

## Original Article



# Management of Enteral Nutrition in the Pediatric Intensive Care Unit: Prokinetic Effects of Amoxicillin/Clavulanate in Real Life Conditions

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## ABSTRACT

**Purpose:** Malnutrition is a common feature in critically ill children. Enteral nutrition (EN) is the main strategy to nutritionally support critical ill children, but its use can be hindered by the development of intolerance. The study aimed to assess the effectiveness and safety of amoxicillin/clavulanate (A/C) to treat EN intolerance.

**Methods:** We retrospectively evaluated patients admitted to the pediatric intensive care unit from October 2018 to October 2019. We conducted a case-control study: in the first 6 months (October 2018-April 2019) we implemented the nutritional protocol of our Institution with no drug, whereas in the second half (May 2019-October 2019) we employed A/C for 1 week at a dose of 10 mg/kg twice daily.

**Results:** Twelve cases were compared with 12 controls. At the final evaluation, enteral intake was significantly higher than that at baseline in the cases (from 2.1±3.7 to 66.1±27.4% of requirement,  $p=0.0001$  by Wilcoxon matched-pairs signed rank test) but not in the controls (from 0.2±0.8 to 6.0±14.1% of the requirement,  $p=NS$ ). Final gastric residual volume at the end of the observation was significantly lower in the cases than in the controls ( $p=0.0398$ ). The drug was well tolerated as shown by the similar safety outcomes in both cases and controls.

**Conclusion:** Malnutrition exposes critically ill children to several complications that affect the severity of disease course, length of stay, and mortality; all may be prevented by early EN. The development of intolerance to EN could be addressed with the use of A/C. Future prospective clinical trials are needed to confirm these conclusions.

**Keywords:** Gastrointestinal motility; Amoxicillin clavulanic acid; Enteral nutrition; Nutrition disorder; Pediatric intensive care unit; Prokinetic; Amoxicillin

## INTRODUCTION

Malnutrition is a common feature in patients admitted to the pediatric intensive care unit (PICU), ranging from 10 to 45% of patients; owing to an imbalance between energy requirements and caloric intake [1-4]. In this setting of care, malnutrition can be life-threatening and can affect the course of infections and the length of ventilation and hospitalization [1-3].

**Conflict of Interest**

The authors have no financial conflicts of interest.

Enteral nutrition (EN) is the main strategy to nutritionally support critical ill children and to treat and prevent malnutrition. It has been suggested that EN should be started within the first 24 h of admission to the PICU and that EN withdrawal should be avoided in an attempt to quickly realize the predicted caloric goal [2,4,5]. However, in the PICU, the EN course can be hindered by many factors, in particular, delayed EN beginning or repeated EN interruptions owing to perceived intolerance or required fasting for procedures [2]. Even up to half of patients treated in the PICU may have a true or suspected EN intolerance [5-7], which would lead to the maintenance or start of parenteral nutrition (PN) regimens and withdrawal of EN [8,9]. Some treatments can improve EN intolerance, however unfortunately, they are contraindicated or not recommended in children or not available in the market in many countries [8,9]. Amoxicillin/clavulanate (A/C), available and easy to manage in the PICU, seems capable of promoting small intestinal motility, even if administered by the enteral route [10-12]. Notably, this drug, if administered into the small bowel lumen before ingestion of a meal, has been shown to induce the development of duodenal phase III-type contractions in the duodenum, with features similar to those present in the fasting state [11]. This observation suggests the potential application of A/C as a prokinetic agent [10-12].

The objective of the present study was to assess the effectiveness and safety of A/C to treat EN intolerance in critically ill children.

## MATERIALS AND METHODS

### Study design

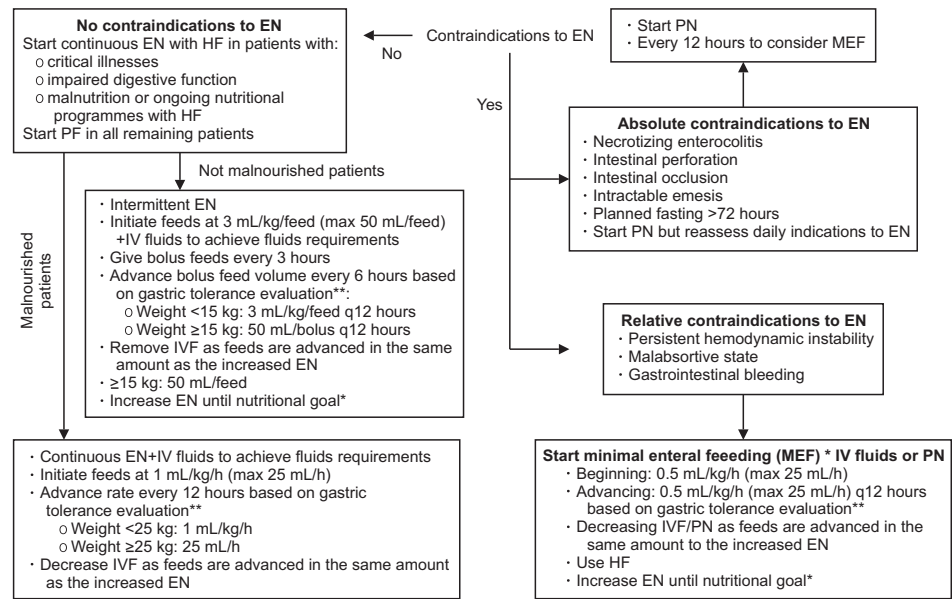
We retrospectively evaluated patients admitted to the PICU from October 2018 to October 2019 and who were treated with the nutritional protocol implemented in our hospital since July 2018 (**Fig. 1**) and focused on critically ill children aged more than 1 month. The study period was divided into two half-year periods (October 2018–April 2019 and May 2019–October 2019) according to the start of the use of A/C and was approved by our Ethical Committee in April 2019 (see below). Therefore, we conducted a case-control study: in the first 6 months (October 2018–April 2019) we implemented the protocol with no drug that could improve intestinal tolerance, whereas in the second half (May 2019–October 2019) we employed A/C as a prokinetic agent in the cases with suspected EN intolerance. The treatment lasted 1 week at a dose of 10 mg/kg twice daily for 7 days and was administered by devices recommended for EN (see below).

Inclusion criteria for the study were:

- a) Age ranging from 1 month to 18 years,
- b) Enteral intake lower than 10% of requirement after 7 days since admission to the PICU,
- c) Neurological impairment,
- d) Indications for admission to the PICU: respiratory failure, seizures, and post-surgery care,
- e) Available naso-gastric tube (NGT) or gastrostomy (PEG)/gastro-jejunostomy (PEG-PEJ) for the nutritional treatment.

Exclusion criteria:

- a) Known allergy to A/C,
- b) Ongoing ketogenic diet,
- c) Clinical contraindications to advance EN feeds.



**Fig. 1.** Enteral feeding management protocol. \*Nutritional goal: 75% of the caloric intake according to national guidelines [13,14] at the 7th day following PICU admission. \*\*Gastric tolerance evaluation was based on the GRV (mL/kg) assessment every 4 hours. GRV was extracted from PEG in all patients and it was discarded before the next dietary process. GRV has been considered suggestive for intolerance if it is  $\geq 50\%$  of the volume/h in continuous EN or if it is  $\geq 50\%$  of the bolus volume in intermittent EN over at least three consecutive evaluations following EN beginning. PICU: pediatric intensive care unit, GRV: gastric residual volume, EN: enteral nutrition, HF: hydrolysate formula, IVF: intravenous fluids, MEF: minimal enteral feeding, PN: parenteral nutrition, PF: polymeric formula.

### Study protocol

We evaluated all patients (cases and controls) over 8 days; the baseline point was day 1 (for the cases, day 1 was the day before starting A/C) and the end point was day 8. At baseline, we collected the following data:

- a) z-scores for weight, height, and body mass index;
- b) EN intake (% of energy requirements); gastric residual volume (GRV) expressed in mL/kg of weight.

At the end point we assessed:

- a) rate of weaning off mechanical ventilation (MV), death, overall treatments required (opiates, sedatives, muscle relaxants, and vasopressors), and diarrhea;
- b) EN intake (% of energy requirements), GRV expressed in mL/kg of weight.

The main outcomes of effectiveness were:

- 1) Enteral intake of 50% of the requirements at the end point,
- 2) GRV reduced by at least 50% at the end point.

The main outcomes of safety were the prevalence of the following:

- 1) Weaning off MV,
- 2) Death.
- 3) Overall drugs required.
- 4) Development of diarrhea (defined as  $\geq 3$  liquid stools/day in patients with previous normal stool and/or increase of  $\geq 50\%$  of the number of liquid stools).

Nutritional requirements were assessed according to the Italian National Guidelines [13,14]. GRV, reported as mL/kg, was assessed every 4 h (according to our protocol, **Fig. 1**). GRV was extracted from PEG in all patients and it was discarded before the next dietary process.

### Statistical analysis

Categorical variables were summarized as percentage and continuous variables as mean±standard deviation. Differences in caloric intake by EN and in GRV from baseline to the end point between cases and controls were compared using the Wilcoxon matched-pairs signed rank test. Differences in baseline and final caloric intake by EN, baseline and final GRV, and prevalence of overall treatments between cases and controls were evaluated using the Mann-Whitney-U-test. Categorical measures (MV dependency, death, and development of diarrhea) were assessed using the Fisher's exact test. A  $p$ -values<0.05 were considered statistically significant. Statistical evaluation and analyses were performed using Graph Pad Prism 6 for Windows (GraphPad Software, Inc., La Jolla, CA, USA).

### Ethics

The Ethical Committee of “Bambino Gesù” Children's Hospital approved the present study (Protocol N° OPBG\_1790/2019). Written informed consent was obtained from a parent or surrogate decision maker.

## RESULTS

Twenty-four patients in total, 12 cases and 12 controls, were included (**Table 1** for details). As shown, indications for admission to the PICU were similar between cases and controls. Age ranges were very wide, and no patient was severely malnourished [15]; access routes for long-term EN were present in 58% of the cases and in 42% of the controls. As shown by the rate of perinatal events, 33% of all patients were affected by cerebral palsy as the primary neurologic disease.

### Effectiveness measures

At final evaluation, in the case group, enteral intake resulted in significantly higher levels than at baseline (from 2.1±3.7 to 66.1±27.4% of the requirement,  $p=0.0001$  by Wilcoxon matched-pairs signed rank test), but not in the control group (from 0.2±0.8 to 6.0±14.1%

**Table 1.** Overview of the characteristics of cases and controls

| Patient characteristics          | Cases (n=12)    | Controls (n=12) | $p$ -value |
|----------------------------------|-----------------|-----------------|------------|
| Age                              | 5.5 (0.67–14)   | 4 (1–17)        | NS         |
| Male/female                      | 4/8             | 6/6             | NS         |
| Weight* (z-score)                | 0.6 (–3.3–1.2)  | 0.9 (–0.02–1.5) | NS         |
| Height* (z-score)                | –1.4 (–3.4–1.0) | 0.3 (–0.6–1.1)  | NS         |
| Body mass index* (z-score)       | 0.7 (–1.4–1.8)  | 1.1 (–0.7–2.0)  | NS         |
| Indication for admission to PICU |                 |                 |            |
| Respiratory failure              | 5               | 5               |            |
| Seizures                         | 5               | 5               |            |
| Post-surgery care                | 3               | 3               |            |
| Perinatal events                 | 4               | 4               | NS         |
| Tracheostomy                     | 6               | 4               | NS         |
| NGT                              | 5               | 7               | NS         |
| PEG/PEJ                          | 7               | 5               | NS         |

Values are presented as mean (range), number only, or median (interquartile range).

PICU: pediatric intensive care unit, NGT: nasogastric tube, PEG: percutaneous endoscopic gastrostomy, PEJ: percutaneous endoscopic jejunostomy, NS: not significant.

\*Reference 15.

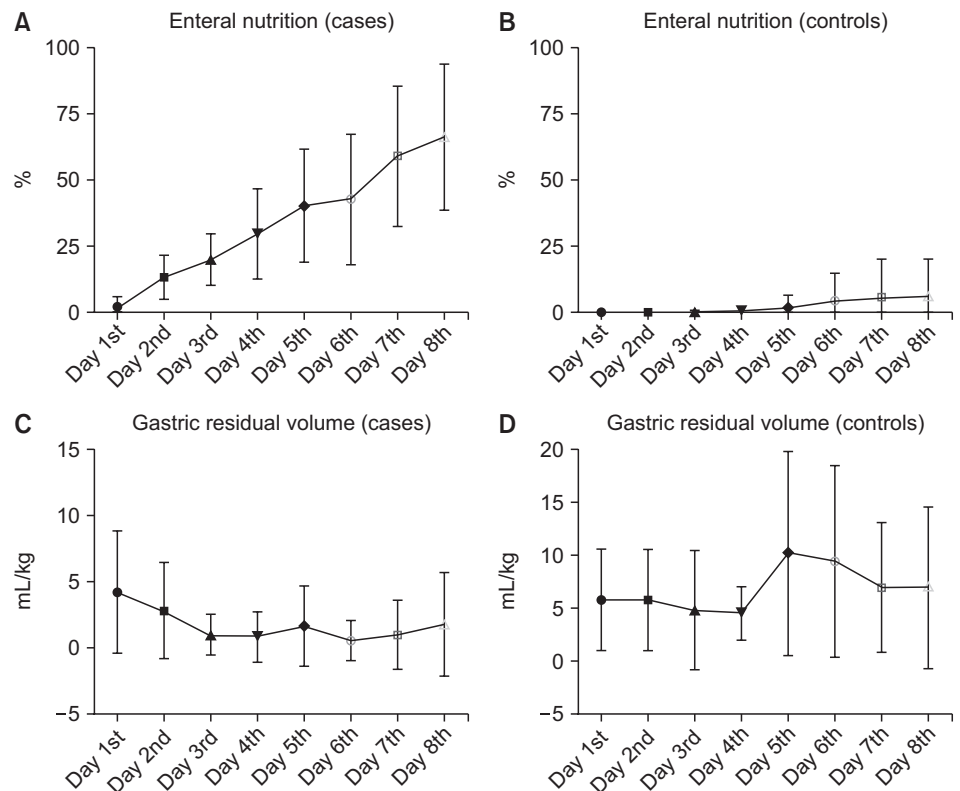
of the requirement,  $p=NS$ ). At the end point, 9 out of 12 cases and none from the control achieved more than 50% of the EN requirements ( $p=0.0003$ ).

Regarding the GRV at final evaluation, in comparison to the baseline, a 50% reduction was observed in the case group, although the change was not significant ( $4.1\pm 4.6$  and  $1.8\pm 3.9$  mL/kg, respectively). In the control group, GRV at baseline and at the end point of the study was  $5.7\pm 6.7$  and  $6.9\pm 7.6$  mL/kg ( $p=NS$ ), respectively. Overall, at the end of the observation, GRV was significantly lower in the cases than that in the controls ( $p=0.0398$ ). Details are presented in **Figs. 2-4**.

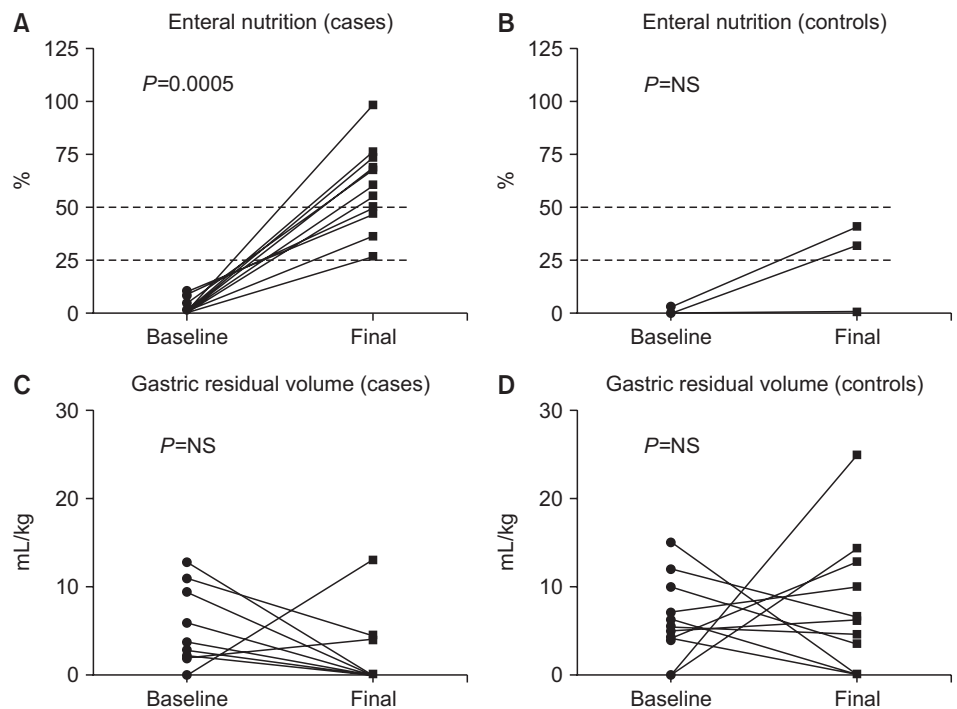
Furthermore, we compared PN, EN, and GRV at baseline with those at the end point according to the access route for EN. Among the 12 cases, 5 were fed by NGT, 6 by PEG, and only 1 by PEG-PEJ; among the controls, 7 patients had an NGT and 5 patients had a PEG. As shown in **Table 2**, we did not find any significant differences in PN, EN, and GRV trends according to the access route. The only patient to be fed by PEG-PEJ never showed a positive GRV.

### Safety measures

Administration of A/C was well tolerated in patients and the safety outcomes were not significantly different between cases and controls. In particular, weaning off MV occurred in six cases and eight controls, death occurred in one case and in none of the controls, and no patient developed diarrhea during observation. The drugs (midazolam, morphine, and



**Fig. 2.** Daily trend in caloric intake by enteral nutrition and gastric residual volume. (A) Average daily trend of increase in caloric intake percent by enteral nutrition in patients treated with amoxicillin/clavulanate. (B) Average daily trend of increase in caloric intake percent by enteral nutrition in controls. (C) Average daily trend of gastric residual volume (mL/kg) in patients treated with amoxicillin/clavulanate. (D) Average daily trend of gastric residual volume (mL/kg) in controls.



**Fig. 3.** Baseline and final assessment of caloric intake by enteral nutrition and gastric residual volume by group (Wilcoxon matched-pairs signed rank test). (A) Trend in caloric intake increase by enteral nutrition (%) from baseline to final assessment patients by patients in cases treated with amoxicilline/clavulanate;  $p=0.0005$ , by Wilcoxon matched-pairs signed rank test. (B) Trend in caloric intake increase by enteral nutrition (%) from baseline to final assessment patients by patients in controls. (C) Gastric residual volume (mL/kg) trend from baseline to final assessment patients by patients in cases treated with amoxicilline/clavulanate. (D) Gastric residual volume (mL/kg) trend from baseline to final assessment patients by patients in controls.

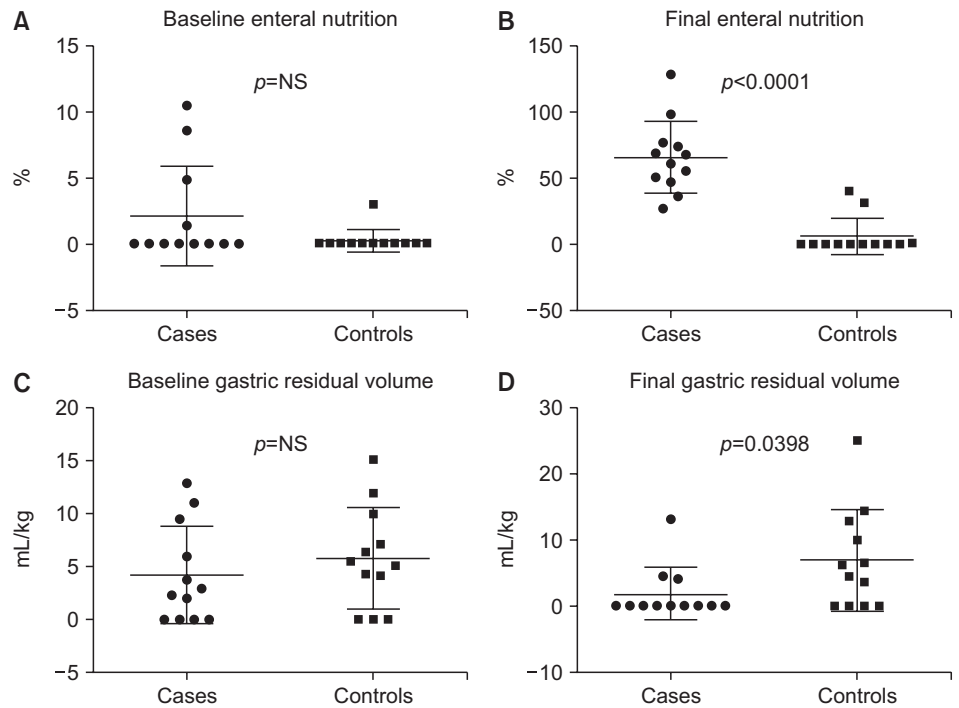
dopamine) required for the overall treatment of the condition was not significantly different between the groups. Notably, eight out of the 12 cases vs. all the controls ( $p=0.0932$ ) and six out of the 12 cases vs. seven out of the controls ( $p=1.000$ ) received midazolam/morphine/dopamine at the beginning and the end of the study period, respectively.

## DISCUSSION

Nutritional deterioration during hospitalization can worsen the clinical outcome of patients. Clinical guidelines suggest that almost two thirds of the daily caloric requirements should be achieved [16]. The enteral route is the recommended mode to achieve energy requirements for medical and surgical patients who are critically ill [16]. However, EN management is a challenge in several cases, owing to the low tolerance, in particular, in patients with neurological impairment [16-18].

Children with neurological impairment can experience poor feeding tolerance owing to hypothalamus or autonomic dysfunction (central and peripheral nervous systems) that can affect gastrointestinal motility resulting in visceral pain, bowel dysmotility, vomiting, and gastrointestinal distention [17-19].

At our Institution, a nutritional rehabilitation protocol for the PICU was released in July 2018. Therefore, in October 2018 we started to re-feed patients admitted in the PICU



**Fig. 4.** Paired baseline and final assessment of caloric intake by enteral nutrition and gastric residual volume by group. (A) Comparison between the mean distribution of caloric intake by enteral nutrition (%) at baseline in the two groups (treated patients versus control patients). (B) Comparison between the mean distribution of caloric intake by enteral nutrition (%) at final assessment in the two groups (treated patients versus control patients). (C) Comparison between the mean gastric residual volume (mL/kg) distribution at baseline in the two groups (treated patients versus control patients). (D) Comparison between the mean gastric residual volume (mL/kg) distribution at final assessment in the two groups (treated patients versus control patients).

**Table 2.** Outcomes according to the access route for enteral nutrition

| Baseline/end point | Cases      |             | Controls    |             |
|--------------------|------------|-------------|-------------|-------------|
|                    | PEG        | NGT         | PEG         | NGT         |
| PN at baseline     | 47.3±25.6  | 33.0±26.3   | 35.6±28.1   | 20.0±18.3   |
| PN at end point    | 17.7±26.7  | 29.0±30.8   | 36.4±19.3   | 49.7±25.0   |
| EN at baseline     | 10.6±7.1*  | 6.1±5.7**   | 0.4±0.9     | 0           |
| EN at end point    | 43.5±20.9* | 32.4±10.8** | 10.0±13.9   | 0.9±1.6     |
| GRV at baseline    | 26.7±30.8  | 115.0±153.5 | 263.0±361.7 | 224.3±373.4 |
| GRV at end point   | 8.3±20.4   | 122.0±199.8 | 166.0±219.7 | 169.2±140.3 |

Values are presented as mean±standard deviation.

PEG: percutaneous endoscopic gastrostomy, NGT: naso-gastric tube, PN: parenteral nutrition, EN: enteral nutrition, GRV: gastric residual volume.

\* $p=0.0022$ ; \*\* $p=0.0159$ ; Mann-Whitney-U-test.

according to the new protocol. However, we observed that some patients with neurological impairments experienced difficulties in progressing to EN because of delayed gastric emptying. We then applied to our Hospital's Ethics Committee for approval to use A/C as a prokinetic agent to support nutritional rehabilitation in patients with neurological impairments admitted to the PICU. In the present study, although the cases and controls were included in two consecutive semesters, the selected sample was homogeneous for primary disease and for nutritional treatment.

Thus, we found that in patients with neurological disability, A/C improves EN tolerance and it does not cause side effects. Notably, the EN intake at final assessment was 50% more than the basal level in 75% of the cases and in only 17% of the controls. Regarding GRV, although

it resulted in the end point being reduced by 50% in 42% of patients of both the case and control groups, it was significantly different between the two groups. This finding justifies the differences in the amount of EN tolerated at the end point between the groups. Concerning safety outcomes, one patient treated with A/C died; he was a 1-year-old baby affected by neurological disability due to a rare metabolic disease. Death occurred 20 days following A/C discontinuation; drug administration was discontinued because of the worsening of neurological complaints and the development of pulmonary hemorrhage. In fact, the patient received anticoagulant therapy for thrombosis of a central vein as a complication of CVC placement. No patient developed diarrhea even when intravenous antibiotic therapy was started (in three cases and five controls) owing to the appearance of fever and suspected infectious disease.

In adults, there is vast experience on the use of different prokinetics (erythromycin, domperidone, metoclopramide, azithromycin, and neostigmine); however, many of these agents cannot be used in pediatric populations owing to side effects. Acute extra-pyramidal reactions, dyskinesia, and QT interval corrected on ECG prolongation are side effects that do not suggest the prescription of dopamine-2 receptor antagonists (metoclopramide and domperidone) to increase enteral feeding tolerance in the pediatric population.

Neostigmine and pyridostigmine have been demonstrated to be effective in improving enteral feeding tolerance in patients with intestinal pseudo-obstruction [20-22].

Erythromycin has been studied with contrasting results and side effects (increased QT interval corrected on ECG and pyloric stenosis) owing to different protocols, sample size, dosing, and time of administration [23].

A/C showed prokinetic effects in a group of seven healthy adults, where A/C administration increased small bowel motility [10]; in the pediatric population, A/C also showed the ability to increase duodenal motility and small bowel transit, probably because of the stimulation local receptors [11].

An important restriction on the use of A/C as a prokinetic agent may be the potential induction of bacterial resistance [24]. In PICUs, the incidence of antimicrobial resistance for *Klebsiella* and *Escherichia coli* is approximately 6.7% and 3.5% of the tested isolates, respectively [24]. However, the development of bacterial resistance is related to duration and therapeutic dosages of antibiotics [24]. Considering all these reasons, we limited our trial to only one week of treatment and to a dosage below the standard prescribed.

To the best of our knowledge, this is the first study on the use of A/C, by enteral administration, as a prokinetic for pediatric critically ill patients with neurological impairment. However, some limitations should be highlighted. The small number and the clinical characteristics of patients (all with neurological impairment) do not allow extension of the results of this study to the whole paediatric population. Furthermore, the risk of developing bacterial resistance suggests that this treatment should be limited to selected severe and intractable EN intolerance to avoid PN. In clinical practice, it may also be useful to conduct microbiological investigations before and after treatment with A/C to test for possible development of bacterial resistance. Another limitation could be the lack of any motility evaluation; indeed, the clinically unstable conditions of the patients, prevented us from performing manometry or scintigraphy, because in our Institution, the areas designed for these evaluations are very far from the PICU.



In conclusion, malnutrition exposes critically ill children to several complications that affect the severity of disease course, length of stay, and mortality; all may be prevented by early EN. The development of intolerance to EN could be addressed with the use of A/C. Future prospective clinical trials are needed to confirm these conclusions.

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