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Implementation of a bowel regimen protocol in critically ill children: A pilot study

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Abstract. No studies have evaluated the outcomes of a bowel regimen (BR) in critically ill children receiving enteral nutrition. In fall 2010, a comprehensive feeding protocol and BR protocol were initiated in our institution. Six age-based BR protocols were developed, each of which included a four-step approach. This retrospective study evaluated children <18 years of age who received the BR between July 18, 2010 and April 31, 2012. The primary objective was to determine the percentage of patients requiring BR escalation beyond the initial step in the protocol (Step 1). Secondary objectives included the number of patients with a protocol deviation and the frequency of adverse events. Fifty-four patients were included. The majority were male with a median age of 0.25-year-old (range 0.08–15 yr). Forty-three (79.6%) patients received opioid continuous infusions. The BR was initiated on pediatric intensive care unit day 1 (range 1–25 d). Thirty patients (55.6%) required escalation beyond "Step 1". All patients who received "Step 2" and "Step 3" had a protocol deviation. Opioid duration was significantly associated with protocol escalation (odds ratio, 0.83; 95% confidence interval 0.689–0.997; $P = 0.047$). This pilot study is the first to describe the outcomes of the implementation of a four-step BR in critically ill children. Future studies should focus on the optimal regimen to alleviate constipation in critically ill children.

Keywords: Children, bowel regimen, critically ill, constipation

1. Introduction

In the pediatric intensive care unit (PICU), enteral nutrition is preferred over parenteral nutrition in patients with a functional gastrointestinal (GI) tract. Enteral nutrition is associated with decreased rates of infection, decreased intensive care unit length of stay, and overall improved clinical outcomes in critically ill adult patients [1]. These benefits have not been directly evaluated in critically ill children. The use of enteral nutrition is not without concerns in critically ill children. It may cause abdominal distention, discomfort, and need for increased sedation [1,2]. These GI effects can result in holding or decreasing enteral feedings by up to 50%, thereby reducing optimal caloric intake [3]. Decreased caloric intake can have many effects on a critically ill child including delayed clinical improvement and prolonged reliance on parenteral nutrition [2]. Many studies examining the use of enteral feedings noted the most common reasons for holding or discontinuation of feeds

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are constipation and other GI side effects (e.g., abdominal distention, and abdominal pain/discomfort) [2,4–6].

It is possible that a bowel regimen (BR) could decrease the rate of constipation in children receiving enteral feeds. However, no studies in critically ill children have evaluated the efficacy of a BR as their primary focus. One group of investigators evaluated the impact of implementation of an early, aggressive, enteral feeding protocol. These researchers included a comprehensive BR as part of the enteral feeding protocol implementation and identified a decrease in constipation and shorter time to goal caloric intake [7]. There continues to be a paucity of data regarding the implementation and efficacy of BRs in critically ill children. In fall 2010, comprehensive feeding and BR protocols were initiated in our institution. Six age-based protocols were developed. The objective of this study was to evaluate the efficacy of the BR protocol.

2. Materials and methods

2.1. Study design

This was a retrospective, cross-sectional study that included patients less than 18-years of age admitted to the PICU that received one of the six, age-based comprehensive feeding and BR protocols between July 18, 2010 and April 31, 2012. The PICU is a 25-bed medical and surgical unit that provides comprehensive services including extracorporeal membrane oxygenation and continuous renal replacement therapy. The BR included a four-step approach. Table 1 contains an example comprehensive feeding and BR protocol for 5–8-year-old children. Between the six age-based protocols, the medications were similar for each of the steps, but the dosing was specific for the age group. The only exception related to the age-based protocol was the omission of erythromycin lactobionate for children less than 1-year of age. Erythromycin lactobionate was not included due to concerns for the association of pyloric stenosis in this population [8]. Patients were excluded if they did not receive at least one "Step 1" medication or had incomplete medical records.

Table 1
Example comprehensive feeding and bowel regimen protocols for 5–8-year-old patients

Steps	Enteral feeding protocol
Step 1	Initiate enteral feeding protocol at current weight _____ kg
Step 2	Obtain daily weights
Step 3	Place nasogastric tube for feeds
Step 4	Abdominal girth q 24 h
Step 5	Goal feeding rate _____mL/h
Step 6	Use_____formula
Step 7	Initiate formula below at 10 mL/h, advance by 5 mL/h every 2 h until goal reached
Step 8	If on intravenous fluids, decrease by equal amounts for each increase in feeds, heplock intravenous once on goal feeds, may use intravenous fluids as carrier fluid for drips as needed
	Bowel regimen protocol
Step 1	Immediately upon initiation of feeding protocol begin docusate sodium and polyethylene glycol 3350 (Miralax®): Begin docusate sodium 50 mg nasogastric every 12 h Polyethylene glycol 3350 (Miralax®) ¾ packet (12.75 g) nasogastric every evening
Step 2	If patient has no stool production within 48 h then: Begin metoclopramide (0.1 mg/kg/dose) _____mg nasogastric/intravenous every 6 h (max dose 10 mg/dose) AND Increase polyethylene glycol 3350 (Miralax®) ¾ packet (12.75 g) nasogastric every 12 h AND Adult glycerin suppository 1 per rectum daily
Step 3	If patient has no stool production within 24 h of starting metoclopramide and polyethylene glycol 3350 (Miralax®) or is already on them then give: Milk and molasses enema AND Lactulose 20 mL nasogastric every 12 h
Step 4	If no stool within 24 h of starting lactulose then: Erythromycin lactobionate (10 mg/kg/dose) _____mg intravenous every 6 h times 4 doses (max 250 mg/dose)

2.2. Data collection and study objectives

Demographic data was collected on all patients using a standardized data collection form and was collected by a single investigator. Data was accessed via the electronic database, Meditech (Medical Information Technology, Inc.; Westwood, Massachusetts). Additional data not found in the Meditech database were collected from nursing and dietary records. Basic demographic data collected included gender, age at initiation of the BR protocol, PICU length of stay, PICU admission diagnosis (e.g., surgery, infection/septic shock, pulmonary disease, etc.) and ventilator status. Additional data related to the BR protocol included the day of PICU stay that the protocol was initiated, type of enteral formula used, feeding regimen (i.e., continuous or bolus feeds), and route of administration of enteral feeds (e.g., nasogastric tube, transpyloric tube).

Data for each patient's BR protocol was collected in a stepwise fashion according to the steps of the BR. This data included the medications utilized in each step and dosing regimen (i.e. dose, frequency, duration). These medications were also assessed for the appropriate order of initiation based on the four-step approach. It was noted if the patient deviated from the protocol in "Step 2" through "Step 4". For the purpose of this study, a protocol deviation was defined as omission of a medication from "Step 2", "Step 3", or "Step 4". The number of stools per day, diarrhea, constipation, held feeds, and reasons given for held feeds were also collected. Opioid exposure in total duration (days), and cumulative dose (μg/kg fentanyl equivalents) was collected to evaluate the effects of opioid exposure on patients receiving the BR.

The primary objective of the study was to identify the percentage of children who required escalation of the BR protocol beyond "Step 1". Secondary objectives included identification of the number of patients who had a protocol deviation or escalation from "Step 1" and frequency of adverse events (e.g., diarrhea, held feeds). Additionally, identification of patient-specific factors associated with protocol escalation were evaluated.

2.3. Statistical analysis

Descriptive and inferential statistics were performed. Factors potentially associated with protocol escalation were analyzed via bivariate and multivariate analyses. Independent Student's *t*-test was used to compare the fentanyl continuous infusion data among patients who required protocol escalation versus those who required only "Step 1" therapy. Nominal data were compared using Fischer's exact test. A multiple logistic regression analysis was used to identify potential covariates associated with protocol escalation. These covariates included diagnosis (i.e., surgery vs. no surgery), age, PICU length of stay, duration of opioid continuous infusions, and cumulative opioid exposure (i.e., μg/kg fentanyl equivalents). Data management and analyses were conducted using Stata v10, with the a priori alpha set at $P < 0.05$ [9].

3. Results

A total of 54 patients were included. Fifteen patients were excluded from analysis because they did not receive at least one "Step 1" agent (n = 6) or were initiated on multiple steps of the BR simultaneously (n = 9). Demographic data is outlined in Table 2. The majority of the patients in this study were male with a median age of 3-months. Most patients required mechanical ventilation during the study period (Table 2).

Table 2
Demographic data (n = 54)

Variables	Mean ± SD (range)
Age (yr)	1.5 ± 3.0 (0.08–15)
Pediatric intensive care unit length of stay (h)	298.7 ± 272.6 (61–1704)
Day of pediatric intensive care unit stay protocol was initiated	1.8 ± 3.3 (1–25)
	n (%)
Gender	
Male	34 (62.9)
Female	20 (37.1)
Required mechanical ventilation	47 (87)
Pediatric intensive care unit admitting diagnosis/disease state	
Post-op cardio/thoracic surgery	2 (3.7)
Other post-op surgery	4 (7.4)
Infection/septic shock	32 (59.3)
Pulmonary disease	1 (1.2)
Other	15 (28.4)
Not listed	0

3.1. BR protocol and stool frequency

The BR protocol was started on a median of 1 d after PICU admission (range 1–25 d). One patient was not initiated on the protocol until PICU day 25. This patient had a prolonged hospital course complicated by persistent respiratory distress and multiple congenital heart defects. The patient received parenteral nutrition for the majority of the hospital stay secondary to poor gut perfusion and surgical complications. In study patients, the BR protocol was continued for a mean duration of 10.1 ± 8.5 d. The majority of patients received dual "Step 1" therapy (Fig. 1). Thirty patients (55.6%) required escalation beyond "Step 1". There was no statistical difference in the number of children requiring protocol escalation between those who received mono or dual "Step 1" therapy, 11 versus 19 ($P = 0.16$), respectively. All patients who received "Step 2" therapy had a protocol deviation. Specifically, none of these patients received metoclopramide during "Step 2". Three patients (5.6%) required escalation of the BR protocol to "Step 3", with all three of these patients deviating from

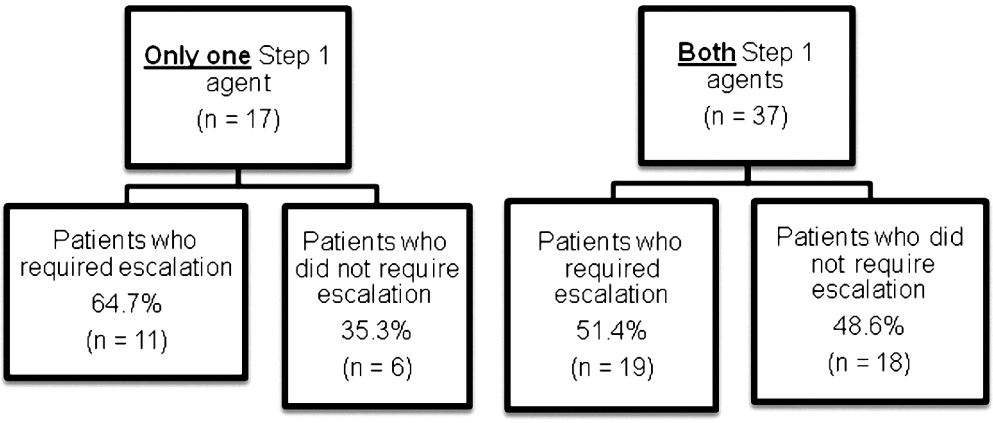

Fig. 1. Escalation rates beyond "Step 1" (n = 54).

Table 3
Stool composition and frequency according to age-group (n = 54)

Variables	1–3 months of age (n = 25)	4–12 months of age (n = 13)	1–4 years old (n = 11)	5–8 years old (n = 1)	9–12 years old (n = 3)	>12 years old (n = 1)
Average number of stools per day (mean ± SD)	3.7 ± 1.6	3.0 ± 1.3	3.4 ± 5.1	0.6	0.08 ± 0.14	1.7
Number of patients with diarrhea [n (%)]	10 (40.0)	4 (30.8)	3 (27.3)	0	0	0
Number of patients with constipation [n (%)]	6 (24.0)	2 (15.4)	7 (63.6)	1 (100)	2 (66.7)	1 (100)

the protocol because a milk of molasses enema was not initiated. No patients required "Step 4" therapy.

Table 3 describes the data for stool composition and frequency. The younger age-groups had a higher mean number of stools per day on the protocol than the older age-groups. Approximately one-third of all patients experienced diarrhea or constipation while on the BR protocol. There were a greater number of children less than 1-year-old who experienced either diarrhea or constipation (Table 3).

3.2. Enteral nutrition regimen

Table 4 contains the types of enteral formulas that the patients received along with the BR. The majority of patients (70.4%) received an infant formula. Selection of formula utilized differed based on the age of the patient. Cow's milk-based formulas were most commonly used in the infant population. Fifty-one patients (94.4%) received their enteral feeds as a continuous enteral infusion. Most patients were fed via the nasogastric tube (77.8%).

Table 4
Feeding formula used (n = 54)

Formula classification	n (%)
Soy-based*	3 (5.6)
Cow's milk**	25 (46.3)
Casein based***	3 (5.6)
Neonatal formula****	6 (11.1)
Human milk	1 (1.9)
Pediatric formulas*****	16 (29.5)

*Similac Isomil®;
**Similac Advance®, Enfamil Premium Infant®, Gerber GoodStart®;
***Pregestimil®, Nutramigen®;
****NeoSure®,
*****Pediasure®, Vivonex®, Jevity®, Elecare®

Forty-two patients (77.8%) had their enteral feeding regimen held during the study period. Only seven patients (13%) had their feeds held at least one time secondary to GI intolerance, and all but one of these patients was receiving a pediatric formula. The majority of the feedings held (79.4%) were due to preparation for extubation or a scheduled surgery.

Table 5
Continuous opioid infusions (n = 43)

Variables	Mean ± SD	Median (range)
Total days of opioid exposure	7.9 ± 13	4.6 (0–91)
Total opioid exposure (μg/kg fentanyl)	544.1 ± 1050.2	198 (0–5712)
Continuous infusion total (μg fentanyl)	7382.5 ± 18836.2	1539.1 (103.4–92420)
Additional bolus total (μg fentanyl)	536.2 ± 1119.3	135.1 (0–5297)

3.3. Continuous opioid infusions

Forty-three patients (79.6%) received fentanyl via continuous infusion during the study period. There were wide variations in duration and total dose (μg/kg) of fentanyl received (Table 5). Twenty-five of these patients (58.1%) required escalation beyond "Step 1" therapy. There was a noticeable, but not statistically significant, difference in the opioid duration between the patients who required escalation beyond "Step 1" therapy and those who did not, 13.0 ± 17.4 d versus 5.6 ± 4.1 d, respectively (P = 0.051). However, there was a statistically significant difference in the cumulative fentanyl exposure (μg/kg) between patients who required escalation beyond "Step 1" therapy and those who did not, 997 ± 1406.4 μg/kg versus 245.4 ± 241.3 μg/kg, respectively (P = 0.015).

3.4. Regression analysis

A multivariable logistic regression was performed simultaneously to assess the effect of various factors on the need for escalation of the BR protocol beyond the "Step 1" therapy. The total days of continuous opioid infusion exposure was significantly associated with protocol escalation (odds ratio [OR], 0.83; 95% confidence interval [CI] 0.689–0.997; P = 0.047). All other variables assessed (Patient age [OR, 1.24; 95% CI 0.91–1.69; P = 0.174], PICU length of stay [OR, 1.01; 95% CI 0.999–1.016; P = 0.077], surgical diagnosis [OR, 1.47; 95% CI 0.197–10.97; P = 0.709], and cumulative opioid exposure [i.e., μg/kg fentanyl] [OR, 1.00; 95% CI 0.999–1.00; P = 0.448]) were not significantly associated with protocol escalation.

4. Discussion

To our knowledge, this pilot study in the PICU is the first to specifically report on the efficacy of a BR protocol in critically ill children. Constipation is a frequent complication. In addition to enteral feeds, these children may have other risk factors for constipation including limited physical activity, electrolyte abnormalities, and use of concomitant medications (e.g., opioid analgesics) [10]. The initiation of a BR in children receiving enteral feeds may help achieve optimal caloric intake and potentially improve clinical outcomes.

Although not the primary endpoint of the study, Petrillo-Albarano et al. [7] compared children, receiving a feeding protocol and accompanying BR versus a historical control group. The BR protocol was a multi-step protocol that progressed based on lack of stool production similar to our protocol. They found an 18% decrease in constipation and a shorter time to goal caloric intake in the protocol patients. Despite these positive results, it is difficult to determine whether these effects were attributed to the BR, the feeding protocol, or the combination of the two, since both protocols were initiated simultaneously. This study also found that only 2% of patients on the BR experienced diarrhea, compared to 31% of children in our study. The retrospective nature of our study makes it difficult to draw any significant conclusions regarding this finding.

Our BR protocol included a four-step approach. All children were initiated on a "Step 1" therapy upon initiation of the enteral feeding protocol that included docusate and polyethene glycol 3350. The protocol was escalated based on the lack of stool production within a specific period (Table 1). The doses for all agents were based upon patient age. There are three major differences between our protocol and the protocol by Pertillo-Albarano et al. [7]. First, their protocol specified that children receiving opioid infusions were automatically initiated on a BR with metoclopramide and docusate. Our protocol did not delineate the use of specific medications based on opioid exposure. This being said, the authors do not clearly state what percent of their population received opioid infusions along with metoclopramide and docusate. Second, unlike our BR, their protocol was not implemented upon initiation of enteral feeds for patients who did not receive opioid infusions. Their BR was initiated for treatment of constipation versus prevention, because patients were initiated on the first step of the BR after 48 h of no stool production. Lastly, there are differences in the medications and dosing regimens in each step making it difficult to compare results of BR protocols.

Thirty patients (55.6%) in our study required escalation of the protocol, suggesting that implementation

of the protocol when beginning enteral feedings is prudent. There was no statistical difference in the number of children who required escalation of the BR between those who received "Step 1" monotherapy versus "Step 1" dual therapy. Based on this finding, it seems reasonable that a single agent may be sufficient for "Step 1". Some authors recommend polythene glycol 3350 as first-line therapy for constipation due to higher quality studies and safety profile compared to other agents [11,12].

We noted that not all patients who went on to "Step 2" and "Step 3" received all of the agents from the established protocol. Specifically, none of the patients received metoclopramide, which is a dopamine receptor antagonist that is associated with acceleration of motility in the GI tract [13]. Two studies evaluating an enteral feeding protocol in children have included metoclopramide as part of the protocol either for its effects on pro-motility and/or treatment of constipation [7,14]. Anecdotally, some clinicians documented concerns for extrapyramidal side effects with metoclopramide and chose to eliminate it when implementing the protocol. Three patients (5.6%) required escalation beyond "Step 2". None of the three received a milk of molasses enema as part of "Step 3". Pertillo-Albarano et al. [7] also included this agent in the second step of their protocol. However, this agent is not considered a medication and is obtained from dietary services. It is not clear if clinicians chose to eliminate this agent because of difficulty of preparation and administration, a lack of familiarity with this agent, or for other reasons. As a part of quality improvement initiative at our institution, we are in the process of revising the BR protocol based on the results of this current study.

As a marker for efficacy, we assessed the number of stools per day. A previous study by Dominguez and Borrego [15] assessed the baseline number of stools per day of 58 children admitted to the PICU from the parents/caregivers and compared it to the number of stools per day in the PICU. The researchers noted that stool frequency was diminished by as much 75% from baseline. In a linear regression model, these investigators determined that male gender and increased PICU stay was associated with a greater frequency of stools per day, and that opioid use was associated with a decreased number of stools per day. In our study, we did not compare the number of stools at baseline compared to the number of stools in the PICU. However, we performed a multiple logistic regression model evaluating the number of patients requiring a protocol escalation to treat their constipation. We found no association between PICU lengths of stay and protocol escalation. Similar to Dominguez and Borrego, we found that opioid duration was independently associated with protocol escalation. We also detected a clinically significant association between both the numbers of patients with a longer duration of opioids as well as higher cumulative opioid dose who required escalation beyond "Step 1". These results are not surprising considering constipation is a common adverse event noted with opioids and the significant opioid exposure that patients in this cohort received during their PICU stay.

As a secondary objective, we attempted to evaluate the frequency of held feeds, diarrhea, and constipation as surrogate markers for efficacy and safety. In addition, we also identified their enteral nutrition formulas. Most of the patients in this study were infants and received an infant enteral nutrition formula (Table 4). Due to the small sample size, it is difficult to correlate the specific formulas received to the clinical outcomes. The majority of patients who had their feeds held while receiving the enteral feeding and BR protocol were for preparation for extubation or prior to surgery. One-third of children experienced diarrhea or constipation on the BR (Table 3). It is also difficult to make specific comments on these findings due to the small sample size.

This study has several limitations. First, this was a retrospective study, and we were not able to compare the number of stools per day after protocol initiation to each patient's baseline in an effort to assess the true efficacy of the protocol. Second, a number of patients who escalated beyond "Step 2" experienced a protocol deviation and did not receive metoclopramide or milk of molasses enemas. As previously mentioned, there may have been several reasons why these two therapies were omitted, but with the current data, it is difficult to assess the effectiveness of "Step 2" and "Step 3". Last, the study included a small sample size. Most of the patients in the current study were less than 1-year of age, so it may be difficult to extrapolate all the results of the study to older children and adolescents. Despite these limitations, the present pilot study provides some data to support the use of a BR and some areas for future modification of the current protocol.

In conclusions, this pilot study is the first study to describe the outcomes of the implementation of a four-step BR in critically ill children. Constipation and GI intolerance are commonly noted consequences of enteral nutrition in the PICU. Approximately half of all patients required escalation of the BR. There was a clinically significant difference in the number of children

with a longer duration and higher cumulative opioid dose. Opioid duration was independently associated with protocol escalation. Future studies should focus on the optimal regimen to alleviate constipation in critically ill children.

References

[1] Barr J, Hecht M, Flavin KE, Khorana A, Gould MK. Outcomes in critically ill patients before and after the implementation of an evidence-based nutritional management protocol. Chest 2004; 125(4):1446–57.

[2] Mehta NM, McAleer D, Hamilton S, Naples E, Leavitt K, Mitchell P, et al. Challenges to optimal enteral nutrition in a multidisciplinary pediatric intensive care unit. JPEN J Parenter Enteral Nutr 2010;34(1):38–45.

[3] Mostafa SM, Bhandari S, Ritchie G, Gratton N, Wenstone R. Constipation and its implications in the critically ill patient. Br J Anaesth 2003;91(6):815–9.

[4] Mehta NM. Approach to enteral feeding in the PICU. Nutr Clin Pract 2009;24(3):377–87.

[5] Ritz MA, Fraser R, Tam W, Dent J. Impacts and patterns of disturbed gastrointestinal function in critically ill patients. Am J Gastroenterol 2000;95(11):3044–52.

[6] King W, Petrillo T, Pettignano R. Enteral nutrition and cardiovascular medications in the pediatric intensive care unit. JPEN J Parenter Enteral Nutr 2004;28(5):334–8.

[7] Petrillo-Albarano T, Pettignano R, Asfaw M, Easley K. Use of a feeding protocol to improve nutritional support through early, aggressive, enteral nutrition in the pediatric intensive care unit. Pediatr Crit Care Med 2006;7(4):340–4.

[8] Erythromycin lactobionate monograph. Lexi-Comp Online™, Pediatric Lexi-Drugs Online™, Hudson, OH: Lexi-Comp, 2011; July 18, 2012. Available from http://www.lexicomp.com.

[9] STATA statistical software. Version 10. [CD-ROM]. College Station, TX: StataCorp LP; 2007.

[10] Baker SS, Liptak GS, Colletti RB, Croffie JM, Di Lorenzo C, Ector W, et al. Constipation in infants and children: evaluation and treatment. A medical position statement of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr 1999;29(5):612–26. Erratum in: J Pediatr Gastroenterol Nutr 2000;30(1):109.

[11] Constipation Guideline Committee of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Evaluation and treatment of constipation in infants and children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediat Gastroenterol Nutr 2006;43(3):e1–13.

[12] Candy D, Belsey J. Macrogol (polyethylene glycol) laxatives in children with functional constipation and faecal impaction: a systematic review. Arch Dis Child 2009;94(2):156–60.

[13] Metoclopramide monograph. Lexi-Comp Online™, Pediatric Lexi-Drugs Online™, Hudson, OH: Lexi-Comp, 2011; July 18, 2012. Available from http://www.lexicomp.com.

[14] del Castillo SL, McCulley ME, Khemani RG, Jeffries HE, Thomas DW, Peregrine J, et al. Reducing the incidence of necrotizing enterocolitis in neonates with hypoplastic left heart syndrome with the introduction of an enteral feed protocol. Pediatr Crit Care Med 2010;11(3):373–7.

[15] Dominguez KD, Borrego ME. Bowel frequency in critically ill children. J Pediatr Pharmacol Ther 2004;9(3):187–91.