration of therapy and possible drug interaction secondary to interference with cytochrome P450 enzymes. Dose adjustments are also required in patients with renal dysfunction. PPIs inhibit the hydrogen–potassium ATPase enzyme at the

parietal cell surface, thereby preventing H+ transport out of the cell. This inhibition of acid transport takes place irrespective of the cell stimulant (e.g., histamine, gastrin). In general, PPIs are well tolerated. Meta-analyses suggest that PPIs are associated with less bleeding than H2 blockers without affecting rates of nosocomial pneumonia or mortality [20]. In February 2012 the American Food and Drug Administration issued a warning that PPI use may predispose to Clotstridium difficile infection (CDI). Two meta-analyses published in 2012 attempted to address this association, but were based on a heterogenous group of observational studies that did not define the length of exposure or comorbidities. At this time a causal relationship cannot be established, but clinicians should be aware of the possible association and consider this risk in the context of comborbidities and concurrent risk factors for CDI including antibiotic use [21, 22].

Concern that acid suppression therapy may be associated with increased rates of nosocomial pneumonia has not been demonstrated conclusively. The suggested mechanism for this potential association is bacterial colonization secondary to a less acidic milieu in the stomach. Consideration of this risk may be more applicable to patients who do not meet the criteria for stress ulcer prophylaxis as outlined above but are being considered for prophylaxis because of clinical context. The role of enteral nutrition in stress ulcer prophylaxis is not well delineated. It is likely that enteral nutrition does have a protective effect on SRMD, but there is no good evidence to suggest feeding alone is sufficient in the populations warranting stress ulcer prophylaxis. Cost is another consideration in choosing appropriate agents. Enteral PPIs are a reasonable first choice for prophylaxis in critically ill patients who tolerate enteral intake.

Management of the patient with clinically-significant upper GI bleeding in the critical care setting should involve standard resuscitation interventions including fluids, transfusions as indicated, correcting coagulopathy, and intravenous infusion of PPIs until endoscopy can be performed to confirm the diagnosis and control the bleeding source. Further treatments are determined by findings at the time of endoscopy. There is no compelling evidence for the routine use of octreotide in non-variceal upper GI bleeding.

Dysmotility and Feeding Intolerance

Delayed gastric emptying (DGE) occurs frequently in critically ill populations and is associated with impaired feeding tolerance. Consequences of DGE therefore include malnutrition and increased risk of aspiration pneumonia. For a population already under catabolic stress and with systemic inflammatory activation, the implications of malnutrition include immune dysfunction and an increased risk of infections, weakened skeletal and respiratory muscles and ventilatory drive, and GI dysfunction including GER and esophagitis. The pathophysiologic mechanisms involved in DGE are complex and an area of ongoing study. The main mechanisms associated with DGE in the ICU population are thought to be as follows:

1. Autonomic Nerve Dysfunction
   Parasympathetic supply to the stomach is mediated by the vagus nerve. Dysfunction of the vagal nerve interferes with normal fundic relaxation in response to distension; it also impairs pyloric relaxation. Medical issues including diabetes, Parkinson's disease, and multiple sclerosis are well-described risk factors for gastroparesis, likely secondary to their effect on the vagal nerve. Anticholinergic medications (e.g., atropine, diphenhydramine) are implicated in DGE through this mechanism.
2. Enteric Nerve Dysfunction
   The interstitial cells of Cajal (ICC) are considered the "pacemaker cells" of the gut, and are responsible for the slow wave electrical activity causing phasic contractions of smooth muscle. Histopathologic studies of DGE demonstrate qualitative (dysmorphic) or quantitative loss of ICC, as well as a loss of expression of neuronal nitric oxide synthase (nNOS) [23]. Nitric oxide is synthesized by nNOS, and plays an important role in smooth muscle relaxation. nNOS is expressed in enteric nerves and functions to control tone of the LES, pylorus and the peristaltic reflex of the small intestine. It is possible that the upregulation of the feedback loop that normally guides gastric emptying (through inhibition of antral motility and increased pyloric tone seen in response to nutrient exposure) may be mediated by enteric nerve dysfunction. Loss of ICC is seen in models of diabetes and hyperglycemia [23, 24]. Opioids, a class of medications frequently used in the ICU, are thought to mediate their dysmotile effects via endogenous opioid receptors of the enteric nervous system.
3. Smooth Muscle Cells
   The role of smooth muscle cells in the development of DGE is clear as the endpoint of the nerve dysfunction discussed above. Interestingly, loss of ICC is also associated with smooth muscle atrophy, possibly related to decreased expression of stem cell factors.

The development of dysmotility in the critical care patient is multifactorial and influenced by a combination of the patients' baseline medical issues with the superimposed electrolyte abnormalities, hemodynamic shifts and medications associated with critical illness.

Clinical evidence of DGE has typically been defined by vomiting/regurgitation, and what was thought to be a preceding factor, high gastric residual volume (GRV). The measurement of GRV is neither standardized nor validated, but nevertheless it is widely used in the ICU setting. The concern with vomiting, regurgitation, and high GRV is the perceived increased risk of aspiration pneumonia. Interestingly, a recent randomized controlled trial (RCT) evaluating mechanically ventilated patients receiving early enteral nutrition demonstrated no significant differences in the rates of ventilator-associated pneumonia when comparing routine measurement of GRV versus no measurement (17 versus 16 %) [25]. Moreover, there were no significant differences in other ICU-acquired infections, mechanical ventilation duration, ICU length of stay, or mortality rates between groups. In fact, many trials have implicated measurement of so-called "high" GRV in severe underfeeding in the ICU population because the common practice once high GRV is measured is to

hold enteral feeding [26]. Indeed, in the recent RCT by Reignier and colleagues, the proportion of patients receiving 100 % of their caloric goal was significantly higher in the group without GRV measurements (odds ratio 1.77; 90 % confidence interval 1.25–2.51) [25]. If ongoing measurement continues while further research is done, enteral feeding should only be held if single GRV measurement is 250–500 mL or a cumulative 1,000 mL is measured in 24 h of feeding. In these cases, after ruling out a distal obstruction, consideration may be given to adding prokinetic agents (e.g., metoclopramide, domperidone, or erythromycin).

The prokinetic activity of domperidone and metoclopramide is mediated through their antidopaminergic activity, and in the case of metoclopramide, enhanced cholinergic transmission (via the 5-HT_4 receptor) effects. The antidopaminergic effects include increased LES pressure, antral contractility, and antroduodenal coordination. Erythromycin enhances gastric emptying by binding to the motilin receptors in the antrum and duodenum.

There is reasonable evidence for postpyloric feeding for patients who demonstrate feeding intolerance in the form of recurrent aspiration, GER, and DGE. The reduction in rates of nosocomial pneumonia has not, however, been consistently demonstrated in patients who do not exhibit symptoms of feeding intolerance. In the 2013 Canadian Clinical Practice Guidelines, it is recommended that where post pyloric tube placement is feasible, routine small bowel feeding should be implemented. This is predicated on the likelihood that post pyloric feeding decreases rates of aspiration pneumonia, and studies based on previous guidelines demonstrate patients receive a greater percentage of their calculated caloric requirements [27]. Studies comparing enteral and parenteral feeding do not show a difference in terms of mortality, but do suggest a lower risk of infection with enteral feeding. A randomized multicenter trial published in 2011 demonstrated a lower rate of infectious complications without a significant difference in mortality in patients for whom parenteral nutrition was initiated after 8 days compared to within 48 h of ICU admission [28]. These results suggest that there may be an 8-day window for patients admitted to the ICU to be stabilized and optimized to attempt enteral feeding if appropriate. These studies do not address patients who are malnourished at the time of ICU admission.

In terms of management of nutrition in critically ill patients, recommendations can be summarized as follows:

1. Early enteral feeding (within 24–48 h of admission), when there are no contraindications.
2. Withholding of feeds only in extreme hemodynamic instability and suspicion of associated bowel ischemia, or clinical suspicion of other abdominal surgical pathology.
3. Routine use of post pyloric feeding where technically feasible.
4. Addition of prokinetics (preferred agent: metoclopramide) in the setting of feeding intolerance after ruling out distal obstruction, with a threshold for GRV of 250–500 mL to guide decisions regarding feeding tolerance.
5. Consideration of parenteral nutrition after 7 days of inadequate enteral nutrition intake.

Hepatobiliary

Acute Acalculous Cholecystitis

Acute acalculous cholecystitis is acute inflammation of the gallbladder in the absence of cholelithiasis. The incidence in the ICU population is between 0.5 and 3 % [29]. Although the pathogenesis of this disease is multifactorial, the common underlying pathway involves ischemia of the gallbladder wall and bile stasis. Risk factors for acute acalculous cholecystitis include mechanical ventilation greater than 72 h, systemic inflammatory response syndrome, and hemodynamic shifts that result in decreased splanchnic blood flow, including shock and use of vasopressors. Other important risk factors include prolonged fasting, dehydration, and total parenteral nutrition (TPN) (Table 5.2).

Clinical manifestations of acalculous cholecystitis are often non-specific in the critically ill patient, with inconsistent physical exam and laboratory findings. Diagnosis of this clinical entity relies on imaging studies, primarily that of ultrasound which is the modality of choice in initial imaging of the biliary system. Computed tomography (CT) is also useful in the diagnostic work-up of signs and symptoms suggestive of acalculous cholecystitis as it can help to rule out other intra-abdominal pathology.

Management of suspected acute acalculous cholecystitis should include blood cultures followed by prompt initiation of broad-spectrum antibiotics targeting enteric flora including gram-negative bacteria, anaerobes, and *Enterococcus* species. Surgical consultation is also warranted. The definitive management of cholecystitis is cholecystectomy, which may not be feasible or appropriate in unstable critically ill patients. In these cases consideration may be given to percutaneous drainage with a cholecystostomy tube. Risks of the procedure include tube dislodgement with bile peritonitis, hemobilia, and bowel injury. Patient selection for a less invasive approach (i.e., antibiotics with or without cholecystostomy tube) is very important. Patients with diabetes and immunosuppression, for example, have a higher rate of serious

Table 5.2 Risk factors for acute acalculous cholecstitis

Conditions promoting bile stasis
Fasting
TPN
Ileus
Conditions promoting gallbladder ischemia
Mechanical ventilation
Shock
Burn
Sepsis
Trauma
Vascular disease
Other
Immunodeficiency
Chronic medical illness: diabetes, hypertension, obesity

complications from cholecystitis including gangrene or perforation. Clinical improvement should be expected within 24 h of drainage [29]. If no clinical improvement is seen within this time frame, surgical intervention is indicated.

Liver Dysfunction

Liver dysfunction is a frequent finding in the critically ill, typically occurring initially with abnormal laboratory values. Patterns of abnormal liver tests must be interpreted in the clinical context of the patient, and in the ICU population there are generally two patterns of dysfunction: cholestasis and ischemic hepatopathy ("shock liver"). Each of these entities has important implications in the management of ICU patients because of the hematologic, metabolic, and immunologic functions of this organ.

Ischemic Hepatopathy

Hepatic blood supply originates from a combination of the portal vein, with inflow from the superior mesenteric and splenic veins, and the hepatic artery, typically branching from the celiac axis. The hepatic artery response is the homeostatic mechanism that maintains blood flow to the liver, with an inverse change of flow as a response to portal venous flow. An important anatomic distinction of the hepatic artery is that it forms the sole blood supply of the bile ducts of the liver. At baseline the liver receives approximately 25 % of cardiac output, but this is significantly decreased at times of systemic stress as the body preferentially delivers blood flow to the cerebral and cardiac circulation. This can lead to hepatocellular hypoxia, which along with reperfusion injury results in hepatic injury. Passive venous congestion is another contributory factor in the development of ischemic hepatitis, and is most often seen in the setting of right-sided heart failure. Ischemic hepatopathy, then, refers to a diffuse pattern of injury resulting from decreased blood flow to the liver, passive venous congestion, or hypoxemia from a different primary source (e.g., lung injury).

Clinical diagnosis of this disorder is based primarily on abnormal liver tests that usually manifest within 24–48 h of an ischemic insult. The "hepatocellular" abnormalities include aminotransferase levels greater than 25 times the upper limit of normal with an early and precipitous rise in lactate, but only minimal evidence of synthetic dysfunction as measured by international normalized ratio (INR) and partial prothromboplastin time (PTT). The aminotransferases usually return to normal within 7–10 days of stabilized hemodynamics [30]. Hyperbilirubinemia may be present but rarely exceeds three to four times the upper limit of normal, and is generally the last abnormality to resolve. It is important to exclude an anatomic vascular cause of compromised hepatic flow by Doppler ultrasound of the liver. Depending on the clinical context, additional investigations may be required to address the differential diagnosis of a hepatocellular pattern of dysfunction including viral infection (e.g., hepatitis B or C), drug-induced toxicity (e.g., acetaminophen), or autoimmune hepatitis.

Management of ischemic hepatopathy focuses on restoring adequate cardiac output and addressing the underlying etiology of hemodynamic instability. Ischemic hepatopathy is typically self-limited (presuming the underlying insult is reversed), and morbidity and mortality are usually related to underlying systemic disease. Progression to fulminant hepatic failure is rare (2–5 %), with the majority of cases of fulminant hepatic failure having underlying baseline congestive or cirrhotic disease [30].

Cholestasis

Cholestasis is the most frequent hepatic abnormality noted in the critically ill, found in up to 40 % of ICU patients [30]. The implications of cholestasis include bacterial infections, hypotension secondary to the vasodilatory effects of bile acids, alterations of glucose and lipid metabolism, and renal toxicity leading to acute tubular necrosis. This diagnosis can be approached from an anatomic and physiologic perspective: prehepatic (e.g., hemolysis, hematoma resorption), hepatic (e.g., autoimmune and medication causes), and extrahepatic (e.g., biliary obstruction from gallstone, pancreatic head mass). In the ICU setting the most common causes of cholestasis fall into the intrahepatic category—shock, sepsis, medications, and parenteral nutrition—all have hepatotoxic effects leading to impairment in bile production and transport.

Shock and mechanisms of hepatocellular damage were discussed in the previous section. Sepsis has been implicated in impaired bile acid transport at a cellular level, likely mediated by cytokines. Gram-negative sepsis has been specifically identified, with a mechanism possibly related to endotoxin release. Several forms of cholestatic liver injury can be caused by medications, with variable mechanism and presentation (Table 5.3). The target of injury can vary from a mixed hepatocellular cholestatic injury to impairment of canalicular bile flow resulting in pure intrahepatic cholestasis [31]. The mechanism of TPN-related cholestasis is likely multifactorial including bacterial overgrowth secondary to gut hypomotility, leading to endotoxin absorption that impairs bile acid transport. Another contributory factor is excess nutrient delivery with accumulation of trigylcerides in hepatocytes mediated by upregulation of insulin due to relative insulin resistance in critical illness [32].

Cholestasis is defined by hyperbilirubinemia and elevated alkaline phosphatase (typically greater than three times the upper limit of normal) with only mild associated elevation in aminotransferases. INR may be elevated because of the effect on vitamin K-dependent coagulation factors. The first step in management of ICU cholestasis is to address the underlying mechanism of injury. Restoring hemodynamic stability and treating underlying sepsis is critical. When drug-induced cholestasis is suspected, a careful review of any new medications in the past 3 months should be carried out, with removal of any potentially offending agents (Table 5.3). Addressing TPN-induced cholestasis requires adjustment of composition, assessment of energy balance, and consideration of metronidazole for bacterial overgrowth, which should be done in consultation with a dietician and gastroenterologist.

Table 5.3 Medications frequently implicated in cholestasis

Antimicrobials
Amoxicillin–clavulanate
Nafcillin
Trimethoprim–sulfamethoxazole
Erythromycin
Rifampin
Ketoconazole
Cardiac
Captopril
Amiodarone
Antiretrovirals
Nevirapine
Efavirenz
Endocrine
Ezetimibe
Rosiglitazone
Troglitazone
Estrogens
Anabolic steroids
Immunosuppression
Azathioprine
Infliximab
Other
Chlorpromazine
Carbamazepine

Intestinal

Hemorrhage

The majority of acute gastrointestinal hemorrhage originates in the foregut: esophagus, stomach and duodenum.

Upper GI Bleeding

The most common cause of acute upper GI bleeding (AUGIB) in hospitalized patients is peptic ulcer disease. In general, an approach to diagnosis and management of upper GI bleeding (UGIB) divides this problem into variceal hemorrhage versus non-variceal bleeding, including peptic ulcer disease and stress-related mucosal hemorrhage. Although GI bleeding is a frequently encountered problem in the ICU, bleeding as a complication of ICU stay has become less common in an era of prophylactic acid suppression therapy, because the majority of bleeding seen in this context is secondary to SRMD. Since this topic has been addressed in a previous section, the following section will focus on the management of patients presenting with AUGIB.

Regardless of etiology, the first step in management of bleeding involves hemodynamic monitoring and adequate resuscitation with fluids and blood products as clinically indicated. A nasogastric tube can be placed to confirm an upper GI source of bleeding if it is clinically unclear; however, lack of bloody return does not reliably exclude upper GI bleeding. The tube can also be used to perform lavage to prepare the foregut for visualization during endoscopy, which should be performed within 24 h of the onset of bleeding. Erythromycin can also be used to attempt to clear the stomach of blood to improve visualization. Transfusion targets in the setting of AUGIB have been studied, and a recent RCT supports a relatively restrictive transfusion strategy (targeting a hemoglobin threshold of 7 g/dL compared to a more liberal strategy targeting a hemoglobin threshold of 9 g/dL) in patients with AUGIB. The results of this study suggest that a restrictive strategy is associated with decreased rates of rebleeding and mortality. This study excluded patients who were hemodynamically unstable with massive hemorrhage, and also noted that patients with unstable coronary artery disease were exceptions to this guideline [33]. Coagulopathy should also be corrected with appropriate blood products or replacement therapy.

The management of suspected variceal bleeding prior to endoscopy requires the addition of a somatostatin analogue such as octreotide, to affect splanchnic vasoconstriction and decrease portal pressures, to a PPI infusion. The PPI infusion is provided because patients with cirrhosis are also at high risk for peptic ulcer-related bleeding. Cirrhotics who present with UGIB should also be treated with propylactic third-generation cephalosporins or fluoroquinolones as up to 40 % develop a bacterial infection within one week of AUGIB, which is an independent risk factor for rebleeding and mortality [11]. Of note, in patients with cirrhosis and GI bleeding, platelet targets may be adjusted from the standard target of 50 with active bleeding, to a slightly lower target of 30, since thrombocytopenia is seen commonly in cirrhotics and does not necessarily convey risk of bleeding. Many cases of variceal bleeding will stabilize with vasoactive treatment alone, but endoscopy is still required for definitive management. Placement of an esophageal/gastric balloon (i.e., Sengstaken–Blakemore tube, Linton–Nachlas tube) can be considered in cases of massive UGIB that is inadequately controlled with endoscopic therapy. This should be considered a bridge to more definitive management of portal hypertension with variceal bleeding, such as transjugular intrahepatic portosystemic shunt (TIPS).

The management of non-variceal bleeding should involve the same initial steps of monitoring, supportive resuscitation with fluids and blood products to appropriate targets, and nasogastric (NG) tube placement. In this case, intravenous (IV) PPI infusion should be started pending endoscopy. The continuation of PPI infusion post-endoscopy is determined by the procedural findings: the Forrest classification is one system that designates endoscopic findings as high and low risk for rebleeding. Patients who are deemed to be a high risk of rebleeding (Forrest Ia + b, IIa + b) should be continued on PPI infusion for 72 h because this has been shown to decrease rates of rebleeding, surgery, and mortality [11]. In general, screening for *Helicobacter pylori* in the critically ill population is not necessary because there is no rebleeding prophylaxis advantage to treating *H. pylori* in the emergency setting. The long-term risk of rebleeding may be improved with *H. pylori* eradication, and

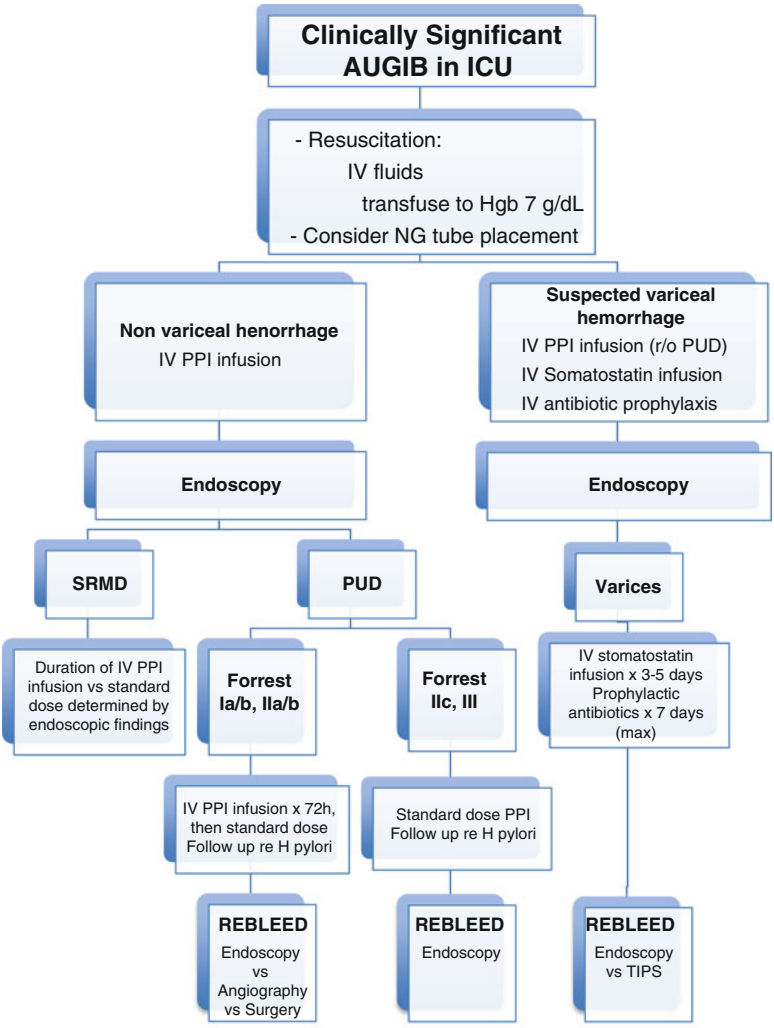

Fig. 5.2 Algorithm for management of acute upper GI bleeding

biopsy screening can be performed during initial endoscopy with little risk of increasing AUGIB [11]. Failure of endoscopic therapy to control non-variceal bleeding should be followed by surgical consultation and discussion with interventional radiology for potential embolization. Endoscopy is usually helpful in at least localizing the problematic area—if there is high-risk stigmata or clearly uncontrolled bleeding at the time of endoscopy, it is helpful if a member of the surgical team can be present at endoscopy (see Fig. 5.2 and Table 5.4).

Table 5.4 Forrest classification of bleeding peptic ulcer disease

Forrest I: Active bleeding
I (a)—spurting bleeding
I (b)—non spurting bleeding
Forrest II: Signs of recent hemorrhage
II (a)—visible vessel, no active bleeding
II (b)—non-bleeding ulcer with overlying clot
II (c)—flat ulcer with pigmented base
Forrest III:
III—clean ulcer base

Lower GI Bleeding

Traditionally lower GI bleeding (LGIB) refers to bleeding occurring distal to the ligament of Treitz (i.e., fourth part of the duodenum). In the ICU setting a hemodynamically-significant LGIB source is uncommon. The first step, in addition to standard resuscitation measures, is to place an NG tube to rule out a brisk UGIB source, which happens at least 10 % of the time. The NG tube can also be used to facilitate colon preparation once UGIB has been ruled out (e.g., with upper endoscopy). The most common causes of LGIB in adults originate in the colon and include diverticulosis, neoplasm, ischemia, and anorectal disease such as hemorrhoids. Small bowel sources of GI bleeding are relatively uncommon, and are identified only about 5 % of the time [11].

The most important diagnostic maneuver for hematochezia is colonoscopy. This also allows visualization of the terminal ileum, and if blood is visible proximally into the small bowel this suggests a source proximal to the colon. If significant diverticulosis is identified as the cause, management is generally supportive and bleeding is usually self-limited. Management of bleeding due to ischemia is discussed below. Neoplasm identified at the time of endoscopy warrants surgical consultation. Anorectal disease can be more challenging to treat, and is determined by endoscopic findings and consultation with Surgery. In general, ensuring regular bowel movements and minimizing the use of rectal tubes is recommended in managing problems such as hemorrhoids and ulceration caused by rectal tubes.

The diagnostic and management dilemma arises when a bleeding source cannot be identified clearly on upper and lower endoscopy, or if bleeding does not stop with endoscopic therapy. In the latter, surgical intervention is usually indicated. For the former, visualizing the small bowel can be done with terminal ileoscopy (i.e., colonoscopy with visualization of up to 30 cm of distal small bowel), and push enteroscopy which allows visualization of approximately 60 cm of small bowel distal to the ligament of Treitz. Other diagnostic maneuvers include capsule endoscopy, CT enteroscopy, and CT enteroclysis [11]. In the critically ill patient, investigation is usually prompted by ongoing hemodynamic instability or transfusion requirements. In this case, if bleeding is brisk enough (at least 0.5 mL/min), angiography is the modality of choice since it has both diagnostic and therapeutic potential. The limitation of this modality is that active bleeding must be seen in order to embolize the offending vessel and derive the therapeutic benefit. The technetium 99 m labeled red blood cell scan is

highly specific and sensitive for active arterial or venous bleeding in the GI tract (it can detect bleeding rates of 0.1 mL/min) but is less specific about localization of bleeding [34]. The other obvious disadvantage is there is no therapeutic potential of the investigation, but it can be used to direct angiography and/or surgical intervention.

Ischemia

Ischemic intestinal injury is generally thought to be a consequence of hypoperfusion, but may also contribute to further hemodynamic instability through the release of inflammatory mediators and bacterial translocation as intestinal injury progresses. A thorough understanding of the risk and pattern of bowel ischemia requires knowledge of the anatomy and physiology of the intestine. The blood supply of the small and large bowel is summarized as follows:

1. Duodenum—supplied by branches of the celiac axis and the superior mesenteric artery.
2. Jejunum, ileum, ascending and proximal transverse colon—supplied by branches of the superior mesenteric artery.
3. Distal transverse, descending and sigmoid colon—supplied by branches of the inferior mesenteric artery.
4. Rectum—supplied by branches of the inferior mesenteric artery and internal iliac artery.

As noted above, the colon is supplied by branches of the superior and inferior mesenteric arteries. The collateral supply between these arteries are important when patients have significant atherosclerotic disease, or in the case of open abdominal aortic surgery, when the inferior mesentery is sometimes sacrificed. Points of transition of major arterial blood supply are referred to as watershed areas. Collaterals are smaller and less abundant at the watershed areas of the splenic flexure and sigmoid colon; these segments are therefore more vulnerable to periods of hypotension leading to colonic hypoperfusion and ischemia.

Small Bowel

There are four distinct pathophysiologic mechanisms that can lead to acute mesenteric ischemia:

1. Arterial embolus
2. Arterial thrombosis
3. Venous thrombosis
4. Non-occlusive mesenteric ischemia

The most common overall cause of acute mesenteric ischemia is arterial embolus, accounting for 50 % of ischemic bowel presentations. The most common embolic source is the heart. In contrast, the ischemic mechanism most often seen in the

critically ill is non-occlusive, resulting from splanchnic hypoperfusion usually on a background of pre-existing atherosclerotic disease. Hypoperfusion results in mesenteric vasospasm, a homeostatic mechanism that redistributes blood flow to maintain cardiac and cerebral perfusion.

At a physiologic level, the bowel is vulnerable to ischemic injury because of relatively low mucosal oxygenation at the tips of intestinal villi, a consequence of countercurrent blood flow designed to maximize nutrient absorption. Interestingly, studies have shown splanchnic vasoconstriction to persist even after systemic hemodynamic stability has been restored. Injury to the bowel from ischemic insult is both a result of hypoxia and also free radical and inflammatory response in reperfusion injury. The duration and extent of injury is, therefore, difficult to measure with clinical information and investigations [10, 35].

Clinical presentation of small bowel ischemia in the critically ill population is usually insidious and difficult to diagnose early. The classic presentation of acute mesenteric ischemia is sudden onset of severe abdominal pain out of proportion to clinical exam, associated with nausea, vomiting and sometimes diarrhea, none of which are easy to assess in ICU patients who are often intubated and sedated. Unfortunately, abdominal distension, bloody enteral outputs (diarrhea or hematemesis), and peritonitis are relatively late clinical findings in the ischemia pathway, often once transmural ischemia and necrosis have occurred. For this reason, clinical suspicion should direct laboratory and imaging studies early on when a patient develops signs of sepsis with clinical change in either the abdominal examination or bowel function. Concurrent with fluid repletion and NG decompression, laboratory studies including complete blood count (CBC), lactate, and an arterial blood gas should be drawn. Blood cultures should also be collected and empiric broad-spectrum antibiotics covering for enteric pathogens initiated while awaiting diagnostic studies. Plain abdominal radiographs are generally not useful in the diagnosis of bowel ischemia, and will only precipitate intervention when demonstrating free intraperitoneal air. CT scan with IV contrast is the most useful test in diagnosing bowel ischemia, but unfortunately carries the risk of transport and contrast-induced nephropathy in a patient who likely already has compromised renal function. Surgical intervention is warranted when there is evidence of segmental infarction or free air. The most important consideration is whether there is a clear underlying occlusive lesion in the proximal vasculature which will need to be addressed either by angiography or surgery. If such a lesion is identified, therapeutic anticoagulation should be initiated while awaiting definitive management.

Large Bowel

Ischemic colitis is the most common form of large bowel ischemia, and the pathophysiologic mechanisms are identical to those seen in small bowel ischemia. The colon is more vulnerable to hypoperfusion than the small bowel because it receives less blood flow compared to the rest of the GI tract, and the microvascular supply at the level of the colon wall is less developed and robust than that of the small intestine [35].

Ischemic colitis usually occurs in elderly patients with a history of atherosclerotic risk factors and disease. Abdominal pain (usually less severe than in small bowel ischemia) typically localizes over the involved bowel segment. Commonly it is the left colon, and more specifically, the splenic flexure, which is involved because anatomically this is a "watershed area" of vascular supply. This is usually accompanied by hematochezia, fever, and leukocytosis. In its more severe form, this will progress to acidosis and peritoneal findings when there is full thickness ischemic insult to the bowel wall. As discussed above in the small bowel ischemia section, clinical symptoms are non-specific and difficult to interpret in ICU patients, and thus ancilliary testing should be initiated when the diagnosis is suspected. CT findings of colitis in a watershed area are typically used to diagnose ischemic colitis. This can be supported with colonoscopy, which may be considered in the setting of hematochezia.

The course of ischemic colitis is usually self-limited and responds to supportive care with IV fluids and bowel rest. Antibiotics are typically started to treat potential bacterial translocation, and are usually stopped with resolution of fever, leukocytosis, and abdominal pain on clinical exam. If symptoms fail to respond to conservative management, or the patient becomes increasingly unstable, this may indicate progression to transmural ischemia and necrosis, warranting surgical intervention. The extent of resection, with or without diversion, is decided at the time of operation.

Pseudo-Obstruction

Colonic pseudo-obstruction (Ogilvie's syndrome) is a clinical entity characterized by gross cecal and colonic dilation without mechanical obstruction. The cecum is most vulnerable for this complication because of Laplace's law, which states that the pressure required to distend a pliable tube is inversely proportional to its diameter. The pathogenesis of this disorder is unclear and likely multifactorial. Risk factors for pseudo-obstruction include male sex, age >60, trauma, orthopedic or cardiovascular surgery, and immobilization. Chemotherapy is another emerging risk factor for the development of colonic pseudo-obstruction [36, 37].

Clinical manifestations of this disorder include abdominal distension, obstipation/constipation, and nausea/vomiting. There are no pathognomonic laboratory studies to diagnose this condition although there is an established association with electrolyte abnormalities (e.g., hypokalemia, hypocalcemia, hypomagnesemia). In the setting of abdominal distension and leukocytosis, impending perforation should be ruled out. The etiology of the pseudo-obstruction should also be considered (e.g., sepsis). The most important ancillary study in making the diagnosis is imaging with a CT scan or hypaque enema to rule out a mechanical cause of colonic dilation. The distinction is important because it guides further management.

In the absence of abdominal tenderness or severe colonic distension on imaging, a trial of conservative management is appropriate. This treatment involves making the patient nil per os (NPO or nothing by mouth), using NG and rectal tube decompression, IV fluid support, and addressing any precipitants (e.g., minimizing narcotics, correcting electrolyte abnormalities). Surgical consultation is appropriate upon failure of these conservative measures to address the problem.

The use of pharmacologic agents has been described, with the most studied agent being neostigmine, an acetylcholinesterase inhibitor. The standard dose of this agent is 1.5–2 mg IV in the setting of continuous cardiac monitoring. Co-administration with glycopyrrolate is useful in mitigating the bradycardic and bronchspastic effects of neostigmine, but atropine should also be available at the bedside. The time to onset of action has been reported in the literature to be on the order of 3–10 min [36, 38]. Contraindications to the use of neostigmine in this population include mechanical obstruction, underlying bradyarrhythmia, recent myocardial infarction, and a relative contraindication of concurrent use of beta-blockers. Trials of neostigmine suggest a success rate of 80–100 % in achieving decompression, with recurrence as high as 30 %. It is reasonable to repeat neostigmine treatment if an interval greater than 24 h has elapsed from the initial treatment [38]. Erythromycin has also been described in case reports as sometimes being effective in this disorder.

Should pharmacologic decompression fail or be contraindicated, evaluation for endoscopic decompression is appropriate. Success rates for this procedure are in the order of 60–90 % [37]. Recurrence rates after successful decompression can be as high as 40 %. Complications of endoscopy include bleeding and perforation, which is estimated at 1–3 % [37]. More invasive management options should be discussed in the context of a surgical consult. These include percutaneous tube cecostomy and colostomy. Surgical resection/decompression is usually performed in the setting of a serious complication of pseudo-obstruction (e.g., perforation). See Fig. 5.3 for the management algorithm of acute colonic dilatation.

Diarrhea

Up to 50 % of critically ill patients develop diarrhea during their ICU stay. The Working Group on Abdominal Problems of the European Society of Intensive Care Medicine defines diarrhea as the passage of three or more loose or liquid stool with volume greater than 250 mL daily [39]. This clinical problem can have significant implications on hemodynamics and nutrition, so it is important to understand how to determine its etiology and devise an appropriate management plan. The etiology of diarrhea as a complication of ICU stay can be divided into infectious and non-infectious causes.

Infectious: *Clostridium difficile*

The infectious category, assuming baseline immunocompetence, most commonly involves *Clostridium difficile*. The incidence of *C. difficile* infection (CDI) in the ICU population ranges from 10 to 60 % [40]. Mortality of ICU-acquired CDI is high, approximately 60–70 % [40]. The pathophysiology of *C. difficile*-associated

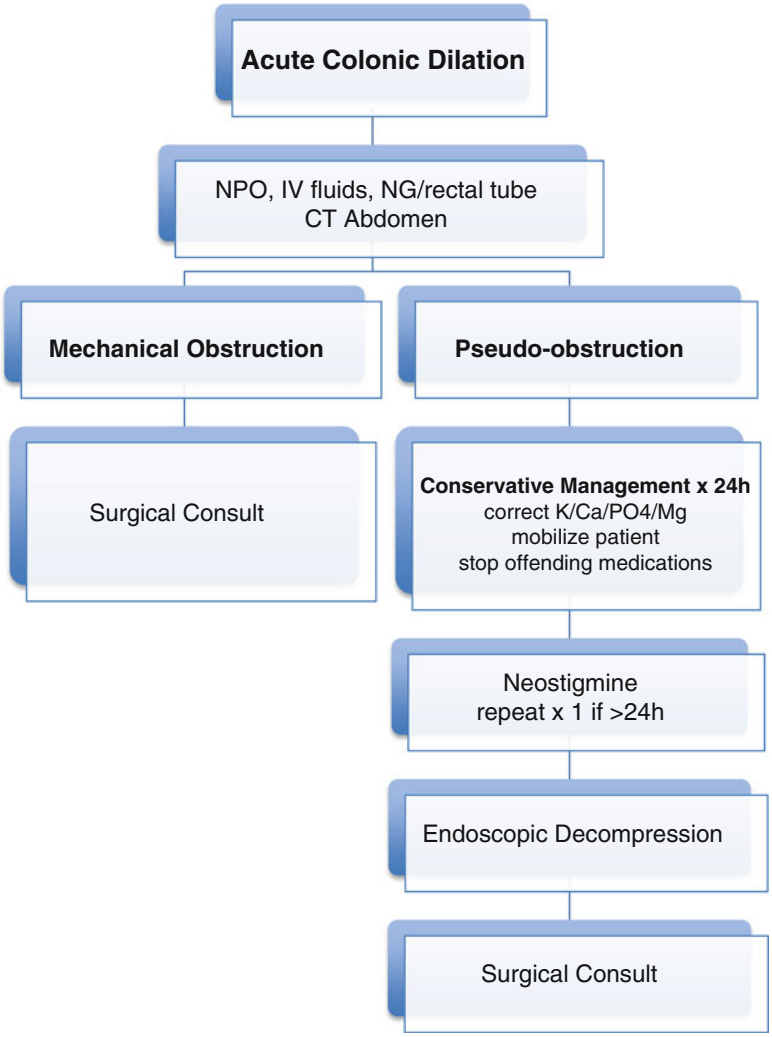

Fig. 5.3 Algorithm for management of acute colonic dilation. At any point if there is evidence of ischemia, perforation or peritonitis, a surgical consult should be requested. Adapted from Harrison ME, Anderson MA, Appalaneni V, et al. The role of endoscopy in the management of patients with known and suspected colonic obstruction and pseudo-obstruction. Gastrointest Endosc 2010; 71(4):669–79

diarrhea (CDAD) involves three major steps. The first includes alteration of normal gut flora, usually secondary to antibiotics. Although clindamycin, fluoroquinolones, and cephalosporins have been specifically implicated, any antibiotic can be associated with the development of CDI. Chemotherapeutic agents can also cause this alteration in gut flora. The next major step is acquisition of the microorganism. *C. difficile* is an anaerobic gram-positive bacillus. Outside the colon, the organism

survives in a heat-, acid-, and antibiotic-resistant spore form. Once spores are in the colon, they convert into their virulent, toxin-producing form. Transmission of spores is fecal-oral and acquired in a healthcare setting through patient-to-patient transmission with healthcare workers as the vector. The final step in the pathway is clinical manifestation of disease. The symptoms of colitis and diarrhea are mediated by exotoxins released by the microbe. Both toxin A and B inactivate cell regulation pathways, activate a significant cytokine response, and disrupt intracellular tight junctions leading to increased vascular permeability and hemorrhage. Toxin A mediates inflammatory processes, but toxin B has been shown in studies to lend *C. difficile* its virulence [41].

Clinical manifestation of CDAD typically includes watery non-hemorrhagic diarrhea, accompanied by significant leukocytosis and fever. Abdominal distension and pain are also important clinical features and are often suggestive of complications such as fulminant colitis with megacolon or pre-perforation ischemic changes. The most common test used to diagnose CDI is an enzyme-linked immunosorbent assay (ELISA) for toxin A or both toxins A and B. The sensitivity of this test is estimated 65–85 %, with a specificity of more than 95 %. The traditional gold standard test is the tissue culture cytotoxic assay which measures toxin B and has a sensitivity of 80–90 % and a specificity of 99 %. This test requires tissue culture, is costly, and has a 24–48 h turnaround time which is why the ELISA test is used more commonly. A real-time polymerase chain reaction (PCR) study measuring both toxins A and B is also available in some hospitals, with sensitivity and specificity comparable to that of the cytotoxic assay [41]. If available, this is the diagnostic test of choice as it has comparable sensitivity and specificity but a rapid turnaround time of an hour. Sigmoidoscopy may also be considered to identify pseudomembranes and send tissue cultures if the diagnosis is unclear. Imaging studies are not required for diagnostic purposes, but they may used to monitor for signs of complications or progression. Computed tomography can be used to determine the extent of colonic involvement and rule out microperforations that may not be captured by plain abdominal radiographs.

The management of CDAD requires supportive care in the form of monitoring, IV fluid, and antimicrobial therapy. According to the most recent Infectious Disease Society of America guidelines, CDAD without signs of systemic toxicity can be managed with enteral or IV metronidazole, whereas severe CDAD should be managed with oral vancomycin [42]. Intravenous vancomycin has no role in the treatment of CDI, as it is not excreted into the colon. Patients exhibiting signs of toxic colitis warrant surgical consultation. Patients with megacolon or free air of any amount on imaging warrant surgical intervention. Note that a lower threshold for surgical consultation should be applied to immunocompromised patients as their clinical exam (e.g., for peritonitis) is often unreliable. Failure to respond to medical management is another indication for surgical intervention. The standard surgical procedure for serious complications of CDI is subtotal colectomy.

As one of the main pathophysiologic steps in developing CDI is altered gut flora secondary to antibiotic use, there is preliminary research suggesting there may be a role for probiotic use in the ICU, but results are not conclusive at this time.

Recurrence rates of CDI within 60 days after successful treatment with metronidazole or vancomycin are reported between 20 and 30 % [43]. Retreatment with metronidazole or vancomycin is sufficient in two-thirds of patients with recurrence. The remaining subset of patients poses a management dilemma. A randomized trial published in 2011 demonstrated lower rates of recurrence with fidaxomicin compared with vancomycin (15.4 versus 25.3 %, $p=0.005$) in treatment of primary CDI [43]. Another recently published study compared vancomycin and duodenal fecal infusion in a RCT. This study suggests that duodenal infusion of healthy donor feces is significantly more effective in treating recurrent CDAD than vancomycin [44]. The presumed mechanism underlying the efficacy of fecal infusion is reestablishment of normal intestinal flora as a host defense against CDI [44].

Non-infectious: Enteral Feeding

The majority of patients receive enteral nutrition at some point in their ICU stay. The most common complication of enteral feeding is diarrhea, which occurs in up to 20 % of this population. The pathophysiology of diarrhea associated with enteral feedings is likely multifactorial. Altered gut motility, changes in intestinal flora, composition of feeds, and method of delivery are important factors in the development of diarrhea. A high caloric load in the stomach and proximal small bowel stimulates a gastrocolonic reflex that results in increased colonic contractility, whereas lower calorie loads have little to no impact on colonic contractility. The caloric load is likely an explanation for why continuous pump delivery to ensure a constant rate of feeding results in a decreased rate of diarrhea when compared to gravity delivery and intermittent/bolus feeds. Importantly, the location of nutrient delivery does not change the rates of diarrhea in the critically ill: gastric and post-pyloric feeding have a similar incidence. The composition of feeds has been implicated in the rates of feeding-associated diarrhea, with specific factors of feeding formula osmolarity, non-absorbable carbohydrates, and bacterial contamination all being implicated. The evidence to date suggests that isotonic or low osmolarity feedings enriched with fiber improve feeding tolerance, including decreasing rates of diarrhea. This effect is thought to be mediated by the release of short chain fatty acids (SCFAs) upon fermentation of fiber. These SCFAs are used by colonocytes as an energy source and therefore improve resorption of water and electrolytes by the colon. Water-soluble fibers have been shown to have greater potential trophic effects, likely secondary to the increased viscosity of feedings which therefore decreases transit time from stomach to colon.

The most important consideration when addressing enteral feeding associated diarrhea is ruling out other contributory causes. The presence of diarrhea alone should not prompt withholding of feedings, which results in further malnutrition and the potential for bacterial overgrowth in the dysmotile gut. It should be noted that hypoalbuminemia has also been associated with increased rates of diarrhea, but this has not been proven to be a causal effect. The use of pre- and probiotics for prevention of diarrhea is an area of ongoing study without any conclusive evidence to support their routine use at this time.

Non-infectious: Medications

The most easily modifiable cause of diarrhea in the ICU population is medication-related. The mechanism of diarrhea may be:

1. Osmotic—as seen with administration of medications containing sorbitol (e.g., liquid acetaminophen), laxatives (e.g., lactulose), and magnesium salts as used in antacids.
2. Secretory—stimulant laxatives, which increase intraluminal water and electrolytes by increasing secretion of decreasing reabsorption in the small and large bowel.
3. Exudative—mucosal disruption secondary to inflammation from chemotherapeutic agents.
4. Hypermotility—as seen with prokinetics such as erythromycin and metoclopramide.

Simple antibiotic-associated diarrhea is likely mediated by altered intestinal flora, leading to impaired fermentation of carbohydrates and therefore decreased production of SCFAs causing decreased fluid reabsorption by the colon. This type of antibiotic-associated diarrhea, unlike CDAD, usually resolves with withdrawal of the antibiotics.

Retroperitoneal-Based Complications

Spontaneous Retroperitoneal Bleeding

The literature discussing spontaneous retroperitoneal bleeding (SRB) is limited to observational studies and retrospective chart reviews. Of the larger studies, both published within the last 10 years, neither identifies the number of patients diagnosed with SRB as a complication of ICU stay, though 40–50 % of patients required ICU for management. The biggest risk factors for SRB were age greater than 60 and anticoagulation–antiplatelet combination therapy [45, 46]. Only 15 % of patients were not on any blood-thinning regimen. The problem with this diagnosis is its non-specific clinical presentation. In patients with the above risk factors, sudden hemodynamic shifts and complaints of abdominal or flank pain should prompt consideration of the diagnosis. Classically described flank ecchymosis is rare. Laboratory investigations should include CBC, coagulation profile, and crossmatch. Resuscitation with fluids and blood products should be carried out before CT imaging is performed. If the diagnosis is confirmed, further management is dictated by response to resuscitation measures. The majority of patients respond to supportive care with reversal of anticoagulation. In approximately 25 % of patients interventional radiology embolization or coiling of bleeding was carried out successfully. Surgery was required in less than 10 % of patients, and was either indicated because of failure of IR management or other complications requiring surgery including perforation or nerve compression symptoms [46].

Key Points

1. Intra-Abdominal Hypertension
   - Screen patients for IAH based on risk factors
   - Measure trans-bladder pressure using an institutionally standardized approach
   - Institute non-invasive and/or invasive measures to prevent progression of IAH to ACS, which is associated with high morbidity and mortality
2. Stress-Related Mucosal Disease
   - A preventable cause of ICU morbidity and mortality
   - Prophylaxis should be instituted for defined at-risk patients, ideally in the form of enteral PPIs
   - The risk of acid suppression causing nosocomial pneumonia is not well defined
3. Dysmotility and Feeding Intolerance
   - ICU patients are at risk for malnutrition and aspiration pneumonia secondary to GI dysmotility
   - Enteral feeding should be instituted as early as possible on ICU admission
   - GRVs of 250–500 mL should prompt assessment for possible dysmotility but should not automatically result in withholding of feeds
   - Post-pyloric feeding tubes should be used when feasible
   - Consider institution of parenteral nutrition after 7 days of inadequate enteral intake
4. GI Bleeding
   - Clinically important bleeding is a cause of increased morbidity, mortality and length of ICU stay
   - The initial pathway in managing any clinically significant bleeding includes resuscitation with IV fluids, blood products for correction of coagulopathy and targeting a hemoglobin above 7 g/dL
   - Adjuncts to initial resuscitation should be guided by suspected source: upper versus lower, non-variceal versus variceal
5. Diarrhea
   - Starting point is to rule out infectious etiology and discontinue potentially contributory medications
   - If *C. difficile* is diagnosed in the context of systemic toxicity, first line agent is vancomycin, with surgical consult if peritoneal findings or no clinical response within 24 h
   - Fidaxomicin is associated with reduced recurrence rates when used in the treatment of primary CDI
   - Low osmolarity feeds enriched with fiber are associated with decreased rates of diarrhea

References

1. Kirkpatrick A, Roberts DJ, De Waele J, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med. 2013;39:1190.
2. Katsios C, Ye C, Hoad N, et al. Intra-abdominal hypertension in the critically ill: interrater reliability of bladder pressure measurement. J Crit Care. 2013;28(5):886.e1–6
3. Malbrain ML, Chiumello D, Pelosi P, et al. Prevalence of intra-abdominal hypertension in critically ill patients: a multicentre epidemiological study. Intensive Care Med. 2004;30(5):822.
4. Malbrain ML, Chiumello D, Pelosi P, et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. Crit Care Med. 2005;33(2):315.
5. O'Mara MS, Slater H, Goldfarb IW, et al. A prospective, randomized evaluation of intra-abdominal pressures with crystalloid and colloid resuscitation in burn patients. J Trauma. 2005;58(5):1011.
6. De Waele J, Hoste E, Malbrain ML. Decompressive laparotomy for abdominal compartment syndrome – a critical analysis. Crit Care. 2006;10(2):R51.
7. Mularski RA, Sippel JM, Osborne ML. Pneumoperitoneum: a review of nonsurgical causes. Crit Care Med. 2000;28(7):2638.
8. Gayer G, Hertz M, Zissin R. Postoperative pneumoperitoneum: prevalence, duration, and possible significance. Semin Ultrasound CT MR. 2004;25(3):286.
9. Mulhall BP, Wong RK. Infectious esophagitis. Curr Treat Options Gastroenterol. 2003;6(1):55.
10. Mutlu GM, Mutlu EA, Factor P. GI complications in patients receiving mechanical ventilation. Chest. 2001;19(4):1222.
11. Osman D, Djibre M, Da Silva D, et al. Management by the intensivist of gastrointestinal bleeding in adults and children. Ann Intensive Care. 2012;2(1):46.
12. Nind G, Chen WH, Protheroe R, et al. Mechanisms of gastroesophageal reflux in critically ill mechanically ventilated patients. Gastroenterology. 2005;128(3):600–6.
13. Wang WH, Huang JQ, Zheng GF, et al. Head-to-head comparison of H2-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: a meta-analysis. World J Gastroenterol. 2005;11(26):4067.
14. Koek GH, Tack J, Sifrim D, et al. The role of acid and duodenal gastroesophageal reflux in symptomatic GERD. Am J Gastroenterol. 2001;96:2033.
15. Vaezi MF, Sears R, Richter JE. Placebo-controlled trial of cisapride in postgastrectomy patients with duodenogastroesophageal reflux. Dig Dis Sci. 1996;41(4):754–63.
16. Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. N Engl J Med. 1994;330(6):377.
17. Cook DJ, Griffith LE, Walter SD, et al. The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. Crit Care. 2001;5(6):368.
18. Stollman N, Metz DC. Pathophysiology and prophylaxis of stress ulcer in intensive care unit patients. J Crit Care. 2005;20(1):35–45.
19. ASHP therapeutic guidelines on stress ulcer prophylaxis. ASHP commission on therapeutics approved by the ASHP board of directors on November 14, 1998. Am J Health Syst Pharm. 1999;56(4):347.
20. Barkun AN, Bardou M, Pham CQ, et al. Proton pump inhibitors vs histamine 2 receptor antagonists for stress-related mucosal bleeding prophylaxis in critically ill patients: a meta-analysis. Am J Gastroenterol. 2012;107(4):507.
21. Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. Am J Gastroenterol. 2012;107(7):1001–10.
22. Kwok CS, Arthur AK, Anibueze DG, et al. Risk of Clostridium difficile infection with acid suppression agents and antibiotics: meta-analysis. Am J Gastroenterol. 2012;107(7):1011–9.

23. Oh JH, Pasricha PJ. Recent advances in the pathophysiology and treatment of gastroparesis. J Neurogastroenterol Motil. 2013;19(1):18.
24. Corke C. Gastric emptying in the critically ill patient. Crit Care Resucs. 1999;1:39.
25. Reignier J, Mercler E, Le Gouge A, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. JAMA. 2013;309(3):249–56.
26. Montejo JC, Minambres E, Bordeje L, et al. Gastric residual volume during enteral nutrition in ICU patients: the REGANE study. Intensive Care Med. 2010;36(8):1386–93.
27. Strategies to optimize deliver and minimize risks of enteral nutrition: small bowel feeding vs gastric. Canadian Clinica Practice Guidelines 2013
28. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365(6):506.
29. Huffman JL, Schenker S. Acute acalculous cholecystitis: a review. Clin Gastroenterol Hepatol. 2010;8:15–22.
30. Horvatits T, Trauner M, Fuhrmann V. Hypoxic liver injury and cholestasis in critically ill patients. Curr Opin Crit Care. 2013;19:128–32.
31. Padda MS, Sanchez M, Akhtar AJ, et al. Drug induced cholestasis. Hepatology. 2011;53(4): 1377–87.
32. Jeejeebhoy KN. Management of parenteral nutrition-induced cholestasis. Pract Gastroenterol. 2005;24:62.
33. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368:11.
34. Syed MI, Shaikh A. Accurate localization of life threatening colonic hemorrhage during nuclear medicine bleeding scan as an aid to selective angiography. World J Emerg Surg. 2009;4:20.
35. Rosenblum JD, Boyle CM, Schwartz LB. The mesenteric circulation. Anatomy and physiology. Surg Clin North Am. 1997;77(2):289.
36. Eisen GM, Baron TH, Dominitz JA, et al. Acute colonic pseudo-obstruction. Gastrointest Endosc. 2002;56(6):789–92.
37. Harrison ME, Anderson MA, Appalaneni V, et al. The role of endoscopy in the management of patients with known and suspected colonic obstruction and pseudo-obstruction. Gastrointest Endosc. 2010;71(4):669–79.
38. Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. N Engl J Med. 1999;341(3):137.
39. Blaser AR, Malbrain ML, Starkopf J, et al. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM working group on abdominal problems. Intensive Care Med. 2012;38:384.
40. Wiesena P, Van Gossumb A, Preisera JC. Diarrhea in the critically ill. Curr Opin Crit Care. 2006;12:149–54.
41. Kuehne SA, Cartman ST, Heap JT, et al. The role of toxin A and toxin B in Clostridium difficile infection. Nature. 2010;467(7136):711.
42. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hop Epidemiol. 2010;31(5):431–55.
43. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med. 2011;364(5):423.
44. Van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med. 2013;368(5):407.
45. Ivascu FA, Janczyk RJ, Bair HA, et al. Spontaneous retroperitoneal hemorrhage. Am J Surg. 2005;189(3):345.
46. Sunga KL, Bellolio MF, Gilmore RM, et al. Spontaneous retroperitoneal hematoma: etiology, characteristics, management and outcome. J Emerg Med. 2012;43(2):157–61.