Gastric disorders: modifications of gastric content, antacids and drugs influencing gastric secretions and motility

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Abstract

Gastric disorders have significant relevance to the fields of both anaesthesia and intensive care medicine. Pneumonitis and development of pneumonia in the perioperative period are significant complications following aspiration of gastric acid and stomach contents. Anaesthetists play a key role in minimizing this risk through careful patient selection, pre-assessment and pharmacological management of gastric acid. Proton pump inhibitors are the most used drug class to reduce the risk of stress-related mucosal damage in intensive care and perioperatively. Histamine-2 receptor antagonists and sucralfate are also effective but not routinely used in clinical practice. Sodium citrate is still commonly used in obstetric anaesthesia. Ventilated patients in intensive care may also suffer from intestinal failure either subsequent to postoperative ileus, pharmacological treatments or as part of multi-organ dysfunction. Many strategies have been proposed for the management of intestinal failure in critical care; however, evidence is lacking in this area. Prokinetics including metoclopramide and erythromycin remain key drugs in the management of intestinal failure in current practice.

Keywords Critical care; gastric acid; histamine H2 agonists; intestinal failure; proton pump inhibitors

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Learning objectives

After reading this article you should be able to:

- describe basic gastric physiology and the components of gastric acid
- discuss the various pharmacological strategies to reduce the risk of aspiration of gastric contents in the perioperative setting
- discuss intestinal failure in critical care and describe currently utilized pharmacological strategies for managing intestinal failure in the intensive care unit

Introduction

Airway protection is an important consideration of the anaesthetist and intensive care physician, and as such an understanding of the physiology of gastric acid secretion and disorders is of vital importance. The stomach is the primary organ involved in: the initial digestion of food; the absorption of certain nutrients and drugs; and killing ingested microorganisms to reduce intestinal infections. Gastric acid physiology and its manipulation have important implications for airway aspiration, ventilator-associated pneumonia and stress ulceration.

Aspiration of gastric contents in the absence of protective laryngeal reflexes is an important risk in anaesthesia, with potentially fatal consequences. Risk factors for aspiration of gastric contents include: emergency surgery, abdominal surgery, the lithotomy position, obesity, functional dyspepsia, gastroparesis, lack of patient fasting, certain drugs (such as opioids and clonidine) and severe illness. The anaesthetist must consider these predisposing factors in order to mitigate the risk of regurgitation and pulmonary aspiration.

Pulmonary aspiration of solid contents can result in airway obstruction, whilst aspiration of gastric fluid results in an inflammatory pneumonitis. Factors predisposing to pneumonitis following aspiration include: a gastric content with pH <2.5, increased volume of aspirate, reduced lower or upper oesophageal sphincter tone, poor swallow coordination and a depression of protective airway reflexes. Other important conditions include peptic ulcer disease and functional dyspepsia, both of which require treatment.

Gastric physiology

An understanding of the basic gastric physiology is essential in order to understand the pharmacology of the drugs which modify its function. The stomach is a dilated, muscular hollow organ located between the oesophagus and the duodenum. The functions of the stomach include:

- temporary storage of food
- secretion of digestive enzymes
- mechanical breakdown of food
- secretion of gastric acid
- secretion of intrinsic factor
- hormonal secretion.

The stomach consists of four anatomical areas: the fundus, cardia, body and pylorus (Figure 1) and contains two distinct

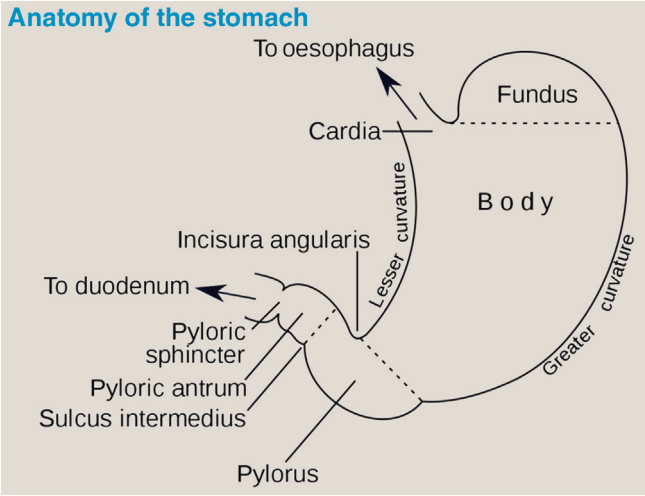


Figure 1

functional areas: the oxyntic and the pyloric. The oxyntic area occupies most of the stomach and contains two types of cell: the parietal cells and the chief cells (Figure 2). Parietal cells release hydrochloric acid and intrinsic factor. Chief cells are found at the base of the gastric glands and secrete pepsinogen. The pyloric area contains mainly G cells which secrete gastrin.

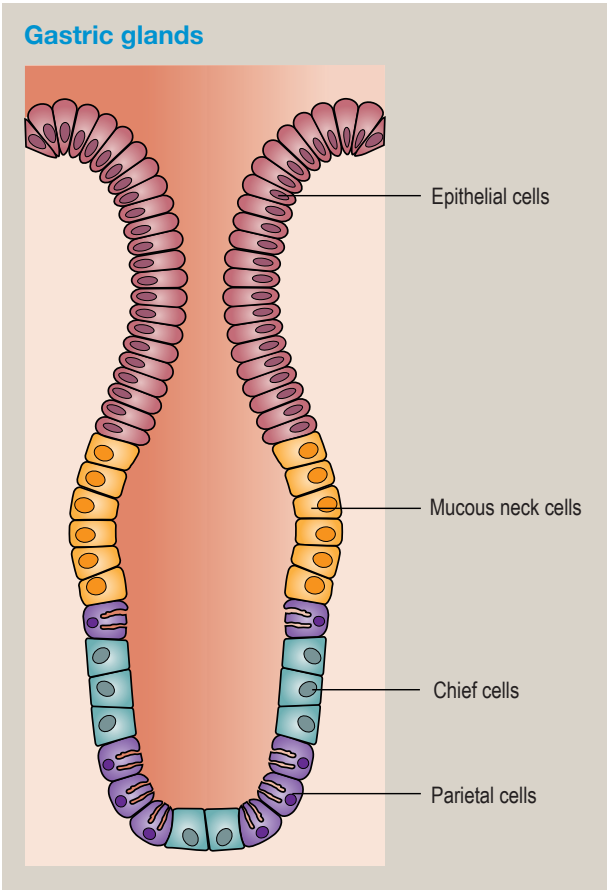


Figure 2

Gastric acid

The stomach produces 2 litres of gastric fluid per day containing a mixture of hydrochloric acid, pepsinogen, gastrin, intrinsic factor and mucus. Their functions are given in Table 1.

Hydrochloric acid (HCl), released by parietal cells, has a pH of 0.8. Parietal cells are stimulated by histamine, the parasympathetic nervous system and gastrin. Pepsinogen, a proenzyme, is converted to pepsin, a peptidase that begins protein digestion. Pepsinogen secretion is stimulated by gastrin and parasympathetic activity. Gastrin is a peptide hormone which acts to increase HCl secretion, increase gastrin secretion and to increase gastric motility. Intrinsic factor, released by parietal cells, is essential for vitamin B_{12} absorption. Mucus is secreted onto the gastric mucosa in order to protect it from the harsh acidic environment and to lubricate food. The secretion of hydrochloric acid from parietal cells is described in Figure 3.

Gastric acid secretion comprises three phases: cephalic, gastric and intestinal. The cephalic phase is the parasympathetic response to the sight, smell and anticipation of food. This results in secretion of HCl, gastrin and pepsinogen. The gastric phase is triggered by the distention of the stomach by food which stimulates the release of gastrin release from G cells, which in turn promotes pepsinogen, histamine and HCl secretion. The intestinal phase occurs when churned food (chyme) enters the duodenum. This results in secretin release from the duodenum, which reduces the acidity of the chyme.

Gastric emptying

During gastric emptying, chyme is delivered to the distal stomach where it is gradually allowed to pass into the duodenum by the pyloric sphincter. The opening of the pylorus is controlled by gastrin, which increases gastric motility, and by the presence of undigested food in the duodenum. Peptides such as cholecystokinin (CCK), secretin, gastric inhibitory peptide and enteroglucagon are secreted from the duodenum and alter motility patterns and gastric emptying. Motility is also stimulated throughout the gastrointestinal (GI) tract by serotonin (5-HT), secreted from enterochromaffin cells in response to food in the lumen, and by motilin, a peptide that increases peristalsis.

Drug absorption

Most drug absorption occurs in the small intestine where there is a less hostile environment and a much greater surface area. Some clinically significant absorption of small molecules occurs in the stomach including amino acids and some water-soluble vitamins. Water is also absorbed from the stomach in the presence of dehydration. Drugs absorbed in the stomach include aspirin, caffeine and ethanol.

Stress ulceration

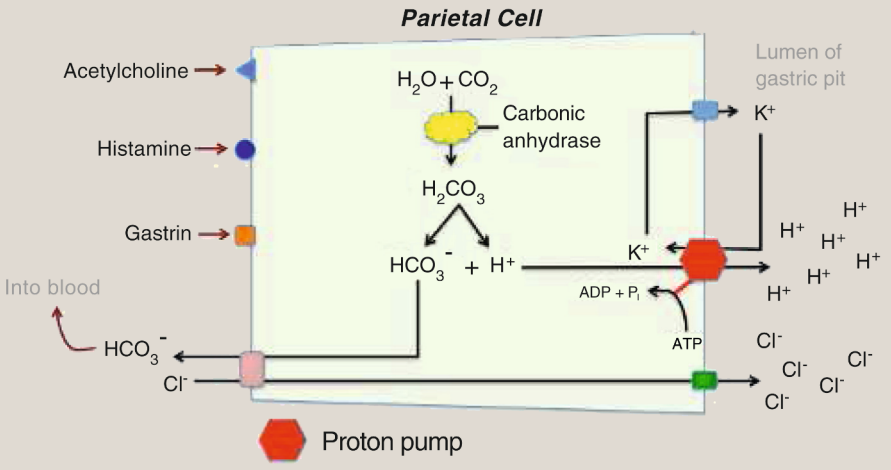
Stress ulceration refers to the ulceration of the upper GI tract (oesophagus, stomach, duodenum) as a consequence of hospitalization and is caused by impaired mucosal protection and hypersecretion of gastric acid. The usual protection from mucosal cells is affected by hypovolaemia, shock, sepsis and trauma. In some critical care pathologies, such as neurotrauma, there is hypersecretion of gastric acid due to activation of G cells and secretion of gastrin. Stress-related mucosal damage (SRMD)

Components of gastric acid

Component	Secreted by	Stimulated by	Function
Hydrochloric acid	Parietal cells	Histamine Parasympathetic stimulation Gastrin	• Breakdown of protein • Activates pepsinogen to pepsin • Improves absorption of calcium and iron • Kills pathogenic microorganisms
Pepsinogen	Chief cells	Parasympathetic stimulation Gastrin	• Proenzyme of pepsin • Converted to pepsin by the acidic environment • Begins the process of protein breakdown
Gastrin	G cells	Parasympathetic stimulation Stomach distention Presence of partially digested proteins in stomach	• Stimulation of parietal cells to secrete HCl • Stimulation of enterochromaffin-like cells to secrete histamine • Stimulation of chief cells to secrete pepsinogen • Stimulation of gastric motility
Intrinsic factor	Parietal cells	—	• Glycopeptide involved in the absorption of vitamin B_{12}
Mucus	Mucus cells	—	• Protection of gastric mucosa from acidic environment • Lubrication of the stomach wall

Table 1

Hydrochloric acid secretion from parietal cells



This process involves: 1. Diffusion of CO_2 into the cell from the blood. 2. Formation of bicarbonate and H^+ from H_2O and CO_2. 3. Secretion of H^+ is secreted into lumen in exchange with K^+ in through the H^+/K^+ adenosine triphosphatase (ATPase; the proton pump). 4. Exchange of HCO_3^- with Cl^- at the basolateral membrane, Cl^- leaves with K^+ across the apical membrane.

Figure 3

is common in critically ill patients. The Canadian Critical Care Trials Group identified mechanical ventilation for more than 48 hours and coagulopathy/thrombocytopenia as major risk factors in addition to other potential risk factors (see Box 1).

The main risk of stress ulceration is secondary GI bleeding. The incidence of clinically important bleeding events (defined as macroscopic bleeding resulting in haemodynamic instability or the need for red blood cell transfusion) is approximately 3.5% of patients ventilated for 48 hours or more. The most common sites for stress ulcers are in the fundus and body of the stomach. Lesions here tend to occur early (within hours), are shallow and do not usually result in major haemorrhage. Ulcers that develop after the first few days of critical illness tend to be deeper and more distal with a greater risk of major haemorrhage and perforation.

The incidence of stress ulcers in the critical care patients with no prophylaxis is very high (>75%). However, the incidence of clinically significant bleeding is much lower at around 1%. Nonetheless, the increased mortality associated with a GI bleed has resulted in a trend towards regular pharmacological stress-ulcer prophylaxis.

Stress ulcer prophylaxis

The most commonly used group of agents for stress ulcer prophylaxis are proton pump inhibitors (PPIs). Histamine H2

Potential risk factors for stress ulceration

- Shock
- Sepsis
- Hepatic failure
- Renal failure and renal replacement therapy
- History of peptic ulcer disease and upper gastrointestinal bleeding
- Multi-morbidity
- Extracorporeal life support
- Major trauma
- Neuro-trauma
- Major burns
- Organ transplantation
- Antiplatelet agents
- Non-steroidal anti-inflammatory drugs (NSAIDs)

Box 1

receptor antagonists (H2RAs) and sucralfate can also be used. Drug metabolism is an important consideration as organ dysfunction is common in critical illness and dosing alterations may be required.

Sucralfate

Sucralfate is less efficacious than both PPIs and H2RAs but may be used when these are contraindicated. It must be administered enterally and therefore requires the presence of a nasogastric tube patients who are intubated. Sucralfate is a basic aluminium salt of sucrose octasulphate and forms a viscous paste which adheres preferentially to ulcers by ionic binding, so acts without altering gastric pH and does not increase the risk of ventilator-associated pneumonia. However, it may have reduced effectiveness after administration of feed or acid-suppressing agents and can reduce the efficacy of warfarin, phenytoin, digoxin and fluoroquinolones by drug binding. Adverse effects include constipation, feeding tube occlusion, bezoar formation, aluminium accumulation (particularly in renal impairment) and hypophosphataemia. It is not commonly used as a consequence of its adverse effects and route of administration.

Histamine H2 receptor antagonists

H2RAs significantly reduce the risk of stress ulcers compared with placebo. They are also used for treatment of peptic ulcer disease and reflux oesophagitis and prior to general anaesthesia, in patients at risk of acid aspiration. They act via competitive blockade of histaminergic H2 receptors as histamine is a direct secretagogue and is necessary to potentiate the action of gastrin and acetylcholine on the gastric parietal cell. Tachyphylaxis to H2RAs develops during prolonged IV dosing, meaning pH is not reliably maintained above 4. Tolerance can develop in 48 hours, thought to be caused by increasing competitive inhibition from endogenous histamine. H2RAs do not inhibit vagally-induced acid secretion, lessening their efficacy in neurosurgical or brain injury patients.

Adverse effects include headaches, dizziness, diarrhoea, nausea, constipation and, rarely, thrombocytopenia, changes in liver function and interstitial nephritis. By raising gastric pH, they promote the proliferation of Gram-negative bacteria in the stomach and increase the risk of ventilator-associated pneumonia. H2RAs are renally excreted and require dose adjustment in patients with renal impairment. Despite the efficacy of H2RAs, their practical use has been significantly limited since 2020 when the US Food and Drug Administration (FDA) requested withdrawal of ranitidine from the market due to an investigation over contamination with N-methyl-D-aspartate (NMDA). Cimetidine was the prototype H2RA but is not routinely used in the intensive care unit (ICU) because of its extensive adverse effect profile and multiple drug interactions. Nizatidine and famotidine are not associated with significant drug interactions but are not commonly used in the ICU setting.

Proton pump inhibitors

PPIs are the most commonly used agents for stress ulcer prophylaxis. The parietal cell hydrogen potassium adenosine triphosphatase (HK-ATPase) pump is the final common pathway of gastric acid secretion, to which derivatives of PPIs bind irreversibly, non-competitively inhibiting its action and hence reducing acid secretion. Tachyphylaxis has not been demonstrated with PPIs and evidence suggests they improved efficacy compared to H2RAs in the reduction of stress ulcers.

PPIs are also used in critical care to treat clinically significant mucosal bleeding caused by stress ulceration, upper GI bleed due to peptic ulcer disease, Zollinger–Ellison syndrome and *Helicobacter pylori* infection. Adverse effects include headaches, diarrhoea, nausea, constipation and pruritis. PPIs may be associated with an increase in ventilator-associated pneumonia and with an increased risk of developing *Clostridioides difficile* infection. PPIs are also a cause of drug-induced acute interstitial nephritis.

PPIs are metabolized via hepatic cytochrome P450 enzymes, with CYP2C19 predominating. Polymorphisms of CYP2C19 result in rapid and intermediate metabolizers which can impact on the effectiveness of PPIs in these individuals. At present there is no routine pharmacogenomic testing with PPIs. In hepatic failure, omeprazole and lansoprazole may need dosing adjustments. However, due to its linear dosing characteristics, no adjustments need to be made for pantoprazole. Although renally excreted, there are no dose adjustments that need to be made for any of the PPIs in patients with renal failure or renal replacement therapy.

The extent of drug interactions among the PPI class varies considerably. Whilst omeprazole has shown interactions with warfarin, diazepam, phenytoin, digoxin, carbamazepine and clopidogrel; pantoprazole shows no meaningful drug interactions.

Antacids

There is little evidence to support the routine use of agents which reduce the risk of aspiration during anaesthesia. However, in those at particularly high risk of aspiration, e.g. full stomach and gastrooesophageal reflux, antacids may be used. Antacids work by neutralizing stomach acid and reducing delivery of acidic content to the duodenum. They are typically salts of calcium, magnesium, sodium or aluminium. The neutralization of hydrochloric acid results in a rise in stomach pH.

The best example of this is the full-term pregnant patient undergoing general anaesthesia. In this circumstance 30 ml of 0.3 molar sodium citrate given 10 minutes before induction of anaesthesia will raise the pH of intra-gastric contents. However, the clinically meaningful benefits of this intervention have not been shown.[1] Potential adverse effects of antacids include aluminium toxicity (if the antacid contains aluminium), electrolyte disturbance, diarrhoea and feeding tube blockage.

Intestinal failure

In addition to SRMD, many patients suffer from intestinal failure either as a result of postoperative ileus or as a consequence of multi-organ dysfunction and associated treatments. Intestinal failure is the inability of the gut to absorb sufficient water, macronutrients (carbohydrate, protein and fat), micronutrients and electrolytes. It can be associated with disturbances in motility and absorption, breaches in mucosal integrity, increased intra-abdominal pressure and predisposes the patient to further life-threatening emergencies including ischaemic bowel, sepsis, GI haemorrhage and GI tract perforation.

Clinical signs of gut failure can be suggested by absent bowel sounds, regurgitation, vomiting, high gastric aspirate volumes, diarrhoea and/or abdominal distension. The lack of specific radiological signs of intestinal failure often leads to delays in recognition and poor clinical outcomes.

In terms of clinical assessment, several methods to assess gastric emptying have been employed in clinical research (e.g. scintigraphy, paracetamol absorption test) but these are not useful in clinical practice. Some work has been undertaken exploring the use of novel biomarkers such as citrulline, which is thought to represent enterocyte function whereby a serum citrulline concentration <10 micromol/litre is associated with increased mortality. Unfortunately, the translation of biomarkers to clinical practice has been limited by several factors including timing of sampling, extent of surgically induced damage, co-existence of other organ dysfunction and previous gut surgery and length of intact bowel.

When enteral feeding is established, most ICUs will intermittently measure the gastric residual volume and consider reducing the rate of enteral feeding once the residual volume meets a pre-set volume – anywhere between 150 ml and 500 ml. One study from 2011 did demonstrate no benefit to measuring residual volumes and in fact found no difference in incidence of ventilator-associated pneumonia or overall outcome when the residual volume was not measured at all during the ICU stay.[2] However, high gastric aspirates remain one of the most commonly used surrogates suggestive of intestinal failure in ICU.

Drugs affecting gastrointestinal motility

The risk of intestinal failure can be mitigated with the use of drugs affecting GI motility. This class of drugs is one of the most common pharmacological interventions involving the GI tract in critically ill patients.

Metoclopramide is an anti-emetic and prokinetic which primarily works via antagonism of peripheral dopaminergic (D2) receptors and selective stimulation of gastric muscarinic receptors. Although it can be given orally, oral bioavailability is variable (30–90%) so is most often given intravenously at a dose of 10 mg every 6 hours. At this dose, metoclopramide is shown to reduce gastric residual volumes by 30% at 24 hours however this effect is short lived. Domperidone, another dopamine antagonist, has also been used although it is only available as an oral preparation which limits its use in critically unwell ventilated patients.

Erythromycin, a macrolide antibiotic, has also been used to stimulate motilin receptors in the GI tract. While evidence suggests it may be more effective than metoclopramide its use is limited by concerns about antimicrobial resistance. While combination of both erythromycin and metoclopramide has been shown to be more effective than either agent alone, tachyphylaxis and arrhythmias prevent this from being commonly used in clinical practice.[3,4]

A non-antibiotic motilin agonist was developed for the prevention of intestinal failure but failed to demonstrate any significant difference in feed absorption between the treatment and control arms of a large randomized control trial.[5] The lack of any other novel pharmacological agents means that management strategies largely advocate the use of metoclopramide and erythromycin and emphasize multidisciplinary assessment as the mainstay of treatment.

Given that stimulation of opioid or α-2 adrenergic receptors can inhibit gastric motility, some research has shown that in post-operative management following colorectal surgery, restoration of GI motility is achieved with early postoperative feeding, multimodal analgesia and opiate restriction, though there is a lack of evidence to support this in general ICU populations, but it is worth bearing in mind the likelihood of opiates in contributing to critical care related intestinal failure when managing this patient group.[6]

Conclusions

Gastric complications such as SRMD, GI bleeding, aspiration pneumonia and intestinal failure are common in critically ill patients and associated with significant morbidity and mortality. A variety of pharmacological strategies are available but there is a clear need for novel agents with improved efficacy and fewer interactions and adverse effects. ◆

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