Review

Gastrointestinal complications in critical care patients and effects of mechanical ventilation on the gastrointestinal tract

Adham E Obeidat MD [1], Sandeep Randhawa MD [1]

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Abstract

Patients in the intensive care unit (ICU) especially those who require mechanical ventilation are at increased risk for developing gastrointestinal (GI) complications such as bleeding, infection, and motility dysfunction. It is estimated that the prevalence of GI complications in those patients is approximately 50-80% and lots of those go undiagnosed.

Complications can affect different parts of the GI system, including the esophagus, stomach, small intestine, large intestine, liver, and pancreas. Effects might include dysmotility, diarrhea, inflammation, infection, direct mucosal injuries, ulcerations, and bleeding, and it can be associated with high mortality rates. Moreover, it is believed that the GI tract has a significant contribution in the development of multiple organ dysfunction syndrome (MODS) in critically ill patients.

Mechanical ventilation either alone or in association with other critical illness may have a multitude of effects on almost all the organs of the gastro-intestinal tract. Attention of those interaction and side effects can improve outcomes and potentially mortality.

In this review, we describe the mechanisms proposed for mechanical ventilation induced GI complications and different GI complications which can affect the critically ill patient.

Keywords: PEEP, Prone position, Dysmotility, GERD, GI bleeding, Ileus, Aspiration, Acalculous cholecystitis,

Authors
1. University of Hawaii, Internal Medicine Residency Program, Honolulu, Hawaii, USA

Corresponding author: Adham E Obeidat: adhamobedat91@gmail.com

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Introduction

Patients in the intensive care unit (ICU) are at increased risk for developing gastrointestinal (GI) complications such as bleeding, infection, and motility dysfunction. It is estimated that the prevalence of GI complications in those patients is approximately 50-80%. [1,2,3]

Complications can affect different parts of the GI system, including the esophagus, stomach, small intestine, large intestine, liver, and pancreas. Effects might include dysmotility, diarrhea, inflammation, infection, direct mucosal injuries, ulcerations and bleeding, and it can be associated with high mortality rates. [1,2,3]

Moreover, it is believed that the GI tract has a significant contribution in the development of multiple organ dysfunction syndrome (MODS) in critically ill patients. [4]

Mechanical ventilation effects on GI organs

Positive End-Expiratory Pressure

Positive End-Expiratory Pressure (PEEP) is the most extensively investigated variable while assessing GI complications of mechanical ventilation and several mechanisms have been proposed.

The effect of PEEP on cardiac output and left ventricular performance were documented for over half a century. [5,6] By increasing the right ventricle preload and afterload, high PEEP levels can lead to increased right atrial pressure and decreased systemic venous return with resulting reduced left ventricle filling and cardiac output. [7]

The splanchnic circulation is particularly susceptible to reduced blood flow due to absence of autoregulation and a possible persistent vasoconstrictor response even after hemodynamic stability is achieved. [8] Indeed, several studies have documented PEEP induced decreased splanchnic flow. [9–17]

Beyer and colleagues evaluated the effect of PEEP in dogs with intact vs. oleic-acid induced lung injury and demonstrated a significant reduction in cardiac output and regional blood flow to splanchnic organs. Further, the decrease in blood flow was inversely proportional to PEEP level and the flow deficit persisted despite volume expansion with dextran. The spleen and pancreas were shown to be susceptible to these effects. [10]

Other studies were able to replicate similar results demonstrating a linear correlation between fall in cardiac output and portal blood flow. [14,17]

The effect of PEEP also appears to be dose related with several studies demonstrating a greater fall in cardiac output and portal flow at higher PEEP levels. [9,11] These suggest that the PEEP induced decreased portal flow to be at least partially a function of volume status. Indeed, studies have demonstrated a significant improvement in PEEP induced decreased portal and hepatic flow with volume expansion. [9,18]

PEEP induced decreased splanchnic flow has also been postulated to be secondary to catecholamine response. [8] Both animal and human studies have demonstrated increased catecholamines in subjects treated with higher PEEP levels. [19–21] Indeed, both dopamine and dopexamine have been shown to at-least partially reverse the effects of PEEP on splanchnic flow. [12,22] The response has also been postulated to be dependent on the alpha-adrenergic stimulation. [23,24] However, one prior study demonstrated that the decreased blood flow to be independent of sympathetic outflow. [25]

Studies evaluating the effect of PEEP on hepatic blood flow have lacked a consistent outcome. While some studies have consistently demonstrated a decrease in hepatic blood flow due to PEEP. [12,15,18] A study performed by Aneman and colleagues demonstrated no change in hepatic blood flow. [25] This has been explained by the Hepatic Arterial Buffer Response (HABR) wherein the decrease in portal blood flow secondary to PEEP is accompanied by increased hepatic arterial flow to preserve total hepatic blood flow. [26] Further, PEEP mediated hepatic flow blood changes are also altered in presence of sepsis. [13] On the contrary, several studies have also failed to demonstrate any PEEP induced changes in splanchnic perfusion. [27–29]

Further, the clinical relevance of these changes in blood flow remains obscure. Decrease in organ blood flow secondary to PEEP should lead to reduced oxygen delivery and consequent organ ischemia. Initially, Fournell and colleagues demonstrated a decrease in intestinal mucosa oxygenation in anesthetized dogs treated with PEEP of 15 cm H_2O. [30] Berendes and colleagues also demonstrated a PEEP induced decrease in hepatic venous oxygen saturation in patients undergoing abdominal surgery which was particularly prominent at PEEP 15 cm H_2O. [31] However, other studies evaluating PEEP induced changes in gastric mucosal blood flow revealed a maintained gastric perfusion. [28,32] Furthermore, although portal blood flow can be decreased with PEEP, the liver is capable of increasing oxygen extraction. Although this may lead to decreased mixed venous oxygen levels, tissue oxygenation and function are maintained.

Indeed, although PEEP has led to a decreased splanchnic perfusion in prior studies, hepatic oxygen consumption has remained stable indicating normal function. [12,15] However a study by Träger and colleagues have shown that ventilation with PEEP of 15 cm H_2O in patients with sepsis lead to altered liver metabolism suggesting impaired perfusion and oxygenation. [33]

To summarize, although PEEP might lead to a decrease in the splanchnic perfusion, its clinical relevance is unclear. The decrease in blood flow also appears to be a function of volume status. Though aggressive volume replacement might lead to worsening pulmonary edema and subsequent difficulty in weaning from ventilator, [34] adequate volume replacement can prevent splanchnic hypoperfusion. This is especially important during ventilating septic patients. Despite a possible decrease in portal blood flow, hepatic blood flow and oxygenation do not seem to be affected by PEEP due to preserved HABR with a compensatory rise in hepatic arterial flow. Prior clinical studies evaluating the effect of PEEP have been conducted at high PEEP levels which are rarely achieved in clinical practice, especially while ventilating patients with ARDS. [35]

Additionally encouraging spontaneous breathing during mechanical ventilation is associated with decreased systemic and pulmonary vascular resistance. [36] This can lead to decreased hepatic vein portal gradient leading to improved portal flow and oxygen delivery. An important limitation for most of the quoted studies is the significantly short duration of exposure to PEEP than in actual clinical scenarios although the same can be difficult to perform due to ethical principles.

Prone Positioning

Prone positioning (PP) was initially proposed as a maneuver to improve gas exchange in ARDS in 1970s. [37] Almost half a century later, it is currently considered the standard of care and is used regularly to ventilate patients with severe ARDS. [35]

Unfortunately, PP has been associated with intra-abdominal hypertension (IAH) which is currently defined as intra-abdominal pressure (IAP) of $\geq$ 12 mm Hg. [38] Although Michelet and colleagues demonstrated that rise in IAP related to PP could be limited by using an air-cushioned mattress, [39] IAH can lead to multiple GI complications and has been associated with increased length of ICU stay. [40]

Furthermore, IAH can lead to higher PEEP levels needed for adequate respiratory system compliance, [41] and this can potentially have several GI complications as listed above.

Despite a minor increase in IAP associated with PP, Hering and colleagues demonstrated that PP did not have any negative impact on hepatic function, gastric mucosal perfusion, effective renal blood flow index, filtration fraction and glomerular filtration rate index. [42,43]

PP was also associated with a mild increase in cardiac index. Similarly, Matejovic and colleagues demonstrated an unchanged hepato-splanchnic perfusion and gastric mucosal-arterial PCO_2 gap in acute lung injury patients treated with PP, additionally the IAP was unchanged in these patients. [44] Kiefer and colleagues also demonstrated a stable mean intra-gastric pressure in patients treated with PP.[45] Although the gastric mucosal-arterial PCO_2 gradients was mildly elevated in this study population, it was probably clinically irrelevant.

To summarize, although PP is associated with mild increase in IAP and possible IAH, clinical studies so far have failed to demonstrate any negative clinical outcomes and functioning of GI tract appears to be unaffected in these patients. However, certain patient populations such as acute pancreatitis, severe burns, blunt abdominal trauma, etc. are often at risk of IAH. [46–48] These patients would potentially benefit from routine monitoring of IAP when ventilated using PP.

Permissive hypercapnia

Permissive hypercapnia is usually a consequence of lung protective ventilation (LPV) strategy wherein a controlled rise in PCO_2 is permitted to prevent ventilation induced lung injury.

It was initially evaluated in ARDS patients where low tidal volume ventilation (LTV) showed improved mortality despite leading to hypercapnia. [49] Hypercarbia induced improvement in cardiac index has been documented. [50]

Carvalho and colleagues were amongst the first to assess temporal hemodynamic effects of hypercapnia, where it was associated with increased cardiac output, heart rate and a decrease in the systemic vascular resistance. [51] Interestingly, these hemodynamic responses are reversible on correction of blood pH. [52] Although transient pulmonary hypertension was noted, no changes in pulmonary vascular resistance or right ventricular functions were evident. Thus, by allowing smaller tidal volumes and lower PEEP as a part of LPV, permissive hypercapnia may be associated with improved venous return and decreased HVPG secondary to lower intra-thoracic pressures. Further, splanchnic perfusion could be improved secondary to permissive hypercapnia.

While the studies by Kiefer and Mas did not find any hypercapnia induced changes in splanchnic perfusion and metabolism, [53,54] Dutton and colleagues demonstrated that hypercapnia induced an increased in the total liver blood flow which was primarily attributed to increased splanchnic flow. [55]

A biphasic response was proposed where a sympathetic stimulation induced initial reduction in blood flow was followed by increased flow attributed to direct vasodilator response of hypercarbia. Fujita and colleagues evaluated the effects of hypercapnia on splanchnic circulation and hepatic function in dogs using indocyanine green (ICG) dye. [56] While hypercapnia lead to increased portal vein and hepatic arterial flow, ICG clearance was actually decreased suggesting depressed hepatic function. To our knowledge, no further studies have been able to replicate these results.

While initial studies suggested possible association of hypercapnia and increased gastric acid secretion, [57] similar results have since not been replicated and currently there is no clear evidence to suggest the same. [58]

Hypercapnia and related acidosis have been proposed to have a suppressive effect on inflammation. [59] This is related to the acidic nature of the reperfusion fluid and associated gradual restoration of intracellular pH. While the protective effect has previously been demonstrated in rat livers, [60,61] similar studies are lacking in human subjects.

Recently, permissive hypercapnia was found to be associated with better post-operative oxygenation and respiratory function in rectal cancer patients undergoing laparoscopic surgery. [62]

In summary, the clinical relevance of hypercapnia on GI function remains unclear. Although it can lead to increased splanchnic blood flow secondary to hypercarbia and possibly decreased HVPG, no clear effect on liver function or gastric acid secretion have been demonstrated. No definite harmful outcomes are known and clinical relevance of some of the effects seen in animal studies are unclear. Further research evaluating GI outcomes associated with hypercapnia is needed.

GI disorders in the mechanically ventilated and critically ill patient

GI motility disorders

Gastroesophageal reflux disease (GERD)

Reflux of gastric contents into the esophagus is a normal physiological process, but if it starts to occur more frequently, it can cause esophageal mucosal injury and ulceration. Many factors help in preventing esophageal reflux, and thereby minimizing esophageal exposure to the gastric content including lower esophageal sphincter (LES) pressure, diaphragmatic crura, salivary bicarbonate, esophageal peristalsis and mucosa. [1] Any of the previously mentioned protective factors can be affected in critically ill patients.

In a study of 15 patients on mechanical ventilation, Nind and colleagues showed that the basal LES pressure is usually very low and can be even absent in these patients, thus any minimal increase in intra-abdominal pressure, as in coughing or straining which might be stimulated by airway suctioning, can lead to frequent reflux episodes. [63] Moreover, several medications that are commonly used in ICU such as opioids, benzodiazepines, barbiturates, calcium channel blockers and nitrates, can all relax the LES and cause reflux episodes. [1,64]

The supine position is an important risk factor for esophageal reflux disease as well, and this is why it is recommended to elevate the head of the bed in ICU patients. Besides that, salivary secretions which is supposed to be increased in patients with esophageal reflux are decreased in critically ill patients, which is thought to be secondary to the same medications that cause LES relaxation in those patients. [1,65]

Finally, many factors in the ICU are thought to increase the frequency of transient LES relaxations (TLESR), including the presence of the endotracheal tube which stimulates the pharynx to increase the frequency of TLESR, stomach distention by any reason such as enteral feeding, as well as medications that can decrease gastric emptying such as anticholinergic drugs and proton pump inhibitors (PPI). [1,64]

Percutaneous endoscopic gastric tubes were found to decrease but not prevent the rate of reflux in both intubated and non-intubated patients. [1,64] In addition, pneumonia occurs less frequently when the feeding tube is placed in the second portion of the duodenum or beyond in mechanically ventilated patients. [1,66,67] Thus, it is recommended that patients on mechanical ventilation who require prolonged nutrition to get their feeding tube placed in the jejunum to decrease the risk of esophageal reflux. Two metanalysis showed that patients who receive post pyloric feeding have less risk for micro aspiration and thus for developing pneumonia. [1,68,69] On the other hand, some studies showed no relationship between feeding tube location and the increased risk of reflux. [1,70,71] It is still unclear if intermittent versus continuous feeding can affect the rate of reflux.

Gastroparesis

Gastroparesis is a condition characterized by delayed gastric emptying in the absence of mechanical obstruction. [1,72] Clinical presentation may include abdominal pain, bloating, nausea, vomiting, decreased appetite, early satiety and post prandial fullness. [1,72] The exact prevalence of gastroparesis is unknown, as many patients are underdiagnosed, but some studies suggested that the prevalence is approximately 4-5% in general population, and around 25% of diabetic patients. [1,72] The prevalence of gastroparesis in the critical care setting is

estimated to be even higher, Ritz and colleagues reported that 40-45% of ICU patients have delayed gastric emptying. [1,73]

The diagnosis is made by the combination of clinical presentation and the identification of delayed gastric emptying in the absence of mechanical obstruction. [72] Gastric emptying scintigraphy (GES) is considered the gold standard test for the diagnosis of gastroparesis. [1,72] Gastric emptying breath test (GEBT) is an easy and widely available alternative option with a good accuracy. Other available tests include wireless motility capsule, gastric emptying of radiopaque markers, electrogastrography and antroduodenal manometry. [72] The ^{13}C-octanoate acid breath test seems to be a more practical alternative than GES. [1] Deane and colleagues showed that measurements of gastric emptying by ^{13}C-octanoate acid breath test were internally consistent in a retrospective study of a small number of ICU patients. Ghoos and colleagues have also reported significant correlation between results determined by the breath test and scintigraphy in healthy subjects. [1,74,75]

Measuring gastric residual volume after feeding is the most common method used to assess gastric emptying in critically ill patients. [1,76] A 24-hour gastric residual volume of 150 ml or more can be an indicator of gastroparesis but it should not be used to diagnose patients with gastroparesis as many of them will have normal gastric emptying on GES. [1,72,77] Other method that has been used to define gastroparesis in the critical care setting is the acetaminophen absorption test. This test may be limited by variations in systemic absorption and hepatic metabolism. [1]

There are many potential factors that may contribute to the delayed gastric emptying in critical care patients such as obesity, coughing, frequent suctioning, supine position, and advanced age. [1] It is believed that the severity of critical illness is directly related to delayed gastric emptying. In a retrospective study of 132 mechanically ventilated patients, Nguyen and colleagues found that admission diagnoses can have an impact on the risk for gastroparesis in the ICU after controlling for other potential confounders. [78] Patients with the highest risk are those with head injuries, burns, multisystem trauma and sepsis. Moreover, other comorbidities may delay gastric emptying including raised intracranial pressure, chronic pancreatitis, liver cirrhosis, hiatal hernia, gastric cancer and gastric resection.[1,78]

In a retrospective study of 649 ICU patients, Lam and colleagues found that in critically ill patients who require prolonged enteral nutrition, history of type II diabetes mellitus was not a risk factor for gastroparesis and food intolerance. [79] In a small observational study that compared 15 mechanically ventilated patients to 10 healthy individuals, Chapman and colleagues found that stimulation of pyloric pressure and suppression of antral pressure were increased in intubated patients compared to healthy subjects which is attributed to decreased gastric emptying. [80] Hyperglycemia and electrolyte disturbances also worsen gastric emptying and should be corrected. [1]

The mainstays of gastroparesis management are symptoms control, correction of hyperglycemia and any electrolyte abnormalities, and identification and treatment of potential causes of delayed gastric emptying if possible. Medications that can cause delayed gastric emptying should be avoided, such as opioids and anticholinergics. [1,72] Metoclopramide, a dopamine D2 receptor antagonist, is the first line pharmacological treatment of gastroparesis in general population, and it is the only medication approved by the FDA for this purpose. Its use is limited by the potential extra-pyramidal side effects. [72,81] Domperidone is another dopamine antagonist with same efficacy but less extra-pyramidal side effects. The main side effect is QT prolongation and because of that it is only available in the United States through an FDA investigational drug application. [72] Erythromycin, a motilin agonist, can also be used to treat gastroparesis. It can be given orally or intravenously but unfortunately; orally administered erythromycin has proven ineffective in the management of gastroparesis.

In the critical care setting, the coadministration of erythromycin with metoclopramide is the first line treatment of gastroparesis. Other medications such as methylnaltrexone, mitemcinal, ghrelin agonists and dexloxiglumide, are promising alternatives but require further investigation. [1,82] Refractory cases to pharmacological therapy can be managed by placing a jejunostomy tube to bypass the stomach. It can be placed surgically or endoscopically. [1,83]In patients with high residual gastric volumes, or those who cannot tolerate jejunal feeding or jejunostomy tube placement, parenteral feeding maybe required although enteral nutrition is preferred. Other endoscopic and surgical interventions, such as the placement of decompressive gastrostomy, should be considered in refractory patients. Gastric electrical stimulation has not been used in this context.

Ileus

Ileus is a form of small intestine hypomotility or dysmotility in the absence of mechanical obstruction, and it is considered one of the most common complications in the critical care setting. Most of the times, the degree of ileus is correlated with the severity of the critical care illness. [1] Moreover, observational studies suggested a significant association between constipation and duration of mechanical ventilation,

ICU stay, risk of infection, delay in starting enteral nutrition and ICU mortality.[84]

Reintam and colleagues showed in a large retrospective cohort study of ICU patients that SOFA score on admission was independent predictor for GI failure, and the higher the SOFA on admission the earlier ileus seems to occur. [85]

The exact mechanism of ileus is still largely unknown. Animal studies suggest that both neuronal and local inflammatory responses within the intestinal muscularis might be contributing. The neuronal mechanism involves the release of nitric oxide from inhibitory motor neurons. On the other hand, the inflammatory mechanism involves the release of nitric oxide and prostaglandins from inflammatory cells, macrophages and monocytes, via the induction of nitric oxide synthase and cyclooxygenase-2. [86]

In critically ill patients, the etiology of ileus is multifactorial which includes recent surgery, electrolyte abnormalities, sepsis, trauma, and medications.

Recent surgery is one of the most important causes of ileus in ICU patients. The activation of macrophages in the post-operative state leads to the release of nitric oxide and prostaglandins. Intestinal manipulation during surgery as well is thought to activate mast cells into the muscularis, which leads to the release of proinflammatory cytokines such as IL-2 and IL-6 which induce GI dysmotility. [1,86,87] Same cytokines can be released in stressful conditions such as sepsis in addition to tachykinins such as substance P and neurokinin which can promote dysmotility. Nitric oxide and vasoactive intestinal peptide as well as corticotropin-releasing factor, are all important mediators in sepsis and are associated with gut dysmotility. [1,86–88]

About 40% of patients on chronic opioid therapy with non-malignant pain develop motility dysfunction, and around 90% of patients on chronic opioid therapy with terminal illnesses will develop motility dysfunction. [89] Endogenous opioids act at opioid receptors composed of the mu, delta, and kappa types. Clinically used exogenous opioids act predominantly at the mu receptor which are present in the central and peripheral nervous system, as well as the GI tract. [89] Exogenous opioids can affect the GI tract is deferent ways. They can act through central nervous system mediated effects on the GI tract, as well as peripherally on the GI tract itself. [89]

Other factors that can contribute to GI dysmotility in ICU patients include calcium channel blockers, usage of vasopressors in patients with shock which can lead to further decrease in GI perfusion. Moreover, excessive fluid resuscitation in such patients or postoperatively, can lead to intestinal edema and exacerbate GI dysmotility. [1]

The initial step in ileus management is the correction of any fluid or electrolyte imbalances. Using a nasogastric tube for decompression remains controversial. Early initiation of tube feeding in ICU patients is thought to help in ileus management by promoting gut motility, as well as maintaining intestinal barrier function and gut perfusion. [1] Opioid antagonists can be used to manage the opioid effects in ICU patients. Moreover, Promotility agents such as macrolides and dopamine antagonists can be used. And finally, laxatives such as lactulose and polyethylene glycol can be used, and both have similar effectiveness in ICU patients. [1,90]

Ogilvie's syndrome

Acute colonic pseudo-obstruction (ACPO) refers to the dilatation of the colon in the absence of a mechanical obstruction distal to the dilated segment, and is commonly known as Ogilvie's syndrome. [1] The pathophysiology is not clear. The initial theory, as proposed by Ogilvie, was an imbalance in the activity of autonomic nervous system with parasympathetic overactivity leading to dilation of the colon. [91] However, current evidence favors a relatively increased sympathetic tone and/or decreased parasympathetic tone leading to a functionally obstructing distal colon and a relaxed proximal colon. The evidence in favor of this theory is the association of ACPO with diseases causing a disturbance in the autonomic flow to the gut and a remarkable response to pharmacologic therapy. [92,93]

Patients typically present with recurrent abdominal distention and constipation without any evidence of colonic obstruction. It can still occur in patients without constipation. [1] Diagnosis of Ogilvie's syndrome is mainly clinical and radiologic, and can be treated conservatively or with interventions such as acetylcholinesterase inhibitors (neostigmine), decompressive procedures such as colonoscopy, and surgery in refractory cases. [94]

Diarrhea

Diarrhea is a common complication in ICU patients. In a prospective study by Dark and colleagues on 124 patients with acute respiratory failure, diarrhea was the most common non-hemorrhagic GI complication, it occurred in 51% of patients and it was more in patients who received antacids. [95] The etiology of diarrhea in the critical care setting is multifactorial.

Enteral feeding associated diarrhea can affect up to 25% of ICU patients. [8] In a prospective study by Smith and colleagues on 73 critically ill patients require mechanical ventilation, 63% developed diarrhea associated with enteral feeding, which is higher than critically ill patients who do not require

mechanical ventilation. [89] It also showed that higher infusion rates, greater tube feeding osmolality, and change of feeding products are all associated with higher incidence of diarrhea.

Extensive use of antibiotics is also considered an important risk factor for diarrhea in the ICU. Antibiotics can alter the colonic bacteria, therefore will alter the fermentation process of carbohydrates to non-absorbable metabolites which will lead to osmotic diarrhea. [8] Around 40% of patients who receive antibiotics develop diarrhea, where 15-25% is attributable to clostridium difficile infection. [8] Moreover, a small study done on 15 ICU patients showed that enteral fasting can be associated with significant duodenal mucosal atrophy and altered GI permeability in critically ill patients. [96] This in turn will lead to altered bile absorption, and with resuming enteral feeding this will lead to excessive intraluminal amounts of bile which can lead to choleretic diarrhea. [97]

Hypoalbuminemia as well can contribute to the development of diarrhea in ICU patients. It can lead to gut edema and impaired absorption. Albumin level < 2.6 g/dL have been associated with increased risk of diarrhea. [8]

Gastrointestinal bleeding

ICU patients are at increased risk for stress related GI mucosal damage, which can progress to ulceration and bleeding. The etiology and pathophysiology are not completely understood, but diminished blood flow, mucosal ischemia and reperfusion injury may play an important role. [98,99]

Damage of the gastric mucosa can be found in up to 90 % of critically ill patients after three days in the ICU. However, the clinical importance of these lesions may be limited, as only a small number of these lesions progress to overt and clinically important GI bleeding, which is defined as bleeding causing hemodynamic instability and/or requires transfusion of blood products. [100] Erosive esophagitis can occur in 50% of ICU patients, and it is responsible for about 25% of upper GI bleeding cases in the ICU. [8] Pathophysiology is likely multifactorial, and it includes the insertion of NG tubes, GERD, and duodeno-gastro-esophageal reflux. [8,101]

The reported incidence of GI bleeding in ICU patients varies between 0.6 % to 7.0 %. [100] An international prospective cohort study done by Krag and colleagues in 2014, showed that 4.7 and 2.6 % of ICU patients experienced an overt and clinically important GI bleeding respectively. [100] Half of the patients with clinically important GI bleeding receive endoscopy or surgery, and approximately half of them receive a transfusion of at least two units of packed red blood cells as well. [3] Patients with a bleeding diathesis, including those receiving extracorporeal life support, may have higher rates of overt bleeding, as reported in a study involving 132 patients, 18 of them had overt GI bleeding (13.6%). [102]

Coagulopathy and mechanical ventilation of more than 48 hours were thought to be the most important risk factors for overt and clinically important GI bleeding in ICU patients. [99,103] However, a large multicenter study showed that some additional factors were independently associated with clinically important GI bleeding. These factors were three or more coexisting diseases (OR 8.9, 95% CI 2.7-28.8), liver disease (OR 7.6, 95% CI 3.3-17.6), renal-replacement therapy (OR 6.9, 95% CI 2.7-17.5), acute coagulopathy (OR 4.2, 95% CI 1.7-10.2), high organ failure score (OR 1.4, 95% CI 1.2-1.5), as well as the use of acid suppressants (OR 3.6, 95% CI 1.3-10.2), which may reflect confounding by indication. [99,100]

To prevent GI bleeding in critically ill patients, stress ulcer prophylaxis is recommended in international guidelines and it is considered a standard of care in the ICU. Despite that, indications for initiating stress ulcer prophylaxis vary considerably. [3,100] Proton pump inhibitors (PPI) are the most used agents, followed by H2-blockers, sucralfate and antacids are seldom used. Most guidelines recommend using either a PPI or H2-blockers, but there is some variation in the preferred agent. [3]

Many systemic reviews and metanalysis provided support for stress ulcer prophylaxis in ICU patients, but at the same time, it raised the concerns about possible associated complications, most importantly nosocomial pneumonia, and clostridium difficile infection. Additionally, much of the evidence was of low quality. [104–110] A randomized controlled trial done by Krag and colleagues on 3298 patients, showed no difference in 90-day mortality and the number of clinically important events in ICU patient who were at increased risk for GI bleeding, and who received pantoprazole versus placebo. [110] A new metanalysis by Ye and colleagues showed that stress ulcer prophylaxis with either PPI or H2-blockers can reduce both clinically important GI bleeding and overt GI bleeding, and this reduction can be more important in high risk patients compared to lower risk patients. On the other hand, neither PPI nor H2-blockers affect mortality compared to no prophylaxis. It also showed that both medications may increase the risk for pneumonia. [111]

Pancreas

Pancreatic enzymes elevation is a common complication in the critical care setting. It can occur in up to 80% of patients. [112,113] Elevated pancreatic enzymes can be either due to acute pancreatitis or due to non-specific reasons such as head injury, renal failure, or hemodialysis. [112] Evaluation of pancreatic enzymes elevation in the ICU is challenging, as most of the

patients are sedated and hard to assess clinically, which will lead to delayed diagnosis and management.

ICU patients may develop acute pancreatitis in different mechanisms. Ischemia which can result from hypoperfusion and sepsis, may lead to pancreatic inflammation and necrosis which can lead to severe and irreversible multi-organ damage. Moreover, tissue necrosis can trigger disseminated intravascular coagulation which carries a high mortality rate. [112]

In addition, many medications used in the ICU can induce acute pancreatitis. Propofol for example was reported as a cause of acute pancreatitis in ICU patients although the mechanism is not clear. [112] Hypertriglyceridemia and idiosyncratic drug reaction were suggested as potential mechanisms, and therefore serum triglycerides should be routinely monitored in patients on propofol in the ICU. [112,114,115] Glucocorticoids were also reported to be associated with acute pancreatitis, and the use of vasoconstrictors can lead to ischemia induced tissue inflammation and necrosis. [112]

Other potential risk factor for acute pancreatitis in the ICU is hypercalcemia. Hypercalcemia is a frequent finding among ICU patients, especially those with renal failure and burns. [112] Bai and colleagues reviewed 10 retrospective studies of patients hospitalized with primary hyperparathyroidism (PHPT), and found that the rate of pancreatitis among patients with PHPT was higher than that reported in hospitalized patients without PHPT. [116] This can be explained by the prolonged exposure of pancreatic acinar cells to a high and sustained calcium levels which may lead to premature activation of pancreatic protease enzymes and therefore pancreatitis. [112,116]

Cardiac and abdominal surgeries, as well as MRI contrast agents such as gadobenate dimeglumine and gadolinium has been reported to be associated with acute pancreatitis in the ICU, although this association remains controversial. [112]

Pancreatic enzymes can be elevated in ICU patients without direct pancreatic injury. Elevated levels of amylase and lipase have been observed in head trauma patients and patients with intra-cranial hemorrhage. [112,117,118] Diabetic ketoacidosis (DKA) can also lead to a non-specific elevation of pancreatic enzymes with no direct involvement of the pancreas. [112,119–121]

Renal failure can also cause elevated lipase and amylase levels likely due to defected clearance.[122] Hemodialysis can lead to elevated lipase levels which is attributed to the use of heparin during dialysis. [112]

Clinical consequences of elevated pancreatic enzymes in ICU patients were studied before. Manjuck and colleagues showed in a retrospective study that elevated lipase and amylase levels were associated with increased hospital stay and increased duration of mechanical ventilation, although they were not associated with increased mortality rate. [123] However, Lee and colleagues reported higher mortality rate in patients with elevated amylase levels admitted to the neurosurgical ICU. [124]

As a conclusion, all patients admitted to the ICU should be evaluated for risk factors of acute pancreatitis. Patients who are identified as in risk for, or patients who develop symptoms concerning for acute pancreatitis should be evaluated and managed promptly given the consequences that acute pancreatitis and elevated pancreatic enzymes can carry.

Acalculous Cholecystitis

Acute acalculous cholecystitis (ACC) is defined as a condition involving severe gall-bladder (GB) inflammation in the absence of gallstones [125]. It accounts for roughly 10% of all cholecystitis cases with an incidence of 0.2 to 3% in critically ill patients. [8,126,127]

Early diagnosis is key as risk of complications increase with delay in intervention with reported in-hospital mortality reaching up to 40% in critically ill patients. [128,129] Risk factors implicated include trauma, prolonged mechanical ventilation, shock, recent surgery, burns, sepsis, dehydration and prolonged enteral fasting amongst others. [8,130]

The pathophysiology is believed to be multi-factorial with prior studies demonstrating biliary stasis induced epithelial damage and ischemia as the key mediators. [131]

Patients undergoing mechanical ventilation are certainly at increased risk of both. High PEEP and tidal volume may lead to splanchnic hypo perfusion with resulting GB ischemia, especially in patients at increased risk of hypotension including severe sepsis, burns and polytrauma victims.

Mechanically ventilated patients are also at risk of prolonged periods of fasting. This can prevent normal GB emptying leading to biliary stasis and sludge formation.[132] These risks may further be exacerbated in setting of concomitant use of vasopressors and morphine like analgesics.

Diagnosing in critically ill patients can be especially challenging due to non-specific symptoms and inability of most intubated patients to verbalize symptoms. Subsequently, a high index of suspicion is needed for early diagnosis. Clinical manifestations may range from abdominal pain, persistent fever, leukocytosis and hyper-transminesemia, to altered mental status and sudden clinical deterioration in a previously stable patient. [133]

Definitive diagnosis is radiological; ultrasound (US), computed tomography (CT) and Cholescinitigraphy (HIDA) are the most commonly used modalities. While US offers the possibility of quick bedside diagnosis with demonstration of gall-bladder wall thickening, pericholecystic fluid and sonographic murphy's sign; sensitivity can vary from 30-100% highlighting significant operator dependence and poor reproducibility.[1 30] Although HIDA is the most sensitive imaging modality, CT offers additional imaging of entire abdomen. [134] Both involve difficulty with transporting the critically ill patients. Subsequently, CT should be the imaging of choice if a complication or another intra-abdominal pathology is suspected, although, consensus regarding initial diagnostic imaging remains poor. [130]

The world society of emergency surgery recently updated it's guidelines with US now recommended as the initial diagnostic imaging given cost-effectiveness, availability and ease of bedside use. [134]

Regarding treatment, antibiotics covering members of Enterobacteriaceae family including gram negative rods and anaerobes are used in addition to primary surgical intervention. Laparoscopic cholecystectomy is preferred to percutaneous cholecystectomy with the later reserved for patients who are poor surgical candidates. [130,134,135] Endoscopic

US guided GB drainage may be used is patients who are not candidates for either of above mentioned therapies although outcomes are generally inferior and variable. [136–139]

In summary, patient undergoing mechanical ventilation may be at significant risk of ACC and associated adverse outcomes. Initiation of early enteral nutrition may decrease biliary stasis and incidence of ACC. [140] Early feeding may thus be used routinely to prevent ACC unless clinically contraindicated. Similarly, although we could not find any studies regarding prevention of AAC with adequate volume resuscitation, the same may be beneficial to prevent splanchnic hypo perfusion and GB ischemia, especially in burns and sepsis patients undergoing mechanical ventilation.

Table 1 Summary of the effects of mechanical ventilation on the gastro-intestinal organs

Organ	**Potential complication**	**Mechanical ventilation effect**	**Management**
Esophagus	Esophagitis	Decrease splanchnic perfusion in parallel with decrease in cardiac output.	- Bed head elevation - Jejunal feeding in patients requiring prolonged ventilation
	Gastroesophageal reflux disease		
Stomach	Gastroparesis	Decrease splanchnic perfusion in parallel with decrease in cardiac output.	- Symptom control - Correction of hyperglycemia and other electrolyte abnormalities - Avoid medication induced hypomotility. - Metoclopramide as the first line therapy. - Domperidone, erythromycin and motilin as alternatives.
	Stress ulceration and bleeding		- Stress ulcer prophylaxis in ICU patients at risk for GI bleeding* - Bleeding risk similar with PPI and H2 blockers. - Similar risk of complications including nosocomial pneumonia and clostridium difficile diarrhea

Small and large intestines	Ileus	Decrease splanchnic perfusion in parallel to decrease cardiac output.	- Correction of underlying fluid and/or electrolyte imbalance - Early initiation of enteral nutrition - Opioid antagonists (methylnaltrexone) to manage opioid induced ileus - Promotility agents (e.g. macrolides and D2 antagonists) and laxatives may be used.
	Ogilvie syndrome		- Conservative management with serial abdominal examination and radiography. - Medical management with acetylcholinesterase inhibitors - Decompression with colonoscopy - Surgery in refractory cases
Liver	Decreased Hepatic function	- Possible hypercapnia induced decreased hepatic function - Decreased portal flow with maintained total hepatic flow with HABR	- Limiting high PEEP - Adequate fluid resuscitation
Gallbladder	Acute acalculous cholecystitis	Decrease splanchnic perfusion in parallel to decrease cardiac output	- Limiting high PEEP, adequate fluid resuscitation and early initiation of enteral nutrition for prevention - Antibiotic therapy covering gram negative rods (Enterobacteriaceae family) and anerobes - Laparoscopic cholecystectomy as first line therapy - Percutaneous cholecystostomy in poor surgical candidates - Endoscopic US guided biliary drainage
Pancreas	Acute pancreatitis Pancreatic enzymes elevation	PEEP induced decreased pancreatic perfusion (may persist despite restoration of cardiac output)	- Limiting high PEEP - Prompt management in patients at risk or with symptoms concerning for acute pancreatitis including adequate fluid resuscitation and treating underlying risk factors.
ICU: Intensive care unit; GI: Gastro-intestinal; PPI: Proton pump inhibitor; H2: Histamine 2 receptor; D2: Dopamine D2 receptor; PEEP: Positive End-Expiratory Pressure; HABR: Hepatic arterial buffer response; US: ultrasound			

Conclusion:

Mechanical ventilation either alone or in association with other critical illness may have a multitude of effects on almost all the organs of the gastro-intestinal tract which can add to the morbidity and mortality of such patients. Early recognition and prevention of those interaction and side effects can improve outcomes and potentially mortality

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