N. Valerio Dorrello, MD PhD
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Title: Early and fast advanced enteral feeding in critically ill children.

1) Rationale

Early enteral nutrition support can prevent complications associated with malnutrition; when used appropriately, it could have a positive influence on clinically important outcomes, such as length of stay, morbidity, and mortality. Making decisions regarding the most effective and safe nutrition support can be challenging, and consequently considerable variation exists in the care of critically ill children.

a) Review of the literature

The prevalence of malnutrition among critically ill patients, especially those with protracted clinical course, has remained largely unchanged over the last 2 decades, with a prevalence between 9.8% to 65% (Hulst J. et al., 2004).
The profound and stereotypical metabolic response to critical illness and failure to provide optimal nutrition support therapy during the intensive care unit stay are the principal factors contributing to malnutrition in this setting.
In the Nutritional Support of the Critically Ill Child Guidelines published by A.S.P.E.N. in 2009 there are three major statements about the Enteral Nutrition (EN): 1) in critically ill children with a functioning gastrointestinal tract, enteral nutrition should be the preferred mode of nutrient provision, if tolerated; 2) a variety of barriers to EN exist in the PICU. Clinicians must identify and prevent avoidable interruptions to EN in critically ill children; 3) there are insufficient data to recommend the appropriate site (gastric vs post-pyloric/transpyloric) for enteral feeding in critically ill children. Post pyloric or transpyloric feeds may improve caloric intake when compared to gastric feeds. Post-pyloric feeding may be considered in children at high risk of aspiration or those who have failed a trial of gastric feeding.
The EN is considered to have failed when complications secondary to nutrition occurred that required the interruption of the feeding, such as significant abdominal distention with clinical alteration and/or increase of abdominal pressure, nutrition residual in the gastric aspirate with a volume >50% of the volume administered in the previous 4 h, severe diarrhea (more than five loose stools per day), or necrotizing enterocolitis.

In the PICU there is a huge controversy surrounding the initiation of enteral nutrition.
The data from the multicenter study "Nutrition Support During Pediatric Critical Illness"2009 organized by Boston Children's Hospital showed that the EN is initiated in PICU only in 18.6 % of patients during the first day and 30% during the second day (see table below).

Number of Patients on EN	**Your Site** n=19	**Sister Sites** n=149	**All Sites** n=447
Initiation of EN			
Prior to ICU admission	5 (26.3%)	39 (26.2%)	68 (15.2%)
on the 1st ICU day	1 (5.3%)	30 (20.1%)	83 (18.6%)
on the 2nd ICU day	9 (47.4%)	48 (32.2%)	134 (30.0%)
on the 3rd ICU day	2 (10.5%)	19 (12.8%)	77 (17.2%)
on the 4th ICU day or later	2 (10.5%)	13 (8.7%)	85 (19.0%)

One of the most debating issues regards patients requiring cardiovascular support with vasopressors because of cathecolamine-induced splanchnic vasoconstriction and inhibition of gut motility. Enteral feeding produces an increase in cardiac output and vasodilatation of the mesenteric arteries; on the other side adrenaline and high dose of dopamine can reduce intestinal perfusion and impair the tolerance to nutrition. However, if adrenaline and dopamine increase cardiac output, splanchnic perfusion could be improved at certain level.
In the literature there are several studies looking at this aspect. King W. et al. (2004) studied the enteral feeding tolerance in 52 patients between 1 month to 20 years old treated with dopamine and/ or other vasopressors (norepinephrine, epinephrine, dobutamine and phenylephrine) starting enteral nutrition in the next 24 hrs from the admission. They found that 71% of the patients tolerated enteral nutrition without adverse effects. The other 29% of the patients had feeding held for intolerance (vomiting, abdominal distension, high gastric residual and constipation), not different from the feeding intolerance percentage (15% to 63%) showed in other general ICU populations.
Sanchez et al. (2007) reported better tolerance in critically ill children receiving early (<24hrs after PICU admission) versus late (started after 24hrs) post- pyloric nutrition with reduction in abdominal distension and other gastrointestinal complications (15.5% versus 10%). The 526 children included in this study reflected a general PICU population, including patients treated with vasoactive drugs (dopamine, epinephrine, milrinone).
The same group (Sanchez et al., 2006) looked at transpyloric enteral feeding in the postoperative of cardiac surgery children. They found that the enteral nutrition started at 48 hrs post surgery was well tolerated and not affected by the infusion of vasoactive drugs, sedative or muscle relaxants. They found that abdominal distension was significantly more frequent in the patients undergoing surgery than in other patients (9.4% versus 2.2%), although definitive feeding held was necessary only in in 1.1%. They concluded saying that transpyloric enteral nutrition could be useful to enable a high calorie delivery to be provided with few complications in postoperative period of cardiac surgery in children, including those receiving high dose of sedative, muscle relaxant and vasoactive drugs.
In a following study from the same group (Lopez-Herce et al. 2008) they looked at tolerance of enteral nutrition in critically ill children with shock. They found that the frequency of gastrointestinal complications was significantly higher than in the control group (30.7% versus 15.4%). they argued the results with the following points: a) during shock splanchnic oxygen delivery is reduced while splanchnic oxygen consumption remains unaltered (Berger et al. 2005); feeding can exacerbate the altered oxygen balance, leading to gastrointestinal complications and, in rare cases, small bowel necrosis; b) those patients usually require high dose of vasopressors and these at high levels can reduce intestinal perfusion and impair the tolerance to nutrition; c) bowel motility is extremely reduced in patients with shock due to high doses of sedatives and muscle relaxants; d) children with shock have higher incidence of acute renal failure and mortality than other critically ill children.
In the literature that I reviewed they usually start EN from 0.5-1cc/kg/hr, that is usually considered trophic feeding (as in Sanchez et al., 2007 and Lopez-Herce et al. 2008). They increase of 0.5-1ml/Kg every 3-4 hours if the gastric residue was less than 25% of the volume administered until a caloric goal of 70-100 kcal/metabolized calories per day according to Holiday formula in 24-48hrs.
The importance of trophic feeding is not well studied in critically ill children. Trophic feeding might be important as start in the enteral nutrition support in PICU because it can prevent gut mucosal atrophy, barrier dysfunction and could allow to keep gut hormone secretion and motility.

Many studies of early enteral feeding have been executed in neonates and prematures and mostly are focused on trophic feeding (the volume of feeding considered trophic is milk/formula 0.5-

1cc/Kg/hour or up to 25kcal/Kg/day. If more than 25% of the patient's nutritional needs are administered enterally, the feeding should no longer be considered trophic).
The three major Chochrane reviews have valued the early enteral feeding in premature infants (in parenthesis it is indicated if the early/trophic feeding was beneficial according to the studies reviewed):
Bombell et al. Early trophic feeding for very low birth weight infants. Cochrane reviews, issue 3; 2009. There no substantial data to evaluate the effect of trophic feeding on clinically-important outcomes in VLBW infants, the available trial data do not provide evidence of an effect on feed tolerance, growth, or development. Reassuringly, there is also no evidence that trophic feeding has adverse effects, particularly on the risk of necrotising enterocolitis (NEUTRAL).
Bombell et al. Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants. Cochrane reviews, issue 3, 2009. The three available trials provided no evidence that delayed (after 96 hours of postnatal age) introduction of progressive enteral feeds affected the incidence of necrotising enterocolitis, mortality or other neonatal morbidities (NEUTRAL).
J.M. Sondheimer. A critical Perspective on trophic feeding. Journal of Pediatric Gastroenterelogy and Nutrition 38, 237-238; 2004. More studies are needed to evaluate the unconfirmed benefits of trophic feeding before insisting on its use in fragile patients who might be better off fasting and supported by TPN until reasy to feed (NEGATIVE).
Le HD et al. Innovative parenteral and enteral nutrition therapy for intestinal failure. Seminairs in Pediatric Surgery 19, 27-34; 2010. Trophic feeding is important for intestinal adaptation, and EN should be initiated early to help wean patients from PN in postoperative period after intestinal failure (POSITIVE).

From review of the literature it seems that enteral feeding can be initiated in the critically ill children in the PICU within 24-48 hours after admission if the patient is hemodynamically stable with a functioning gastrointestinal gut even if he is still on vasopressors, unless those are at high doses. It will be safe to start EN as trophic feeding and advance it to full volume if tolerated.

b) Study Objectives

A cessation of enteral nutrients may diminish gastrointestinal functional and structural integrity by diminished hormonal activity, growth of intestinal mucosa, nutrient absorption, motor activity, mucosal barrier defense (Tyson JE et al., 2007; Zonta S et al., 2007). These problems can become extensively important in critically ill children where enteral feeding is often delayed, prolonging the hospital stay and the morbidity associated.

The objective of this study is to understand if early enteral feeding in critically ill children admitted to PICU protect the gut mucosa and reduce the length of stay in PICU, improving the long-term the morbidity and mortality of those patients.

2) Study design and Statistical Procedures
This will be a prospective, controlled, randomized, not masked, stratified clinical trial to assess early enteral feeding in critically ill children admitted to the PICU of Children Hospital of New York Presbyterian over a period of 6 months.
The patients will be chosen randomly within12 hours from admission through a computer-generated randomization schedule stratified on the basis of Paediatric Index of Mortality score PIM* (<50%, ≥ 50%), Diagnosis (Medical versus Surgical) and age (30 days old -1 year old

versus >1 year old). Treatment assignment (T1: early enteral nutrition: T2: common practice in PICU according to the clinical judgment of the physician) will be communicated to the investigator only after eligibility criteria for enrollment has been confirmed.
* PIM score is calculated from information collected at the time a child is admitted to the PICU. The following variables are considered: elective admission, underlying condition, response of pupils to bright light, mechanical ventilation, systolic blood pressure, base excess, FiO2 (%)/PaO2 (mmHg).

The clinical data available at the time we are designing the study suggest that patients admitted to the PICU of the Children's Hospital of New York Presbyterian are mostly 50% male, 50% female; population age: 0-7 years (60%); 8-17 (40%); the average length of stay for patients admitted for more then 72 hours is 6 days, with a Standard deviation of 1.5 days; the average of patients admitted to PICU is mostly enterally fed during the second day of stay according to the standard of care in the PICU. In order to achieve 80% power with a p-value of 0.05, applying the unpaired t-test [n in each group = 1+16 (std-devn/effect)^2 n where std-devn is of the outcome measure across subjects; effect is postulated group difference in outcome measure] and considering a significant effect 12 hours difference in Length of Stay I should enroll 145 patients in each group. Based on the amount of patients that are admitted annually at the PICU of Children's Hospital of New York Presbyterian I should be able to enroll these patients in 6-9 months.
I will use a logistic regression model ($z= \beta_0+ \beta_1x_1+\beta_2x_2+\beta_3x_3+\ldots.+ \beta_kx_k$) to compare results between the two groups according to age, gender, diagnosis, PIM score.

Primary outcome:

- Length of stay in PICU in hours

Secondary outcomes:

- Weight
- Total interruptions of enteral feeding and reason of interruption
- Total days that feedings were withheld
- Duration of parenteral nutrition
- Incidence of bacterial infections related to central venous accesses.

3) Study Procedures

Data (age, weight, PIM score, diagnosis, bacterial infections due to central venous access, interruption of enteral feeding, reason of interruption and duration of parenteral nutrition) will be collected by the research investigator from the Hospital EMR (Eclypsis system) after patient has been discharged.
T1: patients will be fed through Naso-Gastric tube with formula according to their age starting from 12 hours from admission. The feeding will start at rate of 24cc/Kg/day (or 25% of the daily caloric goal-trophic feed) with increase of 6cc/kg every 4 hours (or 25% of the initial intake) if the gastric volume residue was less than 25% of then previous volume administered until to full feed according to the volume and caloric goal calculated by a dietician. The volume and caloric goal should be reached in 24-48 hours from the beginning of the enteral feeding. When a gastric aspirate containing volume residue greater than 50% of the volume administered in the previous 4 hours, the feeding rate can be reduced of 50% and measure the residue again after 4 hours before increasing the feed volume.

Reasons to stop the enteral feeding: vomiting, persistent abdominal distension with increase of abdominal pressure, nutrition residual in the gastric aspirate with a volume >50% of the volume administered in the previous 4 hours, severe diarrhea (more than five loose stools per day), or necrotizing enterocolitis (clinical and radiological diagnosis).
Enteral nutrition can be restarted at the last rate reached when the reasons to withhold the feeds are solved.

T2: patients will be started on Enteral Nutrition according to the common standard of care.

5) Study Instruments. N/A

6) Study Subjects
Subjects will be consecutive patients admitted to the PICU of the Children's Hospital of New York Presbyterian according to the inclusion and exclusion criteria.

Inclusion criteria:
Children with age between 1 month and 18 years admitted to the PICU, mechanically ventilated at the admission or intubated in the first 12 hrs from admission with estimated length of stay of three days minimum.

Exclusion criteria:
Patients with hemodynamic instability they require increase of one or multiple vasoactive drugs in first 12 hours of admission to the PICU), significant upper gastrointestinal bleeding, presence or high risk of necrotizing enterocolitis, intestinal obstruction, abdominal surgery, paralyticus ileus, abdominal hemorrhage.
Patients included in the study that will be discharged before 72 hrs from admission, will be excluded from the statistical analysis.

7) Recruitment
Subjects will be identified from the PICU admitting physician during the first 12 hrs from admission. The patient will be included in a computerized system and at the 12 hours from admission if eligible, he/she will be included in one of two arms of the study.

8) Informed Consent
Informed Consent will be given to the parents or legal guardian at the admission or later but before the 12^{th} hour from admission before the study starts.

9) Confidentiality of the Study
Data Confidentiality will be maintained at all times. No personal identifiers will be placed on any study documentation. The patients' medical record number will be used by the PICU site for internal tracking purposes only and will be kept solely by the Columbia study team.
Only authorized personnel will be granted access to information. All information in a computer database will be password protected and stored in a secure area at the PI institute under 2 locks. Any presentation or publication of the results will be aggregated to the site and not patient level. It is not foreseen that any situation will arise whereby confidentiality or anonymity cannot be guaranteed or must be breached.

10) Potential risks
No more than Minimal Risk (45 CFR 46.404/21 CFR 50.51; i.e., 'Section 404')
'Minimal Risk' means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or

during the performance of routine physical or psychological examinations or tests. The exclusion criteria and the feeding intolerance criteria will allow to avoid or stop early enteral feeding in all those conditions that could be detrimental to the patients.

11) Privacy Protections

The following steps will be taken to protect patient information during the conduct of the study:

1) All paper documents pertaining to the study will not leave the hospital and will be stored in a locked cabinet.

2) No patient identifiers will be entered online. All patients will be identified by their study number only.

14) Potential benefits

It could exist a potential personal benefit from taking part in this research study: patients could present a better and faster tolerance of enteral feeding.

The results of this study will highlight the strengths and weaknesses of early enteral feeding versus common practice in PICU nutrition support.

15) Subject compensation

No compensation

16) Alternatives

The alternative is non-participation for the Columbia PICU

17) Location

Columbia as Lead Institution

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