Review Article

Narrative review of constipation in the critically ill child

Jorge López, María Jose Solana, Jesus López-Herce

Pediatric Intensive Care Department, Gregorio Marañón General University Hospital, Gregorio Marañón Health Research Institute, Mother-Child Health and Development Network (RedSAMID) of Carlos III Health Institute, Complutense University of Madrid, Madrid, Spain

Contributions: (I) Conception and design: J López, J López-Herce; (II) Administrative support: J López, MJ Solana; (III) Provision of study materials or patients: J López, MJ Solana, J López-Herce; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jorge López González and Jesús López-Herce Cid. Pediatric Intensive Care Department, Gregorio Marañón General University Hospital, C/ Dr. Castelo 47, 28009 Madrid, Spain. Email: jlopezgonz82@gmail.com and pielvi@hotmail.com.

Background and Objective: Constipation is a common but understudied complication in the critically ill child. Its diagnosis is frequently delayed because it is not usually considered to be such a severe complication for these patients. However, constipation has been associated with worse outcomes in critically ill adults and children.

Methods: It was conducted a review of the literature focused on constipation in critically ill children. Literature review included Medline, Embase and The Cochrane Library databases up to July 2020. Languages: English and Spanish.

Key Content and Findings: There are only few studies in critically ill children focused on epidemiology and risk factors and there are no studies about diagnostic criteria, diagnostic tests or treatments in this population. The lack of studies in this field within critically ill children contrasts with the increasing number of studies in critically ill adults during these past two decades. Constipation clinical findings in children admitted to a pediatric intensive care unit are very similar to those observed in children with functional constipation. However, these critically ill children cannot meet the diagnostic criteria for functional constipation. As there is no a standard definition, carrying out studies about this topic is quite difficult. The treatment of constipation in critically ill children includes pharmacologic and non-pharmacologic therapies but there is also little evidence about this. Polyethylene glycol and lactulose are the preferred therapeutic options but there is a broad range of different possibilities.

Conclusions: Although constipation in critically ill is associated with poor outcomes, only a few studies are focused in pediatric population in contrast to critically ill adults. Early recognition and treatment should be our next target. A new research area has emerged for treatments in opioid-induced constipation. Prophylactic treatments and protocols for constipation management in this population may improve our results.

Keywords: Bowel movements; laxatives; polyethylene glycol; lactulose; pediatric intensive care unit

Received: 29 June 2020; Accepted: 03 February 2021; Published: 28 May 2021.

doi: 10.21037/pm-20-63

View this article at: http://dx.doi.org/10.21037/pm-20-63

Introduction

Constipation in the critically ill child is a poorly studied disease which can represent up to 50% of children admitted to Pediatric Intensive Care Units (PICU) (1-3). López *et al.* studied 150 critically ill children with a constipation incidence of 46.7%. Constipation was independently associated with body weight, Pediatric Index of Mortality 2 score, postoperative PICU admission and vasoconstrictor drugs (1). Smalley *et al.*, in their pilot study with 47 patients (observation period of 219 days) found that those children spent 56.7% of this time without any bowel movements (3).

Constipation is frequently diagnosed only after secondary complications are present, and at this point, constipation is

more difficult to manage (4). This lack of published studies in critically ill children contrasts with the increased number of studies published in critically ill adults over the past two decades. According to these studies, constipation has an incidence between 15–83% (5-12).

Constipation has been classically considered just a symptom due to a difficult bowel movement with hard and a small number of stools (13). It has also been defined more as a secondary symptom to fecal impaction rather than a disease itself (14). The lack of a widely accepted definition is, in part, due to the absence of clear criteria about what a normal bowel movement is. This is a handicap for the development of studies about constipation (14,15).

Constipation can be classified in two groups: functional constipation (90–95%) and organic constipation (5–10%) (14-16). Functional constipation is idiopathic as it cannot be explained by anatomical or physiological abnormalities and follows Rome IV criteria (17,18). In organic constipation, an anatomical or physiological abnormality (e.g., hypothyroidism, Hirschsprung disease, cerebral palsy or some drugs as opioids or iron supplements) is always found and Rome IV criteria cannot be fulfilled. Critically ill children usually have a wide range of organic disorders and that it is why the Rome IV criteria for constipation cannot be applied in these cases (17,18).

The European Society of Intensive Care Medicine (ESICM) Working Group on Abdominal Problems, did not reach a common definition for constipation in critically ill adults because these patients may not express symptoms such as uncomfortable or infrequent bowel movements, hard stool or painful defecation. So they suggested to use the term paralysis of lower gastrointestinal (GI) tract which was defined as the inability of the bowel to pass stool due to impaired peristalsis (11). The main clinical sign of the paralysis of lower GI track was the absence of stools for three or more consecutive days without mechanical obstruction as this time criteria was the most extended in published studies (5,7,11,12). However, other authors set longer periods to define constipation (8,9,19,20).

In the few studies published about constipation in critically ill children, it was applied the same time criterion (three days without bowel movements) (1) or the stool consistency (types 1 or 2 from the Bristol stool chart) (3).

Methods

The literature search for this review was carried out from December 2019 to June 2020. Medline, Embase and The Cochrane Library databases were employed looking for literature about constipation and constipation in critically ill (children and adults) for the past 3 decades (1990-2020). The search for "constipation" was limited to infants and children under 18 years of age while for "constipation in critically ill" no age filter was stablished. Only English and Spanish literature was included. We excluded literature about chronic constipation and most of organic constipation but some guidelines. No other limits about type of publication were applied. According to the section (introduction, physiopathology, clinical findings, diagnosis or treatment) some types of publications were chosen over the other. MeSH terms used were: constipation, critical illness, opioid-induced constipation, defecation and gastrointestinal motility. MeSH terms were combined with free text depending on the section to reduce the number of publications to review.

Physiopathology

GI tract dysmotility is a common disorder in critically ill patients and it can affect every part of the GI tract. GI motility disturbances in the last parts of the small intestine, colon and rectum have the primary but not the sole responsibility for constipation (5,7-9).

Interstitial cells, hormones and enterogastric and gastrocolic reflexes interact with the myenteric plexus which is the main responsible for peristalsis (21,22). A decrease in intestinal contractility with migratory motor complex disturbances are among the main causes of GI tract dysmotility (22). Some common situations in critically ill patients like hyperglycemia, hypokalemia, hypophosphatemia or hypomagnesemia have been associated with lower motility in the duodenum and jejunum. Hypoxia and hypercapnia can cause a malfunction of the myenteric plexus too (23,24). Moreover, sepsis and edema have also been associated with GI dysmotility (21,25,26).

Colon, rectum and sigmoid function has been less studied in the critically ill patient although dysmotility in this area is the second most frequent cause, right after delayed gastric emptying. The physiopathology is barely understood yet and the most accepted hypothesis is that there is an imbalance in colonic autonomic innervation. These disturbances are frequently extended in patients after strokes, heart attacks, peritonitis, sepsis and major surgeries (27).

In addition, there are multiple and frequent factors in critically ill patients which negatively affect one or several

sections of the GI tract: mechanical ventilation, analgesic drugs (opioid or non-opioid) or inotropes, splanchnic hypoperfusion, immobility and delay in the onset of enteral nutrition (EN) (5,7-9,11,19,21,22,28-32).

Clinical findings

Constipation symptoms in the pediatric critically ill patient depend on severity and time from illness onset. At the beginning, clinical findings are very similar to functional constipation with no bowel movements, abdominal pain and distension. Infants can show irritability, inconsolable crying or even feeding reluctance (14,33-35). In the critically ill child, abdominal distension secondary to constipation may be a cause of respiratory distress.

Lumpy or hard stools and straining to pass them may cause anal fissures, hemorrhoids and rectal bleeding (14,33,34). In children (4–12 years old) it is frequent to find fecal incontinence with or without overflow soiling or encopresis. Feeding intolerance may also occur (14,15). In cases of abdominal hypertension, nausea and vomiting may be present. The most severe complications of constipation are abdominal compartmental syndrome and sepsis secondary to bacterial translocation (6,36).

Moreover, constipation in the critically ill adult has been associated with feeding intolerance, delirium and longer time in the ICU and on mechanical ventilation (6-8,19,22,29,37,38). Van der Spoel *et al*. reported more days on mechanical ventilation (19.2 *vs*. 10.9 days, P=0.018) and longer length of ICU stay (21.4 *vs*. 12.6 days, P=0.017) in constipated patients and Mostafa *et al*. reported a higher percentage of failure to wean from mechanical ventilation in constipated patients *vs*. non-constipated ones (42.5% *vs*. 0%, P<0.05) (7,8). Both studies also described a failure to achieve proper amounts of EN in constipated patients without statistical differences.

In critically ill children, only López *et al*. studied the relationship between constipation and complications (1). They found that constipated patients had higher severity scores than non-constipated although no differences in length of PICU stay or mortality were found. Constipated patients received more vasoconstrictors and sedatives (midazolam and fentanyl); extracorporeal membrane oxygenation and continuous renal replacement therapies were also more frequent in these patients. Moreover, constipated patients started EN later, received less volume and suffered abdominal distension more frequently than non-constipated ones. Although, no differences were found in vomiting or EN interruptions. Constipated patients had more days of mechanical ventilation but with no statistical differences (7.8 *vs*. 5.4 days, P=0.07).

Diagnosis

Constipation is exclusively a clinical diagnosis. Probably some criteria as stool frequency and consistency should be used to provide a more thorough definition of constipation in critically ill children. Considering stool frequency (i.e., more than 3 days without a bowel movement) according to the ESICM Working Group on Abdominal Problems criteria, could be reasonable to use as it is the most widely accepted criteria in published studies in adults, and children trend to have a GI transit time shorter than adults (1). Regarding stool consistency, stools from type 1 and 2 on the Bristol Stool Form Scale, could also be accepted as a valid criterion since this scale has been validated in pediatric population (39,40).

There are different tests to study GI motility disorders. The more specific techniques for the lower GI tract are the following:

- Scintigraphy: the gold standard to measure colonic transit time. After the administration of a radiolabeled meal, quantitative parameters and visual inspection of γ-camera images need to be analyzed and interpreted. Scintigraphy can measure global and regional colonic transit time (41,42). It is the most sensitive noninvasive method to diagnose colonic dysmotility and it is widely extended to evaluate colonic motility disorders (41-44). Several limitations apply since specialized and expensive equipment and well-trained staff are required to carry it out and assess the test results (43,44). Although it is a noninvasive test which ensure good reproducibility, a lot of disadvantages and technical limitations have been found in critically ill children such as meal composition, the need for multiple images over consecutive days and the impossibility to perform the test at bedside (22,41-43).
- Colonic transit time (CTT) studies: there are two options depending on the type of marker used. CTT with radiopaque marker consists on single or multiple ingestion of radiopaque pellets followed by a radiography on day 4 or 7, depending on the chosen protocol (45-47). CTT can be calculated according to the number of pellets seen in the plain x-ray multiplied by a constant of time (48).

CTT with radiopaque markers has shown a good correlation with scintigraphy but limitations about its use in critically ill children are similar to the ones mentioned before for scintigraphy test (46,47).

- The second option is CTT measurement by wireless motility capsule (WMC). The WMC is ingested with a standard meal sending information (intraluminal pH, pressure and temperature) to the receiver throughout the GI tract (45). In the adult population, CTT by WMC were very similar to those obtained from radiopaque markers or scintigraphy, but ingestion of the WMC is still a major problem in the critically ill patients, especially for the younger ones (45,49).
- Breath tests: they are used to measure oro and gastrocecal transit time in the gastroenterologists' daily work. Lactulose is a non-absorbable disaccharide that can be fermented by colonic bacteria. This fermentation results in the production of hydrogen which is transported to the lungs through the bloodstream and can be measured in exhaled air. This is an easy to perform, noninvasive, safe and low-cost test that it has shown a good correlation with scintigraphy (45,50,51). However, Miller *et al.* showed that lactulose itself is capable to accelerate small intestine transit time (50) and this test is very difficult to perform in critically ill children (52). Other option is 13C-lactose which can be specifically absorbed inside the colon lumen (51), but antibiotics (frequently used in critically ill patients) can alter its absorption (45).
- Imaging tests: they can be useful but there is still little clinical experience and they require specifically trained medical teams to carry them out and analyze the results (53-56). Magnetic resonance imaging (MRI) provides high-quality image. It is very useful to detect lumbosacral anomalies in up to 9% of children with no response to conventional treatments (43,56,57). MRI is useful in cases of neurologic symptoms especially of the lower limbs or spinal cord defects. However, MRI is expensive, takes a long time to perform and needs sedation in most pediatric patients (43,58). Abdominal ultrasound (US) is an easy and cheap option but it has the downside of gas interference as its major limitation. It can be used to set intestinal motility and perfusion (59). The diameter of the rectum can be measured by endoanal US (better than abdominal US) but it is more invasive. This diameter has been proposed to identify constipated and non-constipated patients but there are no cut-off points published in pediatric populations (15,16,59,60).

Sometimes, there are other tests that may be necessary to identify any other underlying organic disorder:

- Blood analysis with markers of celiac disease, endocrine system alterations (hypothyroidism) and food allergies (cow's milk protein allergy) (18,59).
- Abdominal radiography is useful in cases of very complex physical examination as in obese children and to identify lumbosacral injuries. It has been proposed to evaluate fecal impaction but with conflicting results. In critically ill patients is useful to identify acute abdomen situations (14,17,18,43).
- Barium enema and rectal biopsy are only useful to diagnose Hirschsprung´s disease and other neuropathies. Barium enemas may give false-negative results in children younger than 3 months old and in those children with ultrashort-segment Hirschsprung's disease (18,45,59).

Despite the huge amount of different diagnosis tests that exist, most of them have not been validated for pediatric population while others are too invasive to order them routinely. Because of that, none of them are recommended as a first choice for the diagnosis of constipation (16-18,59). Moreover, some of these options are not available in critically ill patients because they cannot be moved due to their instability.

In critically ill adults, some authors have suggested the development of constipation risk scores to improve constipation diagnosis and start prophylactic treatments, but there is no publication about it in pediatric populations (43,61). These scores could allow physicians to start treatments before complications occur.

Treatment

Different studies have highlighted the importance of developing protocols for constipation management in critically ill patients (1,2,5,7,22,61,62,63). Constipation needs a two-phase treatment. Thus, fecal impaction should be treated before starting a maintenance treatment. In both situations, laxatives are the treatment of choice (*Table 1*) (59,61-67).

Laxatives can be used to treat fecal impaction and

Table 1 Laxatives

Active principle	Daily dose	Maximum	Side effects
Stimulant laxatives			Long-term use (>1 week) may result in laxative dependence
Bisacodil (oral), single dose	3–12 years: 0.3 mg/kg	30 mg	Abdominal cramps, nausea, vomiting, diarrhea, electrolyte and fluid imbalance
	>12 years: 5–15 mg		
Bisacodil (rectal), single dose	<2 years: 5 mg		
	2–11 years: 5–10 mg		
	≥12 years: 10 mg		
Senna, single dose or twice daily	1 month–2 years: 2.2–4.4 mg	8.8 mg	Abdominal cramps, nausea, vomiting, electrolyte and fluid imbalance and discoloration of feces and urine
	2–6 years: 4.4–6.6 mg	13.2 mg	
	6–12 years: 8.8–13.2 mg	26.4 mg	
	>12 years: 17.6–26.4 mg	52.8 mg	
Castor oil, single dose	<2 years: 1–5 mL		Abdominal cramps, nausea, diarrhea, electrolyte and fluid imbalance and dizziness
	2–11 years: 5–15 mL		
	>11 years: 15–60 mL		
Lubricant laxatives			Fats and fat-soluble vitamins malabsorption
Mineral oil (oral), single dose or in divided doses	5–11 years: 5–15 mL		Abdominal cramps, nausea, vomiting, diarrhea and anal itching. Oral form may cause lipid pneumonitis if aspiration (contraindicated in children >4 years)
	≥12 years: 15–45 mL		
Mineral oil (rectal), single dose	2–11 years: 30–60 mL		
	≥12 years: one retention enema (60–150 mL)		
Docusate (oral), 1–4 divided doses	<3 years: 10–40 mg		Abdominal cramps, diarrhea, rash and throat irritation
	3–6 years: 20–60 mg		
	6–12 years: 40–150 mg		
	>12 years: 50–400 mg		
Glycerin (rectal), single doses that can be repeated	Neonates 0.5 mL/kg		Abdominal cramps, diarrhea, nausea, thirst, tenesmus and rectal irritation
	<6 years: 2–5 mL or 1 infant suppository		
	>6 years: 5–15 mL or 1 adult suppository		
Osmotic laxatives			Electrolyte imbalance
Magnesium hydroxide, once or in divided doses	<2 years: 40 mg/kg		Hypermagnesemia. Clinical findings depend on the magnesium serum level
	2–5 years: 400–1,200 mg or 1–2 tablets		
	6–11 years: 1,200–2,400 mg or 3–4 tablets		
	≥12 years: 2,400–4,800 mg or 6-8 tablets		
Magnesium citrate, once or in divided doses	<6 years: 2–4 mL/kg		
	6–12 years: 100–150 mL		
	>12 years: 150–300 mL		

Table 1 (*continued*)

Table 1 (*continued*)

Active principle	Daily dose	Maximum	Side effects
Sodium phosphate (oral), single dose	Different dosages depending on different dosage forms. Not recommended in children younger than 5 years old	30 mL	Abdominal cramps, diarrhea, nausea, vomiting, throat tightness, pharyngeal edema, dysphagia, hyperphosphatemia, hypomagnesemia, hypocalcemia, hypernatremia, metabolic acidosis, hypotension, cardiac arritmias, bronchospasm and dizziness
(rectal), single dose (may repeat)	2–11 years: 1 pediatric enema ≥12 years: 1 adult enema		
PEG o Macrogol 3350 with electrolytes, once or in divided doses	Fecal impaction: >5 years: 1–1.5 g/kg	82.8 g	Abdominal cramps, distension, diarrhea, nausea, vomiting, bloating and electrolyte abnormalities (hyponatremia, hypokalaemia)
	Maintenance: >2 years: 0.5–1.5 g/kg	27.6 g	
	Titrate to effect		
3350/4000 without electrolytes, once or in divided doses.	Fecal impaction: >3 years: 1–1.5 g/kg	100 g	Abdominal cramps, diarrhea, nausea, flatulence and urticaria
	Maintenance: >6 months: 0.5–1.5 g/kg	17 gr	
	Titrate to effect		
Lactulose, single dose	5 g	40 g	Abdominal discomfort, diarrhea, nausea, flatulence and vomiting

PEG, polyethylene glycol.

as maintenance treatment, but laxative type, route of administration and dosage can be different for each treatment option (14-18). The most common side effects reported are diarrhea, gas, bloating, cramping abdominal pain and abdominal distension. The frequency of the side effects associated depends on the type of laxative. Most of them are contraindicated in patients with bowel obstruction (4,14-16). Laxatives can be classified into different groups (*Table 1*):

- ❖ Stimulant laxatives: They can stimulate peristalsis acting directly on the myenteric plexus. Their most frequently reported side effects include abdominal cramping and diarrhea with malabsorption. Short courses of therapy are recommended to avoid laxatives dependence so now they are mostly used as a second-line therapy.
- ❖ Lubricant laxatives (stool softeners): They reduce water absorption from the intestine to facilitate defecation. Their main side effect is that they may alter fats and fat-soluble vitamins absorption so they must be administered without meals.
- ❖ Osmotic laxatives: They increase the amount of water inside the intestinal lumen decreasing intestinal pH or increasing osmolarity. It is necessary to monitor changes in the electrolytes, most noticeably in patients with renal impairment.

Although manual evacuation of the bowel (under anesthesia or not) is a valid option, it is not recommended unless optimum treatments have failed. Pharmacologic disimpaction treatment can be administered through oral or rectal administration. No clear evidence exists to demonstrate higher efficacy of any over the other (68,69). The oral treatment is preferred for maintenance and osmotic laxatives are preferred because they are well tolerated and they do not alter any nutrient absorption (64,66).

In critically ill patients (adults and children), the most common laxatives used were polyethylene glycol (PEG), lactulose, Senna (which active component are Sennosides A and B), milk of magnesia, castor oil and enemas containing phosphate (6,20,37,62,64,70). PEG (with or without electrolytes) and lactulose are the most widely used and recommended by international guidelines in pediatric patients (64).

Macrogol (generic name) or PEG (chemical name) is a high molecular weight polymer capable to absorb up to 100 water molecules for every molecule of PEG. Hence PEG draws water into the stool, improving stool consistency and frequency. There are two PEG molecules according to their molecular weight (PEG 3350 and PEG 4000) with no differences between them. PEG 3350 can be supplemented with electrolytes to increase its osmotic strength (64,65,71).

Table 2 Treatment options for opioid-induced constipation

μ-opioid receptor antagonists	PAMORAs	Secretory medications	Promotility agents
Their limited bioavailability and high first-pass metabolism, limit their ability to enter the central nervous system (CNS) and reverse analgesia	Derivatives of μ-opioid receptor antagonists with molecular characteristics that avoid their penetration into the CNS	Family of drugs capable of increasing secretion of water and chloride into the lumen due to their ability to stimulate the cystic fibrosis transmembrane receptor	Their action over GI serotonin receptors ($5\text{-}HT_4$) stimulates peristalsis
Alvimopan: selective and competitive μ-opioid receptor antagonist	Axelopran: potent peripheral μ and κ-opioid receptor antagonist	Linaclotide: guanylyl cyclase C receptor agonist	Prucalopride: serotonin agonist with high affinity to $5\text{-}HT_4$ receptors
Naltrexone: competitive μ-opioid receptor	Naldemedine: amide derivative of naltrexone	Lubiprostone: bicyclic fatty acid	
Naloxone: selective μ-opioid receptor antagonist if it is used orally	Methylnaltrexone: quaternary ammonium derivative of naltrexone		
	Naloxegol: PEGylated naloxol conjugate		

PAMORAs, peripherally acting μ-opioid receptor antagonists; GI, gastrointestinal.

Lactulose is a nonabsorbable synthetic disaccharide that is partially metabolized by the bacterial flora of the colon decreasing intestinal pH. Lactulose is the best studied osmotic laxative (64,65).

No significant differences were found by van der Spoel *et al*., between PEG and lactulose in critically ill adults in a randomized, double-blind, placebo-controlled trial (37). However, it has been found that PEG is superior to placebo and lactulose in functional constipation in the pediatric population (69-72). Actually, PEG is the first line drug for functional constipation in children while lactulose is a good alternative in case of PEG intolerance (16-18). But there are no published studies in critically ill children.

In critically ill patients, opioid treatments represent a cause of constipation. Opioid-induced constipation (OIC) is the most common gastrointestinal adverse event in patients with chronic pain under opioid therapy. The prevalence of OIC is directly related to the time that the opioids are needed (73-75). A lot of different drugs are available to treat OIC (*Table 2*), but only small retrospective case series of some of these treatments in critically ill children have been published (76-80). Their pharmacokinetic, pharmacodynamic and safety should be studied in this population. Furthermore, constipation in critically ill children is multifactorial, so these treatments are usually not recommended as a first-line treatment. Potentially, the use of sedation protocols to reduce opioids needs may help to decrease OIC and control one of these factors for constipation in the critically ill child, but there are no studies to verify this

Other drugs, such as neuromuscular blocking agents, can induce constipation in critically ill children also. In these cases, anticholinesterase drugs as neostigmine have been employed but only case series have been published in PICU population (79) with more studies in adults (62,78).

Some recent published studies have focused on prophylaxis protocols to treat constipation and the importance of bowel protocols for the management of constipation (61-63), but there is not a published paper so far in critically ill children.

Aside from pharmacological treatment, starting and intensifying hygiene and dietetic measures can help to improve constipation management, mainly in older children (16). Early mobilization and privacy are recommended but it is hard to achieve in some PICUs (1).

Dietary recommendations are focused on normal water and fiber intake (16-18), but critically ill children are under water and feeding restrictions in some cases. Different systematic reviews have showed a lack of effect or a mild improvement in stool frequency but without statistical differences or clinical relevance (81-84).

Evidence about the relationship between the intestinal microbiome and functional constipation is discordant (43,85-87). No clear evidence has been found with

prebiotics, probiotics or symbiotics in healthy children with functional constipation (85,88-90) and they may not be recommended in critically ill children (91). No studies have been yet performed in critically ill children about this topic.

Conclusions

Constipation is a common but understudied disease in critically ill children that is related to higher morbidity. The lack of a standard definition makes it difficult to undertake studies to increase knowledge. The definition employed in critically ill adults (absence of stool for three or more consecutive days without mechanical obstruction) could be suitable for critically ill children as well. Diagnosis for constipation is exclusively clinical and most of the different available tests should be reserved for suspicion of specific diseases. First-line treatment are osmotic laxatives, mainly oral PEG and lactulose. New treatments for OIC are being developed and could be a future option as a second-line treatment but high-quality studies are required in this field. Prophylactic treatments should be studied too. Hygiene, dietetic measures and early mobilization can help to improve constipation management in older children. Developing protocols for constipation management in critically ill children should be compulsory in those PICUs where no protocols have been previously established.

Acknowledgments

This article has been reviewed by a native English speaker provided by Norgine for proper usage of English.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Lyvonne Tume, Frederic Valla and Sascha Verbruggen) for the series "Nutrition in the Critically Ill Child" published in *Pediatric Medicine*. The article has undergone external peer review.

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-20-63/coif). The series "Nutrition in the Critically Ill Child" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. López J, Botrán M, García A, et al. Constipation in the critically ill child: Frequency and related factors. J Pediatr 2015;167:857-61.e1.
2. López-Herce J. Gastrointestinal complications in critically ill patients: what differs between adults and children? Curr Opin Clin Nutr Metab Care 2009;12:180-5.
3. Smalley N, Vangaveti V. Assessing the bowel function of critically ill children: a pilot study. Crit Care Resusc 2014;16:202-5.
4. Xing JH, Soffer EE. Adverse effects of laxatives. Dis Colon Rectum 2001;44:1201-9.
5. Nassar AP Jr, da Silva FM, de Cleva R. Constipation in intensive care unit: incidence and risk factors. J Crit Care 2009;24:630.e9-12.
6. McPeake J, Gilmour H, MacIntosh G. The implementation of a bowel management protocol in an adult intensive care unit. Nurs Crit Care 2011;16:235-42.
7. Mostafa SM, Bhandari S, Ritchie G, et al. Constipation and its implication in the critically ill patient. Br J Anaesth 2003;91:815-9.
8. van der Spoel JI, Schultz MJ, van der Voort PH, et al. Influence of severity of illness, medication and selective decontamination on defecation. Intensive Care Med 2006;32:875-80.
9. Guerra TL, Mendonça SS, Marshall NG. Incidence of constipation in an intensive care unit. Rev Bras Ter Intensiva 2013;25:87-92.
10. Fukuda S, Miyauchi T, Fujita M, et al. Risk factors for late defecation and its association with the outcomes of critically ill patients: a retrospective observational study. J Intensive Care 2016;4:33.

11. Reintam Blaser A, Malbrain ML, Starkopf J, et al. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. Intensive Care Med 2012;38:384-94.
12. Dorman BP, Hill C, McGrath M, et al. Bowel management in the intensive care unit. Intensive Crit Care Nurs 2004;20:320-9.
13. Comas Vives A, Polanco Allué I y Grupo de Trabajo español para el Estudio del estreñimiento en la población infantil. An Esp Pediatr 2005;62:340-45.
14. Cilleruelo ML, Fernández S. Estreñimiento. In: Martin Argüelles F, García Novo MD, et al., editors. Tratado de gastroenterología, hepatología y nutrición pediátrica aplicada de la SEGHNP. Ed Ergon, Madrid. 2010;111-22.
15. Álvarez G, Sánchez C, Tolín M, et al. Guía de estreñimiento en el paciente pediátrico. Ed Ergon, Madrid. 2017.
16. Tabbers MM, Di Lorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr. 2014;58:258-74.
17. Benninga MA, Faure C, Hyman PE, et al. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology 2016;150:1443-55.
18. Hyams JS, Di Lorenzo C, Saps M, et al. Functional disorders: children and adolescents. Gastroenterology 2016;150:1456-68.
19. Gacouin A, Camus C, Gros A, et al. Constipation in long-term ventilated patients: associated factors and impact on intensive care unit outcomes. Crit Care Med 2010;38:1933-8.
20. Patanwala AE, Abarca J, Huckleberry Y, et al. Pharmacologic management of constipation in the critically ill patient. Pharmacotherapy 2006;26:896-902.
21. Ladopoulos T, Giannaki M, Alexopoulou C, et al. Gastrointestinal dysmotility in critically ill patients. Ann Gastroenterol. 2018;31:273-81.
22. Ukleja A. Altered GI motility in critically Ill patients: current understanding of pathophysiology, clinical impact, and diagnostic approach. Nutr Clin Pract 2010;25:16-25.
23. Rostas JW 3rd, Mai TT, Richards WO. Gastric motility physiology and surgical intervention. Surg Clin North Am 2011;91:983-99.
24. Björnsson ES, Urbanavicius V, Eliasson B, et al. Effects of hyperglycemia on interdigestive gastrointestinal motility in humans. Scand J Gastroenterol 1994;29:1096-104.
25. Lobo DN, Bostock KA, Neal KR, et al. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. Lancet 2002;359:1812-8.
26. Fink MP. Effect of critical illness on microbial translocation and gastrointestinal mucosa permeability. Semin Respir Infect 1994;9:256-60.
27. Wells CI, O'Grady G, Bissett IP. Acute colonic pseudo-obstruction: A systematic review of aetiology and mechanisms. World J Gastroenterol 2017;23:5634-44.
28. Morad M, Nelson NP, Merrick J, et al. Prevalence and risk factors of constipation in adults with intellectual disability in residential care centers in Israel. Res Dev Disabil 2007;28:580-6.
29. Mutlu GM, Mutlu EA, Factor P. GI complications in patients receiving mechanical ventilation. Chest 2001;119:1222-41.
30. Nguyen T, Frenette AJ, Johanson C, et al. Impaired gastrointestinal transit and its associated morbidity in the intensive care unit. J Crit Care 2013;28:537.e11-7.
31. Montejo González JC, Estébanez B. Gastrointestinal complications in critically ill patients. Nutr Hosp 2007;22:56-62.
32. Dive A, Foret F, Jamart J, et al. Effect of dopamine on gastrointestinal motility during critical illness. Intensive Care Med 2000;26:901-7.
33. Poddar U. Approach to constipation in children. Indian Pediatr 2016;53:319-27.
34. Soylu OB. Clinical findings of functional and secondary constipation in children. Iran J Pediatr 2013;23:353-6.
35. Loening-Baucke V. Prevalence, symptoms and outcome of constipation in infants and toddlers. J Pediatr 2005;146:359-63.
36. Asai T. Constipation: does it increase morbidity and mortality in critically ill patients? Crit Care Med 2007;35:2861-2.
37. van der Spoel JI, Oudemans-van Straaten HM, Kuiper MA, et al. Laxation of critically ill patients with lactulose or polyethylene glycol: a two-center randomized, double-blind, placebo-controlled trial. Crit Care Med 2007;35:2726-31.
38. Smonig R, Wallenhorst T, Bouju P, et al. Constipation is independently associated with delirium in critically ill ventilated patients. Intensive Care Med 2016;42:126-7.
39. Chumpitazi BP, Lane MM, Czyzewski DI, et al. Creation and initial evaluation of a Stool Form Scale for children. J Pediatr 2010;157:594-7.
40. Lane MM, Czyzewski DI, Chumpitazi BP, et al. Reliability and validity of a modified Bristol Stool Form Scale for

children. J Pediatr 2011;159: 437-41.e1.
41. Couturier O, Bodet-Milin C, Querellou S, et al. Gastric scintigraphy with a liquid-solid radiolabelled meal: performances of solid and liquid parameters. Nucl Med Commun 2004;25:1143-50.
42. Reintam Blaser A, Jakob SM, Starkopf J. Gastrointestinal failure in the ICU. Curr Opin Crit Care 2016;22:128-41.
43. Reintam Blaser A, Preiser JC, Fruhwald S, et al. Gastrointestinal dysfunction in the critically ill: a systematic scoping review and research agenda proposed by the Section of Metabolism, Endocrinology and Nutrition of the European Society of Intensive Care Medicine. Crit Care 2020;24:224.
44. Maurer AH, Camilleri M, Donohoe K, et al. The SNMMI and EANM practice guideline for small-bowel and colon transit 1.0. J Nucl Med 2013;54:2004-13. Corrected in J Nucl Med 2014;55:521.
45. Tambucci R, Quitadamo P, Thapar N, et al. Diagnostic Tests in Pediatric Constipation. J Pediatr Gastroenterol Nutr 2018;66:e89-98.
46. Lundin E, Graf W, Garske U, et al. Segmental colonic transit studies: comparison of a radiological and a scintigraphic method. Colorectal Dis 2007;9:344-51.
47. Southwell BR, Clarke MC, Sutcliffe J, et al. Colonic transit studies: normal values for adults and children with comparison of radiological and scintigraphic methods. Pediatr Surg Int 2009;25:559-72.
48. Bautista Casasnovas A, Varela Cives R, Villanueva Jeremias A, et al. Measurement of colonic transit time in children. J Pediatr Gastroenterol Nutr 1991;13:42-5.
49. Lee YY, Erdogan A, Rao SS. How to assess regional and whole gut transit time with wireless motility capsule. J Neurogastroenterol Motil 2014;20:265-70.
50. Miller MA, Parkman HP, Urbain JL, et al. Comparison of scintigraphy and lactulose breath hydrogen test for assessment of orocecal transit: lactulose accelerates small bowel transit. Dig Dis Sci 1997;42:10-8.
51. Scarpellini E, Abenavoli L, Balsano C, et al. Breath tests for the assessment of the orocecal transit time. Eur Rev Med Pharmacol Sci 2013;17:39-44.
52. López J, Sánchez C, Fernández SN, et al. Is Hydrogen Breath Test with Lactulose Feasible for Measuring Gastrocecal Transit in Critically Ill Children? Pilot Study about Modification of the Technique. Biomed Res Int 2017;2017:5878659.
53. Van de Putte P, Perlas A. Ultrasound assessment of gastric content and volume. Br J Anaesth 2014;113:12-22.
54. Irvine EJ, Tougas G, Lappalainen R, et al. Reliability and interobserver variability of ultrasonographic measurement of gastric emptying rate. Dig Dis Sci 1993;38:803-10.
55. Schwizer W, Steingoetter A, Fox M. Magnetic resonance imaging for the assessment of gastrointestinal function. Scand J Gastroenterol 2006;41:1245-60.
56. Marciani L, Young P, Wright J, et al. Antral motility measurements by magnetic resonance imaging. Neurogastroenterol Motil 2001;13:511-8.
57. Bekkali NL, Hagebeuk EE, Bongers ME, et al. Magnetic resonance imaging of the lumbosacral spine in children with chronic constipation or non-retentive fecal incontinence: a prospective study. J Pediatr 2010;156:461-5.
58. Moreira TV, McQuiggan M. Methods for the assessment of gastric emptying in critically ill, enterally fed adults. Nutr Clin Pract 2009;24:261-73.
59. Constipation in children and young people: diagnosis and management. NICE Clinical Guideline CG99. Published May 2010. Last updated July 2017. Available online: https://www.nice.org.uk/guidance/cg99.
60. Burgers R, de Jong TP, Benninga MA. Rectal examination in children: digital versus transabdominal ultrasound. J Urol 2013;190:667-72.
61. Oczkowski SJW, Duan EH, Groen A, et al. The use of bowel protocols in critically ill adult patients: A systematic review and meta-análisis. Crit Care Med 2017;45:e718-26.
62. Guardiola B, Llompart-Pou JA, Ibáñez J, et al. Prophylaxis versus treatment use of laxative for paralysis of lower gastrointestinal tract in critically ill patients. J Clin Gastroenterol 2016;50:e13-8.
63. Dionne JC, Johnstone J, Smith O, et al. Content analysis of bowel protocols for the management of constipation in adult critically ill patients. J Crit Care 2020;58:98-104.
64. Gordon M, MacDonald JK, Parker CE, et al. Osmotic and stimulant laxatives for the management of childhood constipation. Cochrane Database Syst Rev 2016;(8):CD009118.
65. Constipation in children and young people. NICE Clinical Guideline QS62. Published May 2014. Last updated August 2018. Available online: https://www.nice.org.uk/guidance/qs62
66. Koppen IJ, Lammers LA, Benninga MA, et al. Management of functional constipation in children: therapy in practice. Paediatr Drugs 2015;17:349-60.
67. Lexi-Comp, Inc, and American Pharmacists Association. Pediatric & Neonatal Dosage Handbook. Hudson, Ohio: LexiComp, 2019.
68. Bekkali NL, van den Berg MM, Dijkgraaf MG, et al. Rectal fecal impaction treatment in childhood

constipation: enemas versus high doses oral PEG. Pediatrics 2009;124:e1108-15.
69. Miller MK, Dowd MD, Friesen CA, et al. A randomized trial of enema versus polyethylene glycol 3350 for fecal disimpaction in children presenting to an emergency department. Pediatr Emerg Care 2012;28:115-9.
70. Southwell BR. Treatment of childhood constipation: A synthesis of systematic reviews and meta-analyses. Expert Rev Gastroenterol Hepatol 2020;14:163-74.
71. Alper A, Pashankar DS. Polyethylene glycol: a game-changer laxative for children. J Pediatr Gastroenterol Nutr 2013;57:134-40.
72. Treepongkaruna S, Simakachorn N, Pienvichit P, et al. A randomised, double-blind study of polyethylene glycol 4000 and lactulose in the treatment of constipation in children. BMC Pediatrics 2014;14:153.
73. Vijayvargiya P, Camilleri M, Vijayvargiya P, et al. Systematic review with meta-analysis: efficacy and safety of treatments for opioid-induced constipation. Aliment Pharmacol Ther 2020;52:37-53.
74. Webster LR. Opioid-Induced Constipation. Pain Med 2015;16:S16-21.
75. Mehta N, O'Connell K, Giambrone GP, et al. Efficacy of methylnaltrexone for the treatment of opiod-induced constipation: a meta-analysis and systematic review. Postgrad Med 2016;128:282-9.
76. López J, Fernández SN, Santiago MJ, et al. Methylnaltrexone for the treatment of constipation in critically ill children. J Clin Gastroenterol 2016;50:351-2.
77. Lee JM, Mooney J. Methylnaltrexone in treatment of opioid-induced constipation in a pediatric patient. Clin J Pain 2012;28:338-41.
78. Aghadavoudi O, Abbasi S, Kashefi P, et al. Evaluation of intravenous neostigmine infusion on tolerance of enteral nutrition in Intensive Care Unit patients. J Res Med Sci 2013;18:750-4.
79. González R, López-Herce J, García A, et al. Neostigmine in the treatment of refractory constipation in critically ill children. J Pediatr Gastroenterol Nutr 2011;53:224-6.
80. Tofil NM, Benner KW, Faro SJ, et al. The use of enteral naloxone to treat opioid-induced constipation in a pediatric intensive care unit. Pediatr Crit Care Med 2006;7:252-4.
81. Pijpers MA, Tabbers MM, Benninga MA, et al. Currently recommended treatments of childhood constipation are not evidence based: a systematic literature review on the effect of laxative treatment and dietary measures. Arch Dis Child 2009;94:117-31.
82. Tabbers MM, Boluyt N, Berger MY, et al. Nonpharmacologic treatments for childhood constipation: systematic review. Pediatrics 2011;128:753-61.
83. Piccoli de Mello P, Eifer DA, Daniel de Mello E. Use of fibers in childhood constipation treatment: systematic review with meta-analysis. J Pediatr (Rio J) 2018;94:460-70.
84. Young RJ, Beerman LE, Vanderhoof JA. Increasing oral fluid in chronic constipation in children. Gastroenterol Nurs 1998;21:156-61.
85. Gomes DOVS, Morais MB. Gut microbiota and the use of probiotics in constipation in children and adolescents: Systematic review. Rev Paul Pediatr 2019;38:e2018123.
86. Khalif IL, Quigley EM, Konovitch EA, et al. Alterations in the colonic flora and intestinal permeability and evidence of immune activation in chronic constipation. Dig Liver Dis 2005;37:838-49.
87. Rhee SH, Pothoulakis C, Mayer EA. Principles and clinical implications of the brain-gut-enteric microbiota axis. Nat Rev Gastroenterol Hepatol 2009;6:306-14.
88. Perceval C, Szajewska H, Indrio F, et al. Prophylactic use of probiotics for gastrointestinal disorders in children. Lancet Child Adolesc Health 2019;3:655-62.
89. Wojtyniak K, Szajewska H. Systematic review: probiotics for functional constipation in children. Eur J Pediatr 2017;176:1155-62.
90. Ceresola ER, Ferrarese R, Preti A, et al. Targeting patients' microbiota with probiotics and natural fibers in adults and children with constipation. Eur Rev Med Pharmacol Sci 2018;22:7045-57.
91. Hojsak I, Fabiano V, Pop TL, et al. Guidance on the use of probiotics in clinical practice in children with selected clinical conditions and in specific vulnerable groups. Acta Paediatr 2018;107:927-37.

doi: 10.21037/pm-20-63
Cite this article as: López J, Solana MJ, López-Herce J. Narrative review of constipation in the critically ill child. Pediatr Med 2021;4:14.