INTRODUCTION

The gastrointestinal (GI) tract is anatomically defined by the organs that comprise the tubular structure that extends from the mouth to the anus. In its simplest form, the GI tract serves the critical role in the ingestion, digestion (processing), and assimilation (absorption) of food. As such, in critical illness, the GI tract is the preferred route of delivery of nutrition (enteral nutrition [EN]) in critically ill patients.

Our understanding of the complexity and importance of the GI tract has grown dramatically with discovery of roles in addition to nutrition. The GI tract contains an active neuroendocrine system through which it interacts in a highly complex fashion with virtually all organs and systems in the body. Throughout the entire length of the GI tract is the site of the greatest concentrations of immune cells in the body, playing highly significant and complex roles in health and disease. Finally, there is the more recent appreciation of our symbiotic relationship with a healthy microbiome. Our gut is host to trillions of microorganisms, which—rather than passive bystanders—have essential roles in the defense against pathogens, in the processing and provision of vital nutrients, and in the fine tuning of immune responses.

The GI tract can be a source of critical illness. Multiple disorders, including critical illness, affect this organ and it can be, in itself, a source of life-threatening diseases; we discuss the most important of these below. Maintaining adequate GI function is, thus, paramount to the survival of the critically ill patient.

BASIC GASTROINTESTINAL ANATOMY, HISTOLOGY, AND PHYSIOLOGY

A Primer on Anatomy and Physiology

While GI tract is “simply” a tubular structure that extends from the mouth to the anus, in reality it is a highly complex system with multiple anatomically distinct organs. The mouth provides the initial entry of food into the GI tract. The main function of mouth is the mechanical breakdown of food into a manageable size that allow for the ingestion of food into the stomach and their mixing with GI secretions. The mouth, hypopharynx, pharynx, larynx, and the upper esophagus work in a complex and coordinated fashion to provide for the safe passage of food from the mouth into the esophagus, also known as swallowing.

The esophagus provides safe passage of food and saliva from the mouth and hypopharynx into the stomach. A critical function of the esophagus is to prevent the reflux of acid secretions from the stomach into the hypopharynx. The esophagus, like the mouth, is lined with a mucosal squamous epithelium.

During critical illness, swallowing can be severely affected by anatomic disruption (such as the placement of an endotracheal tube), neurologic illnesses, and medications. Alterations of swallowing is known as dysphagia and can lead to the aspiration of saliva (and the bacteria contained in the mouth), refluxed acid secretions from the stomach, and aspiration of ingested food into the airway; aspiration remains a significant cause of morbidity in the critically ill patient.

The stomach serves as a temporary repository of food, as well providing for the initial steps of digestion. Passage of chime—the mixture of food and GI secretions—into the duodenum is permitted by the pylorus.

The majority of nutrient absorption occurs in the small bowel, composed of the duodenum, jejunum, and ileum. The absorptive surface of the small bowel is significantly increased by villi (Fig. 17.1) (1).

The colon is composed of four portions, the ascending, transverse, descending, and the sigmoid colon. The colon is lined by a columnar epithelium with an abundance of goblet cells, cells that generate large amounts of mucous and are essential for the prevention of invasion of microorganisms in and through the intestinal wall. The last portions of the GI tract include the rectum and anus which provide sensitivity and continence to the presence of stool and flatus.

The mucosal lining of the entire GI tract is constantly renewed. In the small intestine and in the colon, mucosal cells arise from the crypts of Lieberkühn where pluripotent stem cell reside and can give rise to mature epithelial cells. The majority of the cells in the small bowel are mature enterocytes (absorptive cells). Goblet cells are cells that produce mucous and are particularly frequent in the colon. Paneth cells are long-lived cells localized in the small bowel with higher concentrations in the ileum. These cells play highly important antimicrobial roles through the secretion of antimicrobial peptides. Neuroendocrine cells, as their name implies, secrete a variety of hormones and interact with the autonomic nervous system. Tuft cells, relatively infrequent in number, play interesting roles in antigen “sampling” through guanine nucleotide–binding receptors (see below: The Immune System of the Gastrointestinal Tract) (2).

Gastrointestinal Functions

The GI tract provides four basic functions:

1. It serves to break down food, digest, and absorb nutrients (3).
2. A complex system of neuroendocrine functions that carefully regulates local and systemic metabolism in response to food, interacting with other organs and systems.
3. Starting from lymphoid tissues in the mouth and the hypopharynx, specialized immune cells and organs are distributed throughout the entire GI tract, providing us

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The acid environment also nearly sterilizes ingested food. Further digestion occurs in the duodenum where chyme mixes with bile and exocrine pancreatic secretions. The acid pH of chyme coming from the stomach is neutralized post pylorus by the secretion of bicarbonate. Completion of digestion occurs in the brush border of the small bowel mucosa. In addition, the secretion of fluid into the small bowel dilutes chyme to create an isotonic fluid.

Absorption of digested nutrients proceeds in the small bowel, starting proximally in the duodenum with the absorption of iron, proceeding with the absorption of amino acids, dipeptides, and tripeptides; lipids are broken down by lipases liberating mono- and diglycerides and essential fatty acids, which are surrounded by biliary salts to generate chylomicrons, which are absorbed in the distal ileum. Vitamin B₁₂ is also absorbed in the ileum.

The volume of fluid secreted by the GI tract during digestion can be as high as 9 L; absorption of large amounts of this fluid is initiated in the small bowel. The ascending and transverse colon provide a large amount of absorption of fluid and electrolytes so that only a few 100 mL of water are evacuated in the stool.

**Neuroendocrine Regulation**

A normally functional GI tract has to be able to sense the amount and quality of the food, determine the rate of progression of the food bolus through the GI tract, communicate with other organs in the body to create the necessary metabolic and physiologic responses to a meal. To do this, highly specialized communication systems with distinct but overlapping functions had to be created.

The central and autonomic nervous systems interact with all anatomic and physiologic sites of the GI tract. For one, conscious issues of hunger and satiety, thirst and the desire for specific nutrients (water, sugar, lipids, salt, and others), which may appear as volitional and hedonistic brain functions, are a result of a careful interaction with the GI tract. Classic examples demonstrate an increase in salivation and release of gastric juices in response to a visual stimulus. Satiety is in part governed by hormones such as ghrelin and GLP1 providing another example for this interaction.

Mechanical progression of food and chyme is determined by peristaltic waves which, while promoting mixing of food and GI secretions, provide a measured aboral “wave” from the GI tract; peristalsis is governed by the autonomic nervous system.

The secretion of digestive enzymes is modulated by hormones secreted by specialized cells in the GI tract. In the stomach, gastrin produced by G cells increases the secretion of pepsin and HCl. In the pancreas, secretion of secretin increases the release of bicarbonate-rich pancreatic juice. Cholecystokinin increases the secretion of bile by the liver and contractility of the gallbladder.

Governing the communication between food, the GI tract, and the rest of the body are chemical messengers with different functions. Attempts to classify these messengers are difficult due to the constant growth and discovery of different substances and also to the overlapping functions of some of these. Nonetheless, a simple classification suggests the following categories:

1. Endocrine mediators (hormones). GI hormones are peptides released into the circulation generating local and

**Digestion and Absorption**

The primary function of the GI tract is to process food, breaking it down mechanically and then, through digestion, convert it into the different substrates that are absorbed and subsequently serve all metabolic processes within the body. The mouth actively participates in the selection of the appropriate quantity and quality of food. Digestion also starts in the mouth with the secretion of amylase and initial breakdown of carbohydrates. In the stomach, the secretion of hydrochloric acid (HCl) by specialized parietal cells and pepsin by chief cells are essential for the initial digestion of protein into peptides.

**FIGURE 17.1** Schematic depiction of a villus. The villi are foldings of the intestinal epithelium that greatly increase the surface area in contact with the contents within the lumen. They are prominent in the small bowel, where completion of digestion and absorption of nutrients is paramount. Villi are absent in the colon. The cells facing the lumen are composed of a single layer of columnar epithelium consisting of different types of cells. At the base of the villus, stem cells are constantly dividing to produce enterocytes (the most abundant of all cells), goblet cells, neuroendocrine, and Paneth cells. Whereas enterocytes and goblet cells migrate toward the tip of the villus and are shed in just a few days, Paneth cells migrate toward the base (crypt). Goblet cells generate mucous and are most abundant in the colon. Paneth cells produce antimicrobial peptides (AMPs). The tuft cells (not depicted) constitute yet another cell type. Interoepithelial lymphocytes (IEL) can be found in between enterocytes. (From Mowat AM, Agace WW. Regional specialization within the intestinal immune system. Nat Rev Immunol. 2014;14(10):667–685. Reprinted by permission from Macmillan Publishers Ltd.)

Protection from infection, while allowing (tolerating) the growth and proliferation of a healthy microbiome.

4. A healthy microbiome is essential for health, establishing a symbiotic relationship that permits the survival and growth of hundreds of bacterial species that live in the lumen but do not invade the walls of the GI tract.
The Immune System of the Gastrointestinal Tract

Diverse immune tissues are distributed across the entire GI tract where they play significant role in the prevention of invasion by microorganisms. Equally as important, proper immune function creates tolerance against antigenic stimuli that come from food and from symbiotic microorganisms, preventing autoimmune responses and self-injury. The immune system in the GI tract is modulated by nutrients such as vitamin A, by antigens of the microorganisms, and by bacterial products such as short-chain fatty acids.

Immune cells are not equally distributed across the GI tract with significant and dramatic variations in concentrations of cells from organ to organ. Thus, for example, the largest concentration of Th17 cells are located preferentially in the duodenum and jejunum. In contrast, the gut-associated lymphoid tissues (GALT) are preferentially distributed in the distal jejunum, ileum, and cecum. This suggests that there are highly different biologic roles in this distribution, which we are only beginning to delineate (1,3).

The GALT deserves special attention. In the distal small bowel, the GALT is organized in histologically distinct zones called Peyer patches. These contain numerous B-lymphocyte follicles which are flanked by smaller T-cell zones. The Peyer patches appear to be the main source of immunoglobulin A (IgA) in the small bowel. In addition, T lymphocytes are distributed across the intestine. Lymphocytes localized at the basement membrane between enterocytes and are called intraepithelial lymphocytes (IELs), and have a wide variety of regulatory and effector activities. Most frequently, IELs are T lymphocytes and are broadly divided into two categories: conventional (type A IELs) and unconventional (type B IELs).

Both helper T cells (CD4+) and cytotoxic T cells (CD8+) are observed in the lamina propria. Most of these T-cell subsets display a memory phenotype possibly in response to the constant antigenic “sampling” that occurs at the level of the mucosa.

Of growing interest are the so-called innate lymphoid cells (ILCs) distributed across the small and large bowels, that play important and growing roles in the regulation of physiologic responses to antigenic stimuli and may also play pathologic roles during illness. There are three types of ILCs. Of these, the type 2 ILCs (ILC2) appear to play important roles in antigenic sampling. ILC2 cells proliferate in response to interleukin (IL)-25 which is in turn exclusively generated by tuft cells when activated by an antigenic stimulus. ILC2 cells play essential roles in generating type 2 humoral immune responses; ILC2 cells are also controlled by VIP.

Myeloid cells (macrophages and dendritic cells) are also distributed along the GI tract. Macrophages are the most abundant leukocytes in the intestinal lamina propria where they play essential homeostatic roles including phagocytosis, tissue repair, and healing. Intestinal dendritic cells are a distinct subset of dendritic cells as identified by their receptor signature (CD11c+, MHC class II+, CD64–, F4/80–, and expressing ZBTB46).

Disruption of immune responses are independent causative factors of illness. Such is the case of the inflammatory diseases such as celiac disease, Crohn disease, and ulcerative colitis.

The Gut Microbiome

Central to maintaining normal function of the GI tract is a healthy microbiome. While a microbiome exists all the way from the mouth to the anus, the duodenum and jejunum are nearly sterile. The microbial flora in the mouth and colon are distinct from each other and each one contains hundreds to over a thousand distinct bacterial and viral species and archaeabacteria. Protozoa and helminths may also exist, although it is only recently that the role of these organisms in the maintenance of health for the overall microbiome has been recognized. Of all microbiomes the colonic microbiome has currently garnered the most interest.

Technologic advances using the tools of molecular biology have permitted a more complete and diverse mapping of the microbiome than otherwise could be afforded by attempting isolated cultures. In 2010, initiatives in the United States and in Europe created a complete mapping of the microbiome in distinct healthy individuals from different geographic, cultural, and genetic backgrounds. In these samples, over 730,000 distinct genes have been identified; thus, our microbiome contains multiple times more genes than our own cells (4).

Neither the type nor the proportion of bacteria is shared by all individuals. There is also an individual variation in the proportion of bacteria in a given individual in response to dietary changes, although there is a striking stability in bacterial species in a given individual across time.

A healthy microbiome exists in a symbiotic relation with its host that involves the creation of a “tolerant” immune response. The host provides food for bacteria, of which dietary fiber is particularly important. The host also provides for a healthy “temperature and oxygen-controlled” environment. In turn, the microbiome generates important nutrients such as short-chain fatty acids, and other micronutrients that feed the gut mucosa and can be absorbed and distributed systemically.

Disruption of the microbiome can occur as a result of multiple conditions. Acute and chronic alterations can occur as a result of diet. These alterations have been linked to obesity, cardiovascular diseases, and inflammatory bowel diseases such as Crohn disease. Acute disruption of the microbiome associated with antibiotic use causes GI intolerance in acute illness and diarrhea. 

Clostridium difficile colitis constitutes a classic illness associated
with a disrupted microbiome, and is now being managed with interventions aimed at restoring microbial homeostasis.

SPECIFIC DISORDERS

**Acute Pancreatitis**

Acute pancreatitis, a disease process with a wide spectrum of clinical presentations and causes, can challenge any critical care physician. Only 10% to 15% of cases are severe enough to threaten patient survival, and these, therefore, likely involve the critical care physician. Gallstones and alcohol intake cause 85% of the cases of acute pancreatitis (5); the risk in heavy drinkers who also smoke heavily is increased fourfold. Other causes include hyperlipidemia, viral infections, and certain drugs such as propofol (6–8) (Table 17.1).

Of special importance to intensivists is the association between propofol, a medication commonly used for sedation of critically ill patients, and the presence of hypertriglyceridemia and acute pancreatitis. Devlin et al. (6) retrospectively studied 159 patients in the intensive care unit (ICU) with propofol sedation, finding that 29 (18%) patients developed hypertriglyceridemia and, among these 29 patients, three presented a clinical picture of acute pancreatitis. Their final recommendation was to monitor the serum triglycerides levels and pancreas enzymes after 48 hours on propofol.

The diagnosis of acute pancreatitis requires two of the following three criteria: (1) Abdominal pain consistent with acute pancreatitis; (2) pancreatic enzyme elevation to greater than three times the upper limit of normal; and (3) findings characteristic of acute pancreatitis on contrast-enhanced computed tomography (CT) of the abdomen (9). Thus, the usual initial workup for a patient with symptoms consistent with acute pancreatitis is to obtain serum amylase and lipase values and, generally, obtain an abdominal CT (see below). Severity of the disease may be defined using the guidance of the revised Atlanta criteria (Table 17.2). Note, however, that the degree of enzyme elevation at admission does not necessarily forecast eventual disease severity (10).

Acute pancreatitis due to pancreatic duct obstruction—as from a gallstone obstructing the duct—triggers the activation of endogenous pancreatic enzymes such as trypsin, causing autolysis and activation of the inflammatory response which may progress to organ failure (11). Alcohol-induced pancreatitis is more complex, inducing acinar cell dysfunction that leads to precipitation of secretions in the ducts, obstructing outflow (12).

Bacterial seeding of necrotic pancreatic tissue can occur, most probably through bacterial translocation (BT) from the gut, and may lead to sepsis and delayed death (13); a severe septic inflammatory response to pancreatitis may be difficult to differentiate from a septic response due to bacterial contamination. Ideally, in all cases of severe acute pancreatitis, the extent of necrosis should be determined using the gold standard to make such determinations, contrast-enhanced CT. Furthermore, the CT can identify other life-threatening causes of SIRS and shock not uncommonly seen in such critically ill individuals, such as major bleeding and/or hollow viscus erosion/perforation.

After the first 2 to 4 weeks of the disorder it is often seen that initially sterile periampullary inflammatory fluid collections coalesce into structures known as pseudocysts, which often regress spontaneously, but may persist and become infected, warranting drainage. The patient may show a persistent inflammatory state, and can deteriorate with SIRS, sepsis, or septic shock. Although the presence of air bubbles in the pancreas on abdominal CT scan suggests infection, the gold standard to rule out this possibility is CT-guided needle aspiration of the necrotic pancreatic bed. Intervention, however, is not without hazard: “routine” drainage of pancreatic fluid collection often leads to infection in previous sterile collections (14), and thus the suspicion of infection must be convincing before intervention for drainage is undertaken. A variety of modalities of treatment exists to address infected fluid collections, ranging from percutaneous drainage to endoscopic procedures to minimally invasive or open necrosectomy. Studies of patients managed with percutaneous procedures have shown varying results (15). Transgastric drainage guided by endoscopic ultrasound is ideal in certain clinical situations (15), and may compare favorably with surgical intervention as experience develops (16). Surgical choices include the so-called VARD (video-assisted retroperitoneal debridement) technique with single or repeated procedures for removal of necrotic pancreatic tissue, or open complete necrosectomy with drain placement and continuous irrigation in the postoperative period (17). Clearly, with this variety of choices available for treatment, the decision for optimal treatment of a specific patient with acute pancreatitis must be individualized.

**TABLE 17.1 Classification System of Drug-Induced Acute Pancreatitis**

<table>
<thead>
<tr>
<th>Class Ia drugs:</th>
<th>At least one case report with positive rechallenge, excluding all other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class Ib drugs:</td>
<td>At least one case report with positive rechallenge; however, other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs were not ruled out.</td>
</tr>
<tr>
<td>Class II drugs:</td>
<td>At least four cases in the literature; consistent latency (≥75% of cases).</td>
</tr>
<tr>
<td>Class III drugs:</td>
<td>At least two cases in the literature; no consistent latency among cases; no rechallenge.</td>
</tr>
<tr>
<td>Class IV drugs:</td>
<td>Drugs not fitting into the earlier described classes; single case report published in medical literature, without rechallenge.</td>
</tr>
</tbody>
</table>


**TABLE 17.2 Grades of Severity of Acute Pancreatitis**

<table>
<thead>
<tr>
<th>Mild acute pancreatitis</th>
<th>- No organ failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderately severe acute pancreatitis</td>
<td>- Organ failure that results within 48 hrs (transient organ failure) and/or - Local or systemic complications without persistent organ failure</td>
</tr>
<tr>
<td>Severe acute pancreatitis</td>
<td>- Persistent organ failure (&gt;48 hrs) - Single organ failure - Multiple organ failure</td>
</tr>
</tbody>
</table>


- Persistent organ failure (>48 hrs)
- Single organ failure
- Multiple organ failure

**TABLE 17.2 Grades of Severity of Acute Pancreatitis**

- Organ failure that results within 48 hrs (transient organ failure) and/or - Local or systemic complications without persistent organ failure

- Persistent organ failure (>48 hrs)
- Single organ failure
- Multiple organ failure
**Clostridium difficile Colitis**

The selective pressure of antibiotic use may lead to the disruption of normal fecal flora allowing the emergence of resistant organisms and causing disease. Best known of these organisms is *C. difficile*, which can cause diarrheal outbreaks in healthcare institutions. The emergence of a hypervirulent strain of *C. difficile* known as NAP1/B1/ribotype 027 which produces both toxins A and B—and is frequently fluoroquinolone-resistant—has been a problem of particular importance in ICUs in many countries. *C. difficile* colitis can be a lethal disease particularly if treatment is delayed or inadequate. There is an increased risk of developing severe *C. difficile* colitis in the chronically ill, the elderly, and immunosuppressed patients. Early identification and treatment are critical, and the presence of significant leukocytosis should trigger the possibility of such a diagnosis. The severity of disease ranges from asymptomatic carriage, through diarrhea that is mild in frequency and severity, up to a fulminant and rapidly progressive toxic state with profound leukocytosis, hypotension, hypoalbuminemia, and lactic acidosis; the latter condition warrants the most aggressive treatment regimen which often includes emergent surgery (18). Significant abdominal findings warrant radiologic investigation. An initial abdominal radiograph—a KUB (kidney, ureters, and bladder) study—may reveal significant small intestinal or colonic dilatation with pneumatosis in the colonic wall; abdominal CT scan is useful to assess colon integrity and to rule out other pathologies. Definitive diagnosis can be made using one of a variety of laboratory tests. However, the selected test should be performed in individuals with diarrhea so as to avoid treatment of asymptomatic carriers (19). Combination testing designs including immunoassay for *C. difficile* glutamate dehydrogenase antigen followed by a rapid toxin A/B assay in screen-positive samples is a 92% accurate tactic with rapid turnaround (20). Polymerase chain reaction testing for *C. difficile* toxin genes is rapid with high sensitivity and specificity (21). It is important to remember that laboratory tests cannot distinguish between colonization and infection so it is important that diagnostic testing and treatment be made within the appropriate clinical context (22). The current mainstay of medical treatment includes the discontinuation of the inducing antibiotics, if possible (23) and the immediate initiation of oral vancomycin and/or metronidazole—the latter given either intravenously or orally. More serious disease warrants use of high-dose oral vancomycin, vancomycin retention enemas, and possibly fidaxomicin, although the expense of this new medication may limit its availability. The reader is referred to a recent review of treatment recommendations for more detail (24). Aggressive fluid resuscitation—guided by careful monitoring of the clinical condition and volume status—and timely surgical intervention, since this disease entity can progress rapidly to the point of need for surgery, are important to decrease mortality. Despite aggressive treatment of *C. difficile* infection (CDI), however, morbidity from this disease and a significant incidence of recurrence continue to be a problem. Adjunctive treatments such as dietary manipulations, the use of probiotics and toxin-binding agents, and restoration of the colonic flora through the use of fecal transplant are all treatments that are being investigated, although their exact roles are unclear (25). Fecal microbiota transplantation, the administration of fecal flora directly to the lumen of the colon or via a nasogastric (NG) or nasojejunal (NJ) tube to replete the eradicated normal gut bacterial flora, is sometimes used; it appears to have positive effects in recurrent CDI, although with low strength evidence (26). Effectiveness of administration via NG/NJ tube or rectally via colonoscope appears to be equal (27). Some promising findings that warrant further study have been seen in investigations of treatment of CDI with rifampin, rifaximin, nitazoxamide, tigecycline, monoclonal antibodies, and immunoglobulins (28).

**Abdominal Compartment Syndrome**

Increased intra-abdominal pressures (IAP) compromising blood flow to splanchnic organs have been described in an increased percentage of patients in the ICU. Elevated IAP can have a major negative impact on the functioning of all major body systems that are vital for life (29). Malbrain et al. from the European Community analyzed 265 consecutive patients in the ICU, measuring IAP via transduction of the urinary bladder; this work demonstrated that nonsurvivors tended to have higher IAP (30). Furthermore, patients with prior elevated IAP exhibited increased sepsis-related organ failure assessment (SOFA) scores. In an Argentinian study of 83 critically ill patients, 54% displayed intra-abdominal hypertension (IAH) (IAPmean >12 mmHg) during ICU admission, with significantly higher ICU length of stay and hospital mortality (31). The 2013 consensus definitions from the World Society of Abdominal Compartment Syndrome are these: (1) Normal IAP is 5 to 7 mmHg in critically ill adults, as measured using 25 mL of distilled water instilled into the bladder; (2) IAH exists when the sustained or repeated IAP is greater than 12 mmHg; abdominal compartment syndrome (ACS) exists when the sustained IAP is greater than 20 mmHg and/or abdominal perfusion pressure ([mean arterial pressure] MAP-IAP) is less than 60 mmHg and associated with new organ dysfunction/failure (32). Severity is graded from one to four, based upon the IAP, with recommendations for management steps at each grade. A variety of risk factors for this condition exist. Management obviously involves reduction of the pathologically elevated IAP, most often by fluid removal, sedation and chemical paralysis, optimal patient positioning, decompression by NG drainage and, sometimes, by surgical decompression—decompressive laparotomy. Determining when abdominal decompression to improve splanchnic organ perfusion should be done remains controversial and is partially subjective (33). While this procedure can be life-saving, it is associated with considerable morbidity and mortality in both the short and long time frames.

**Acute Mesenteric Ischemia**

The splanchnic organs are perfused by three major arterial systems: those vessels radiating from the celiac axis (the left gastric, common hepatic, and splenic arteries) and perfusing the liver, stomach, and spleen; the superior mesenteric artery (SMA), supplying most of the small bowel and the right side of the colon; and the inferior mesenteric artery (IMA), supplying the left side of the colon, sigmoid, and superior portion of the rectum. Acute mesenteric ischemia may be caused by several conditions, such as classic arterial occlusion due to embolism (40% to 50% of cases), atherosclerosis, states of low cardiac output due to shock—including cardiogenic shock—mesenteric venous occlusion or, less frequently, arterial dissection, vasculitis, or nearby inflammatory conditions (34).
Manifestations of acute mesenteric ischemia may range from subtle findings of mild abdominal distention and/or mild pain to those of a devastating disease process of peritonitis, hypotension, circulatory collapse, and death. Reperfusion of the splanchnic organs with restoration of circulation to the affected organs may provoke a dramatic systemic inflammatory response (35). Difficulty in making a swift and accurate diagnosis, and in formulating and executing timely therapy, most often immediate surgical intervention, leads to staggering mortality: 60% to 80% (36).

Physical, laboratory, and radiologic findings in the patient with acute mesenteric ischemia can be difficult to analyze accurately. The presence of severe abdominal pain with few abdominal findings on physical examination in an individual (very often elderly) with risk factors is suggestive of mesenteric ischemia, and warrants immediate and aggressive investigation of this possibility. Patients with this condition—often sedated and mechanically ventilated ICU patients—making accurate abdominal examination quite difficult. Others may present with sudden overt peritoneal signs leading to pursuit of other acute abdominal conditions and delay in diagnosis. Laboratory investigation may reveal hemoconcentration and/or an otherwise unexplained metabolic acidosis or elevated lactate suggesting that progression to bowel injury has occurred. Occasionally, brisk lower GI tract bleeding or, more subtly, heme-positive stools may be discovered. Plain abdominal films are less specific, findings ranging from normal to the demonstration of ileus, portal vein air, air in the colonic wall, or free intraperitoneal air (Figs. 17.2 and 17.3). A contrast-enhanced abdominal CT scan is useful as it may identify the precise location of the compromised vessel (artery or vein) and the extent of visceral damage. Ominous signs such as air in the portal vein, the bowel wall, or free air in the peritoneal cavity may be seen. Bedside diagnostic laparotomy/laparoscopy is an option for patients too unstable to be moved for a radiologic study. Recently, treatment of acute mesenteric ischemia has evolved into a treatment strategy combining surgical and endovascular techniques. In suitable candidates, vascular occlusion of the SMA may be treated using catheters placed through the femoral or brachial artery to perform aspirative SMA embolectomy, SMA thrombolysis with recombinant tissue plasminogen activator (rtPA), or recanalization and stenting of the SMA. Such a procedure may be performed in combination with surgical intervention (37,38).

**Bacterial Translocation from the Gut**

The GI tract performs a variety of critical physiologic functions. One among them is the maintenance of the physiologic gut mucosal barrier, which prevents the passage of bacteria—or bacterial products such as endotoxin—into the systemic circulation (39). It has been theorized that the failure of the GI tract to maintain its functional integrity during profound physiologic stress—as in major traumatic injuries or severe burns—may contribute to the phenomenon of multiorgan system failure (MOSF) (40); the exact nature of this morbid interaction, however, remains obscure (41).

It is recognized that, once the gut undergoes a predisposing condition, such as an ischemia–reperfusion insult, bacteria and endotoxins can traverse the intestinal barrier and seed distant organs such as mesenteric lymph nodes (MLNs), solid organs, and the bloodstream, a phenomenon termed *bacterial translocation*. Evidence from several studies has linked BT and the systemic inflammatory response with postoperative sepsis in up to 14% of cases (40,42–44), although BT may only be
indicative of MOSF-associated pathologic gut permeability, rather than the cause of MOSF itself in this circumstance (45). Prevention of BT is essential, and is accomplished by careful maintenance of organ perfusion, judicious use of antibiotics, avoidance of excessive IV fluids, and the early institution of EN support (46) in preference to parenteral nutrition, although this assertion is controversial.

**Extrahepatic Biliary Disease**

Benign extrahepatic biliary disease (EBD) is a common reason for admission to the ICU, as it is often associated with sepsis and the inflammatory response. Epidemiologic data are startling: upward of 25 million Americans harbor gallstones, the consequences of which lead to the expenditure of more than $6 billion for medical and surgical treatment (47). The incidence of EBD increases with age, especially in women from all ethnic groups in the United States (48); it is particularly prevalent in native North Americans (49).

The most common form of EBD is “acute cholecystitis,” resulting from cystic duct obstruction, causing increased intraluminal pressure, venous congestion, and impairment of lymphatic drainage leading to inflammation and likely infection if unrelieved. The progression of acute inflammation of the gallbladder caused by cystic duct obstruction (50), to more serious conditions such as cholangitis—bacterial infection complicating biliary tract obstruction (51)—or emphysematous cholecystitis—infection with gas-forming anaerobic organisms (52)—with considerable morbidity and mortality may occur with delay in surgical consultation and in patients with chronic conditions such as diabetes mellitus or immunosuppression. The main cause of EBD is the presence of gallbladder calculi.

Cholecystitis in the absence of calculi (“acalculous cholecystitis,” or ACC) may be observed in those with a variety of critical conditions requiring prolonged intensive care (sepsis, major trauma, substantial life-threatening burns), and who are kept without oral intake and/or are receiving total parenteral nutrition (TPN) (53). Usual findings are fever, hyperbilirubinemia, and right upper quadrant pain, although the only finding may be that of SIRS of obscure origin. Sepsis from acute ACC may be difficult to identify because studies such as ultrasound lose their accuracy in the critically ill (54–56). ACC carries the risk of considerable mortality (57).

The most appropriate initial study when EBD is suspected is **bedside ultrasound of the right upper quadrant**, which is rapid, noninvasive, and relatively accurate (58). Specific signs of inflammation are thickening of the gallbladder wall to greater than 3.5 mm, and/or pericholecystic fluid. Abdominal CT scan may also be helpful in demonstrating pericholecystic fluid and tissue inflammation; the obvious serious disadvantage of CT is the need to transport the patient outside the ICU. Major and minor ultrasound and CT criteria exist which, when combined with radionuclide testing—if movement to the nuclear radiology suite is advisable in a critically ill ICU patient—usually identifies ACC or ACC if the intensivist recognizes often subtle findings and aggressively pursues diagnostic investigation. Of note is that nuclear cholecintigraphy has nearly perfect sensitivity in detection of acute cholecystitis (59), superior to ultrasound and CT, logistical difficulties notwithstanding.

The standard method of surgical treatment of acute cholecystitis is presently laparoscopic cholecystectomy (60). Alternatives to this approach, namely administration of antibiotics and analgesics, or nonsurgical but invasive procedures such as percutaneous transhepatic gallbladder drainage (PTGDB), percutaneous transhepatic gallbladder aspiration (PTGBA), endoscopic transpapillary gallbladder drainage and stenting (ETGBS), and endoscopic ultrasound-guided transmural gallbladder drainage (EUS-GBD) may be considered in the critically ill (61). The former two radiologic procedures provide long-term or transient, respectively, decompression and drainage of material from the enflamed gallbladder without the perils of general anesthesia, theoretically an attractive option to surgery in the critically ill. A Cochrane analysis was, however, unable to determine the role of percutaneous cholecystostomy compared to surgical treatment in the clinical management of high-risk surgical patients with acute cholecystitis (62). Procedures involving bile duct cannulation and placement of an intrabiliary pigtail drainage catheter or pigtail stent under endoscopic guidance show promising results nearly comparable to percutaneous procedures (63). A more recently developed procedure involves an endoscopically guided transgastric transmural needle followed by guidewire placement to the gallbladder and drainage tube or stent placement, offering the advantages of utility in the high-risk patient with perihilar ascites and avoidance of the risks of percutaneous procedures in those with marginal coagulation function (64). As to the very critically ill patient with acute ACC, a study of 1,725 patients revealed improved outcomes with percutaneous drainage compared to surgical (laparoscopic or open) cholecystectomy (65).

**Perforation of a Hollow Viscus**

Perforation of a hollow viscus with resultant intra-abdominal sepsis is a common cause for ICU admission. As such, the intensivist will frequently manage these patients who present a picture of bacterial sepsis. Patients with colonic perforation may demonstrate varying degrees of septic shock, while those with perforated peptic ulcer disease most often present initially with chemical peritonitis and progress rapidly to bacterial peritonitis with time. Surgical management is obviously integral to such a patient’s care, and thus coordination between the anesthesia, surgical, and critical care teams is of great importance.

The combination of an acute abdomen with rapid deterioration of the patient’s condition should warrant investigation of the possibility of a perforated hollow viscus. In those abdominal infections caused by perforation of a hollow viscus, the accumulation of infectious material may reside within a conining space adjacent to the perforated organ, such as in the left lower quadrant in the case of a perforated diverticulum in the descending colon and eventually forming into an abscess cavity if not recognized, or more widespread as with a posterior perforating peptic ulcer (66). The emergent nature of the presentation will dictate the next step. Bedside plain abdomen films may demonstrate pneumoperitoneum (67); ultrasound may show, in experienced hands, pneumoperitoneum (68). CT scan may show very small volumes of free fluid and pneumoperitoneum, identify inflammatory changes of the duodenal wall and of surrounding organs (69), or small volumes of air and spillage from colonic perforation (70). Early source control—removal of inflammatory material—is integral to successful management of perforation-related peritonitis (71).
sometimes employing a “damage control” surgical strategy in the sickest and most marginally compensated patients. Aggressive supportive and perioperative care is also crucial to optimize outcome, including proper selection of antimicrobial coverage (72).

The Abdomen as an “Unknown Source of Sepsis”

Evaluation of the abdomen as the source of sepsis in the ICU patient is difficult, and the stakes are quite high in that mortality from blood stream infection of abdominal origin is high (73). Clinical examination in a neurologically intact patient remains the gold standard used to rule out an acute surgical abdomen and the identification of the abdomen as a source of sepsis. This is not the case in many critically ill patients in whom neurologic impairment due to the primary disease, or resultant from sedation, abrogates good communication with the patient and a dependable clinical examination; indeed, performing a good clinical examination was not possible in 43% to 69% of patients in the ICU (74). Frequently, the elderly (75) or patients immunosuppressed by virtue of antirejection medication for organ transplant (76) may be unable to mount an inflammatory response such that peritoneal signs sufficient to facilitate immediate recognition are present; these patients may appear only to be “getting sick” despite gross peritoneal contamination. Particularly difficult are those who have had recent previous abdominal surgery and in whom an intra-abdominal septic complication could be a potential cause of critical illness.

How is one to open the “black box” of the abdomen and identify an occult source of infection, while significantly not identifying the source of infection, while significantly铝合金 from blood stream infection of abdominal origin is high (73). Clinical examination in a neurologically intact patient remains the gold standard used to rule out an acute surgical abdomen and the identification of the abdomen as a source of sepsis. This is not the case in many critically ill patients in whom neurologic impairment due to the primary disease, or resultant from sedation, abrogates good communication with the patient and a dependable clinical examination; indeed, performing a good clinical examination was not possible in 43% to 69% of patients in the ICU (74). Frequently, the elderly (75) or patients immunosuppressed by virtue of antirejection medication for organ transplant (76) may be unable to mount an inflammatory response such that peritoneal signs sufficient to facilitate immediate recognition are present; these patients may appear only to be “getting sick” despite gross peritoneal contamination. Particularly difficult are those who have had recent previous abdominal surgery and in whom an intra-abdominal septic complication could be a potential cause of critical illness.

How is one to open the “black box” of the abdomen and identify an occult source of infection, while significantly not identifying the source of infection, while significantly...
The diagnosis of ileus is often inaccurate and is based on significant preconceptions that are frequently erroneous. For example, it is often believed that surgical intervention on the GI tract results in ileus and that, postoperatively, this patient should be kept without oral or enteral intake. Similar misconceptions are often observed with artificially established amounts of gastric residuals or NG outputs. Paradoxically, multiple patients are often kept without enteral intake, which only exacerbates GI dysfunction and provides an inadequate and/or inappropriate diagnosis of ileus.

Ileus must be carefully identified by radiographs and a thorough clinical assessment. Careful hydration and restoration of splanchnic blood flow through adequate resuscitation are essential. The judicious use of enteral nutritional support and avoiding prolonged time periods without enteral intake are essential to the prevention and treatment of ileus. Furthermore, the careful treatment of the cause of an ileus, such as sepsis, will often result in the spontaneous resolution of the GI process. Maintenance of fluid and electrolyte balance are also important.

### Enteral Nutrition

#### When to Feed?

Enteral nutrition (EN) has proven to be beneficial, and should be started as soon as possible in the ICU patient, as there are multiple studies demonstrating its benefits. For example, Moore et al. (87) found that starting early enteral nutrition (EEN) significantly decreased the risk of infections ($p < 0.05$). In contrast, the use of TPN (TPN)—particularly when selected instead of EEN—was associated with significant harm when performed by inexperienced personnel and/or if there was inadequate patient selection. In fact, a recent meta-analysis of 18 RCTs illustrated that EN was associated with decreases in infectious complications ($p = 0.004$) and ICU-LOS ($p = 0.0003$) when compared to parenteral nutrition (88).

The mechanisms that explain why EEN is superior to TPN are only partially understood. Routinely, patients on TPN achieve higher caloric goals than on EEN but, despite this practice, patients routinely do better in the absence of TPN. Thus, the benefits of EEN are not linked to the number of calories received by the patient. Starvation is associated with increased mucosal permeability along with increased expression of ICAM-1, favoring the migration of PMNs to the intestine wall.

### Gastrointestinal Dysmotility and Intolerance

Normal GI motility permits a downstream (aboral) progression of secreted fluids and food through the GI tract. It also prevents bacterial overgrowth and provides the adequate contact of nutrients with the gut mucosa, thereby allowing digestion and absorption. Intolerance in enterally fed patients is documented at 30.5% to 33%, with higher levels of intolerance observed in critically ill patients (84,85). The definition of “intolerance” is somewhat subjective. In 2012 the Working Group on Abdominal Problems (WGAP) of the European Society of Intensive Care Medicine (ESICM) developed definitions for GI dysfunction (Table 17.3) (86). Loss of coordinated propulsive motor impulses may result in decreased digestion and absorption of food and liquids, GI intolerance, and the lack of passage of flatus or stool; this is called ileus. Ileus is therefore a functional intestinal obstruction in the absence of mechanical evidence of obstruction.

Ileus, in its worse clinical presentation, is a manifestation of organ (GI) dysfunction or failure. Ileus can result in ACS, severe electrolytic disturbances, and bacterial overgrowth. Furthermore, the presence of ileus precludes successful enteral nutritional interventions. For these reasons, adequate identification of ileus is an essential aspect of care of the critical care physician.

The diagnosis of ileus is often inaccurate and is based on significant preconceptions that are frequently erroneous. For example, it is often believed that surgical intervention on the GI tract results in ileus and that, postoperatively, this patient population should be kept without oral or enteral intake.

### Table 17.3 European Society of Intensive Care Medicine (ESICM) Definitions for GI Dysfunction in the Critically Ill

<table>
<thead>
<tr>
<th>AGI Grade</th>
<th>Definition</th>
<th>Manifestation</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Increased risk of developing GI dysfunction or failure (a self-limiting condition)</td>
<td>Postoperative nausea and/or vomiting during the first days after abdominal surgery; postoperative absence of bowel sounds, diminished bowel motility in the early phase of shock</td>
</tr>
<tr>
<td>II</td>
<td>GI dysfunction (a condition that requires interventions)</td>
<td>Gastroparesis with high gastric residuals or reflux, paralytic of the lower GI tract; diarrhea, intra-abdominal hypertension (IAH) grade I (intra-abdominal pressure (IAP) 12–15 mmHg), visible blood in gastric content or stool. Feeding intolerance is present if at least 20 kcal/kg BW/day via enteral route cannot be reached within 72 hrs of feeding attempt</td>
</tr>
<tr>
<td>III</td>
<td>GI failure (GI function cannot be restored with interventions)</td>
<td>Despite treatment, feeding intolerance is persisting—high gastric residuals, paralytic of GI paralytic, occurrence of worsening of bowel dilatation, progression of IAH to grade II (IAP 15–20 mmHg), low abdominal perfusion pressure (APP) (below 60 mmHg). Feeding intolerance is present and possibly associated with persistence or worsening of MODS.</td>
</tr>
<tr>
<td>IV</td>
<td>Dramatically manifesting GI failure (a condition that is immediately life threatening)</td>
<td>Bowel ischemia with necrosis, GI bleeding leading to hemorrhagic shock. Ogilvie syndrome, abdominal compartment syndrome (ACS) requiring decompression</td>
</tr>
</tbody>
</table>

AGI: acute gastrointestinal injury.

compared with enteral-fed animals (89). Another interesting experiment showed that adding botulinum, an analogue of gastrin-releasing peptide, can recover the GALT in mice on TPN and, indeed, preserve the immune response to infections (90). Kudsk (91) reviewed the literature regarding EEN, finding fewer infections and better outcomes when such therapy was used. In addition, Andrad et al. (92) studied rats receiving either standard TPN or glutamine-enriched TPN. They found less BT in the group on glutamine-enriched TPN, suggesting that glutamine, an amino acid, improves the response to antigens and increases the IgA levels, as reported previously (93). Other authors have reported that EEN prevents GALT atrophy and the development of SIRS/MOD (94–96).

Monitoring Tolerance and Meeting Nutritional Goals

The typical critically ill patient receives less than 40% of their estimated needs (97); higher protein and calorie delivery in the ICU has been shown to significantly increase ventilator-free days (98). Achieving at least 80% of prescribed protein intake has been linked to improved survival (99). Appropriate prophylaxis for and management of feeding intolerance is an important component to meeting nutrition needs in critically ill patients (100,101). Feeding protocols can be effective in increasing the percentage of nutrition needs delivered (97).

SUMMARY

A healthy GI tract is essential for the survival of the patient with acute/critical illness. The GI tract can be a source of severe life-threatening acute illnesses that necessitate care in an ICU setting. On the other hand critical illness associated with hemodynamic instability, sepsis, and shock can cause significant alterations in GI function. An abnormal GI tract can worsen or perpetuate a persistent inflammatory–immunosuppressive response.

EN provides the healthiest and most appropriate form of nutrition in the critical care setting and should be used whenever possible. In addition to its roles in processing food, the GI tract plays other essential neuroendocrine and immunologic roles. Recently, increasing attention to the microbiome has been paid. A healthy microbiome can be severely disrupted during acute/critical illness. Restoring microbial homeostasis may prevent complications in the ICU and help in restoring health.

Key Points

- The classic role of processing and absorbing nutrients continues to be the main route by which patients are fed through their critical illness.
- There are important and specific roles for the different anatomic portions of the GI tract. Thus physiology of the GI can only be understood if we also understand the anatomy.
- The neuroendocrine system in the GI tract is of importance. Thus, the GI tract influences/affects the functions of distant organs/systems including the central nervous system.
- The GI tract is the single most important repository of immune tissues. The complexity is highlighted by the distribution and role of the cells of the immune system across the GI tract.
- There is an increasing awareness of the importance of the microbiome, distributed across the GI tract, in the maintenance of health and in the symbiotic relationship that exists with the host. A growing body of knowledge informs us to the importance of dysbiosis as a cause of disease and the impact of critical illness on microbiome balance.

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