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Getting Critical About Constipation

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Gastrointestinal motility is a complex process, which is often altered during critical illness, an effect that can lead to constipation. There is no consensus definition for constipation and it is therefore difficult to accurately assess incidence across studies. More recently, the term "paralysis of the lower gastrointestinal tract" has been suggested. Constipation can cause abdominal distension and discomfort, and reduce tolerance to enteral feeding. It can impair respiratory function and has been associated with worse patient outcomes including prolonged ICU length of stay and prolonged mechanical ventilation. The etiology of constipation in ICU patients is multifactorial and includes immobility, fluid and electrolyte disturbances, adverse effects of medication, and sepsis. Management must focus on treating the underlying cause and re-establishing regular bowel movements.

INTRODUCTION

Gastrointestinal motility is a complex process regulated by a number of hormones and peptides. Constipation is a frequent problem in intensive care unit (ICU) patients,[1,2] but is often overlooked. Staff often react more quickly to diarrhea, which is usually obvious, than to constipation, which is often less apparent. The definition of constipation is not as simple as it may seem. In the general population, the Rome criteria are frequently used, assessing objective (stool frequency [<3 stool movements per week], need for manual maneuvers to defecate) and subjective (straining, hard stool, sensation of incomplete bowel movement or anorectal blockage) factors.[3] However, in critically ill patients, subjective symptoms are often difficult to assess and a diagnosis of constipation essentially relies on absence of defecation, although the chosen time period varies among studies. Because of the subjective nature of constipation, some debate the use of the term "constipation" in critically ill patients and a recent Working Group on Abdominal Problems from the European Society of Intensive Care Medicine recommended that the term "paralysis of the lower

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Table 1. Summary of Some Studies Reporting Incidence of Constipation in Critically Ill Patients

Study	Results
Montejo et al.[6]	In a multicenter study of 400 critically ill patients receiving EN, 15.7% developed constipation as defined by "need for treatment with laxatives or enemas."
Montejo et al.[7]	In 101 ICU patients receiving early EN, 5% developed constipation defined as "need for treatment with laxatives or enemas."
Mostafa et al.[2]	In a single center study of 48 critically ill patients requiring mechanical ventilation, 83% were constipated, defined as "failure of the bowel to open for three consecutive days".
Van der Spoel et al.[8]	First defecation occurred after a mean of 6 days in critically ill ventilated patients, and 55% of patients had "late" defecation, defined as passing stools for the first time after 6 days.
Nassar et al.[1]	In 106 mechanically ventilated patients, 70% were constipated, defined as "need for treatment with laxatives or enemas".
Gacouin et al.[9]	In ICU patients receiving prolonged mechanical ventilation (≥ 6 days), 58% had "late" passage of stools, defined as ≥ 6 days after ICU admission
Nguyen et al.[10]	In a cohort of 248 critically ill adult patients receiving EN for ≥ 72 hours and mechanical ventilation for ≥ 48 hours, 20% had impaired GI transit, defined as absence of a bowel movement for ≥ 3 days, treatment for constipation, and one of the following: (1) radiologically confirmed ileus, (2) feed intolerance, (3) abdominal distention, or (4) gastric decompression. If the definition was restricted to absence of a bowel movement for > 3 days, 64% of patients met the criterion.
Guardiola et al.[11]	In a cohort of 63 mechanically-ventilated critically ill patients, 90.5% had lower GI tract "paralysis".

gastrointestinal (GI) tract" be preferred.[4] They defined this as "the inability of the bowel to pass stool due to impaired peristalsis" and suggested that clinical signs would include absence of stool for three or more consecutive days without mechanical obstruction regardless of bowel sounds.[4] Indeed, whatever term is employed, bowel sounds, which have been widely used as an indicator of bowel activity, are unreliable and should not form part of the diagnostic criteria.[5]

Epidemiology

There are few published epidemiological data specifically related to constipation in critically ill patients. Constipation has been reported to occur in 5 – 90.5% of patients depending on the specific population studied and the definition used (Table 1).

Clinical Impact

Constipation can cause abdominal distension and discomfort, poor tolerance of enteral feeding, confusion, and intestinal obstruction with vomiting and risk of pulmonary aspiration (Table 2).[2,9,10,12] It may also be associated with raised intra-abdominal pressure, which can impact on respiratory function. Abdominal distension associated with constipation may be associated with bacterial overgrowth[12,13]

and increased bacterial translocation. Gacouin et al. reported reduced bacterial ICU-acquired infections in patients who passed stools early (< 6 days) rather than late (≥ 6 days).[9] Constipation in critically ill patients has been associated with worse outcomes including prolonged ICU length of stay and prolonged mechanical ventilation.[2,8,9,14] Patanwala et al.[15] noted that patients with constipation had more severe illness, as indicated by higher APACHE II scores. Montejo et al. reported that patients with GI complications, including constipation, had longer ICU stays and higher mortality than those without GI complications.[6]

Contributing Factors

A number of factors can contribute to constipation in critically ill patients, some of which are more obvious than others, for example spinal cord injury. Recent abdominal surgery is a common cause, although the delay before first defecation in these patients can vary considerably and may be related to the effects of the anesthesia and analgesia and not just to the surgery per se. Immobility, common in ICU patients, is also an important factor in reduced gut motility and patients who are unconscious or sedated may not feel the need to defecate.

The effects of morphine and other opioids on gut motility are well known,[16,17] but opioids have other effects that also increase the risk of constipation, including reducing intestinal secretions.[16,17] Other medications that may be used in the ICU can also cause gut hypomotility, including dopamine,[18,19] phenothiazines, diltiazem, verapamil, and anticholinergic drugs.[1]

Sepsis may also increase the likelihood of constipation in critically ill patients. Indeed, recent data suggest that sepsis may enhance the inhibitory effects of opioids on colonic motility via Toll-like receptor 4,[20] a key signaling molecule in sepsis pathogenesis.[21]

Electrolyte disturbances, including hypokalemia, hypercalcemia, and hypomagnesemia, can also reduce gut motility and increase the risk of constipation, in part via impaired smooth muscle contraction.[22] Inadequate fluid administration or inappropriate use of diuretics leading to dehydration also promotes constipation, but, conversely, too much fluid can lead to splanchnic edema, impairing gut motility.

Gacouin et al.[9] reported that hypotension, defined as a systolic blood pressure < 90 mmHg, was independently associated with late (≥ 6 days) passage of first stools, as was a PaO_2/FiO_2 ratio of <150 mmHg (hazard ratio

Table 2. Possible Complications Associated with Constipation in the ICU Patient

- Abdominal distension and discomfort
- Vomiting
- Delayed gastric emptying and intolerance of enteral feeding
- Increase intraabdominal hypertension
- Intestinal ischemia and perforation
- Colonic pseudoobstruction
- Bacterial overgrowth and translocation?
- Pulmonary aspiration
- Prolonged mechanical ventilation and ICU length of stay

Table 3. Factors Contributing to Constipation in Critically Ill Patients

- Spinal cord injury
- Neuromuscular disease, such as amyolateral sclerosis
- Underlying dysmotility
- Abdominal surgery
- Immobility
- Use of opioids or other medications that contribute to hypomotility
- Sepsis
- Electrolyte disturbances
- Insufficient or too much fluid administration
- Inappropriate use of diuretics

1.40 [95% confidence interval 1.06-1.60], p=0.003).

In most critically ill patients with constipation, the etiology will be the result of a combination of several of the above factors (Table 3).

Interaction with enteral feeding

The relationship between the type and delivery of enteral nutrition (EN) and constipation is interesting. On the one hand, delayed administration of EN may contribute to constipation,[1] while, on the other hand, constipation in the critically ill can be associated with an intolerance to EN.[10] Early EN is recommended in critically ill patients.[23] Boelens et al.[24] reported that early EN was associated with a significantly shorter time to first defecation compared to early parenteral nutrition (PN) in patients undergoing major rectal surgery. Continuous EN is usually recommended to improve the delivery of nutrients. However, meals and bolus delivery of nutrients cause gastric and colonic distention, leading to increased antro-pyloric pressure waves and motility.[25] In a pseudo-randomized controlled trial in 30 critically ill mechanically ventilated patients receiving EN for more than 72 hr, Kadamani et al. reported that continuous EN was associated with more constipation, defined as absent bowel movements for at least three consecutive days, than bolus EN.[25]

Management

Because of the potential complications associated with constipation listed above, appropriate treatment of constipation is important. The most important factor in treating these patients is to make it a priority to re-establish, and then maintain, regular bowel movements. In a recent prospective randomized controlled trial, de Azevedo et al. (personal communication) reported that maintenance of daily defecation resulted in an improvement in organ function, as reflected by a faster decline in sequential organ failure assessment (SOFA) scores.

Treating the Underlying Cause

Full physical examination must include rectal examination and imaging when necessary to exclude the presence of any mechanical obstruction that requires surgical management. In acute colonic pseudo-obstruction (Ogilvie's syndrome), a therapeutic colonoscopic examination may be required to decompress the pseudo-obstruction.[26, 27] Electrolyte imbalances should be corrected and fluid administration optimized. As part of routine patient management, the need for analgesic agents should be regularly reviewed.[28] Fentanyl may be associated with less constipation than morphine,[29, 30] but these differences may not be large,

Table 4. Laxative Categories

Type of Laxative	Example	Description
Bulking Agents	Bran	Increase stool bulk and stool frequency
Osmotic Laxatives	Lactulose, polyethylene glycol [PEG]	Poorly absorbed by the gut and act as hyperosmolar agents, increasing the water content of stool and making the stool softer
Stimulant Laxatives	Senna	Increase water and electrolyte secretion by the intestinal mucosa and stimulate peristalsis
Stool Softeners	Docusate sodium	Reduce the surface tension of the oil-water interface of the stool, allowing incorporation of water and fat into the stools with resultant softening

Table 5. A Suggested Approach to Preventing and Managing Constipation in General ICU Patients

On Admission:

- Be aware
- Take relevant history
  - Normal BM routine—daily, weekly, etc.?
  - Time and type of last stool (if possible)
  - Regular laxative medication
  - Known bowel disorder (IBS, inflammatory bowel disease…)
- Identify potential risk factors (opiate use, prolonged immobilization, …)
- Consider starting prophylactic laxative agents, especially if risk factors present or taking laxatives prior to admission

No Bowel Movement within Past 24 Hours:

- Correct electrolyte abnormalities and confirm adequate hydration
- Evaluate need for ongoing opiate analgesia and other "constipating" drugs
- Abdominal and rectal exam for presence and nature of stools - disimpact if necessary
- If already receiving prophylactic laxative, increase dose. If not, start laxative (lactulose, PEG, docusate, senna…)
- Re-evaluate daily and increase laxative dose or add a second agent if no response
- If still no response after 24 hours, repeat rectal exam and consider enema
- Consider abdominal x-ray to rule out ileus, impaction, pseudo-obstruction…

especially with short-term use. If continued opioid use is necessary, administration of opioid antagonists, such as methylnaltrexone, should be considered as this can be useful to counteract the effects of opioids on gut motility.[31,32] Methylnaltrexone is a selective opioid μ-receptor antagonist that poorly crosses the blood-brain barrier, and hence interferes with GI effects, but not the central pain-relieving actions of opioids.[33] Lubiprostone, a selective chloride channel-2 activator that acts locally in the small intestine to increase fluid secretion and improve gut motility,[33] has been recently proposed as an alternative.[34] The enteral administration of naloxone, which has low bioavailability when given orally, may represent a cheaper option.[35]

Treating the Constipation

Laxatives and Enemas

There are essentially two types of treatment for constipation after efforts have been made to remove the underlying cause: oral laxatives and suppositories or enemas. Oral laxatives can be broadly divided into bulking agents, osmotic laxatives, stimulant laxatives, and stool softeners (Table 4).[12,36] The choice of laxative is largely a matter of personal preference and availability with few published recommendations, especially in the critically ill population. Lactulose is perhaps the most widely used,[2,37] with a recommended starting dose of 10 ml twice a day increasing to a maximum of 20 ml three times daily. Lactulose use can result in production of intestinal gases with uncomfortable bloating in some patients.[14] Senna (10 ml/day) is a commonly used alternative.[2,15,37] Polyethylene glycol (PEG) is also widely used and can be administered intermittently or continuously. Van der Spoel et al.[14] compared administration of lactulose (13 g three times daily), PEG or placebo in patients with multiple organ failure who were receiving mechanical ventilation and intravenous circulatory support and who had had no defecation by day 3 after admission. The authors reported that lactulose and PEG were both more effective in promoting defecation than placebo. There was an increased occurrence of acute intestinal pseudoobstruction in patients receiving lactulose, possibly related to increased intestinal gas production, and PEG seemed to be more effective than lactulose in patients receiving opioids.[14] Enemas are generally reserved for patients in whom orally administered laxatives do not have an effect.[37]

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Neostigmine

In severe cases of functional colonic pseudo-obstruction, after exclusion of treatable causes, administration of neostigmine, an acetylcholinesterase inhibitor, may be considered to increase peristalsis and promote gut motility. Many studies have shown the efficacy of neostigmine in this situation, including the classical study by Ponec et al.[38] in which 21 patients with acute colonic pseudo-obstruction with no response to ≥ 24 hours of conservative treatment, were randomized to receive a single dose of 2 mg of intravenous neostigmine or intravenous saline. Ten of the 11 patients who received neostigmine had rapid evacuation of flatus or stool, with a median time to response of just 4 minutes, as compared with none of the 10 patients who received placebo ($p<0.001$). Van der Spoel et al.[39] randomized 24 mechanically ventilated patients with multiple organ failure and critical illness-related colonic ileus to a continuous infusion of intravenous neostigmine (0.4-0.8 mg/h over 24 h) or placebo, and again reported good efficacy with 11 of the 13 patients receiving neostigmine passing stools, compared to none of the placebo-treated patients ($p < 0.001$). Neostigmine can cause bradycardia and cardiac arrest has even been reported,[40] so care should be taken, especially in patients with severe cardiocirculatory problems. Neostigmine use has also been associated rarely with colonic perforation.[41]

Prophylaxis of Constipation

A couple of studies have suggested beneficial effects of prophylactic laxative administration in critically ill patients.[11, 42] Masri et al.[42] reported that prophylactic use of lactulose 20 ml twice daily for 3 days in critically ill ventilated patients was associated with increased incidence of bowel movement in the first 72 hours compared to no intervention (18% vs 4%, $p<0.05$). More recently, in a sequential phase trial, Guardiola et al. compared treatment of lower GI tract "paralysis" with prophylaxis. Patients who received PEG as prophylaxis on the first day of mechanical ventilation had more rapid resolution of the paralysis than those who received PEG as treatment on day 4.[11]

It is important to remember that early sitting and mobilization of patients is a cheap and effective way to stimulate gut function. See Table 5 for a summary of suggestions to prevent and treat constipation in the ICU.

CONCLUSION

Constipation is common in ICU patients. Attempts should be made to prevent and treat it when necessary to avoid complications. There are few published data to guide treatment choices in this population. When considering constipation in these patients, one can identify two vicious cycles that need to be avoided. The first is the problem of abdominal distension that can induce discomfort, which results in increased opioids for pain relief, causing more constipation, and so the cycle starts again. The second potential cycle is the development of abdominal bloating, leading to withholding of EN, which in fact can worsen constipation as EN can promote peristalsis. Indeed, although not often considered as such, EN can be considered as, perhaps the optimal form of prophylaxis against constipation! Other general patient management strategies, including ensuring adequate hydration and encouraging mobilization when possible, must not be forgotten. ■

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