Macronutrients Management for Growth in Neonates with Congenital Gastrointestinal Malformation

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Background:
Congenital gastrointestinal (GI) malformations are developmental disorders that can result in secondary intestinal failure. Nutrient intakes must be adapted according to the newborn’s nutritional requirements based on frequent anthropometric and biochemical assessments. Deficiencies or excess of a macronutrient can hinder the growth of the newborn.

Material/Methods:
To assess the clinical condition of newborns with GI malformations, together with the postoperative nutritional status of newborns who underwent surgery due to congenital GI malformations, we performed a case-control study. The study group comprised newborns with digestive malformations (n=51) and the control group consisted of newborns without digestive pathologies (n=102), matched by sex, gestational age, and weight at admission.

Results:
Bivariate comparisons and multiple logistic regression analyses were performed. A P value <0.05 was considered to be statistically significant; these were observed in abdominal distension, gastric residue, and vomiting. The duration of hospitalization was shorter in the case group, as on average, they were transferred to the Pediatric Surgery Department on the 6th day, where they further remained admitted to treat the underlying cause. Differences between groups in administration of breast milk versus formula were not statistically significant.

Conclusions:
We concluded that the clinical examination had a major role in early detection of digestive malformations and in the effective management of specific necessary nutrition. Proper evaluation of when to start enteral feeding can help post-surgical cases to recover faster, minimizing complications. Further studies are required to assess how financial factors affect implementation of the standardized guidelines of nutrition in children and to find possible solutions to financial constraints.

Keywords: Digestive System Abnormalities • Enteral Nutrition • Nutrients

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Background

Congenital gastrointestinal malformations are developmental disorders, or embryopathies, which can involve the bowels or other organ systems [1]. Intestinal failure is defined as a significant reduction in the functional gut mass, resulting in insufficient absorption of essential nutrients necessary to sustain life, including macronutrients (proteins, lipids, and carbohydrates), micronutrients, electrolytes, and most importantly, water [2-5]. Intestinal failure can occur due to surgical resection of the bowel, congenital anomalies, or functional/motility disorders. As such, these individuals require parenteral nutrition (PN) for survival. The subsequent nutritional, medical, and surgical aspects of care are complex [6,7]. The incidence is higher in premature infants with a gestational age of less than 37 weeks than in full-term infants [8]. Pediatric intestinal failure usually occurs secondary to other disorders, and short bowel syndrome (SBS) is a leading etiology [6]. It is characterized by a lack of absorptive capacity due to the severely reduced mucosal surface area. Necrotizing enterocolitis is the leading cause of neonatal SBS [9,10]; other etiologies include gastroschisis, which has a 30% increase in prevalence [11,12], intestinal atresia, malrotation with volvulus, and Hirschsprung’s disease [9].

The standard imaging study for gastrointestinal (GI) pathologies in infants is plain abdominal radiography together with conventional contrast studies. The management of congenital gastrointestinal malformations necessitates a multi-disciplinary approach that includes neonatologists, gynecologists, pediatric surgeons, gastroenterologists, and nurses. Parenteral nutrition (PN) is the life-saving therapy of choice in the management of intestinal failure. It involves a complex mix of appropriate macronutrients such as carbohydrates, proteins, lipids, and electrolytes, as well as micronutrients, delivered through an intravenous infusion to provide essential nutrition [11,13]. The main goal in therapy is to deliver the maximum tolerated quantity of enteral nutrition (EN), supported by PN [14]. The necessity of maintaining growth has to be balanced with the excess macronutrient intake by PN. For this purpose, strict monitoring of laboratory parameters is of extreme importance for newborns on long-term PN [15]. Therefore, it is preferred to initiate early enteral nutrition to prevent the adverse effects of parenteral nutrition. The rate of advancement of enteral feeding depends on stoma/stool output, vomiting, and abdominal distension [16]. The optimal enteral formula has not yet been established [17]. A large-scale, geographically comprehensive, multicenter, prospective cohort study was organized by N.J. Wright, comparing the different possibilities of managing and watching the outcomes of a few common congenital problems in different countries having different per capita income, results of which can be beneficial, taking into account how financial problems affect the health care systems and have immense negative impact on patient health and recovery [18].

Material and Methods

The aim of this study was to assess the nutrition needed to facilitate growth, to minimize fluid, nutritional, and electrolyte losses, and to maximize bowel adaptation. To achieve this, a retrospective case-control clinical study was performed comparing gestational age (GA), sex, weight on admission and discharge measured in grams, length of hospitalization, type of milk administered, pathological clinical signs, and the quantity of macronutrients administered during hospitalization. The study took place at the Department of Neonatology, Children Emergency Hospital “Louis Turcanu” Timisoara, Romania, over a period of 3 years from 1 January 2017 to 31 December 2019.

The study included 2 groups of newborns: the case group (n=51) and the control group (n=102). The inclusion criteria for the case group were newborns with a diagnosis of digestive malformation or who underwent digestive surgery. Target GI anomalies included esophageal atresia, congenital pyloric stenosis, jejunal atresia, duodenal atresia, necrotizing enterocolitis (NEC), and cloaca. The inclusion criteria for the control group were newborns who were hospitalized during the same period, with GA >26 weeks at birth, and not diagnosed with digestive malformation during their hospital stay. The exclusion criteria were similar for both groups: patient files lacking data, unavailability of information in the hospital’s electronic records, GA less than 26 weeks, and other associated genetic malformations.

The newborns’ data were further divided demographically, based on their gestation and perinatal history, and were further reviewed, including the presence of antenatal risk factors for gastrointestinal malformation and congenital anomalies of any kind. All newborns’ medical records were examined. The study was approved by the Ethics Committee for Scientific Research of the Emergency Hospital for Children ‘Louis Turcanu’ (approval no. 78/2020). The authors ensure that the study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients/parents/legal guardian as part of routine admission to our tertiary university hospital for future research and study purposes.

Determination of Gastrointestinal Malformation

All newborns were clinically examined daily by the neonotologist and weighed by the nurse with the same scale. The type of milk and parenteral infusions administered were monitored daily in the observation sheet. The diagnosis of congenital abnormalities depended on the location of the abnormality along the GI tract. Abnormalities in the upper GI tract, the esophagus, the stomach, and the duodenum tend to rapidly become more problematic, opposed to those in the lower GI tract, such as the intestines, the rectum, and the anus, which take longer to become apparent.
Statistical Analysis

Statistical analyses were performed and the group was compared using ANOVA. If ANOVA could not be applied, we used the Kruskal-Wallis rank sum test, Fisher’s exact test, or Pearson’s chi-squared test. A $P$ value of <0.05 was considered to be a statistically significant difference. For numerical values, IQR (inter-quartile range) was used.

Results

During the 3-year study period, 51 newborns met the inclusion criteria in the case group. Out of these, 39% (n=20) were female and 61% (n=31) were male; 39% were premature, 45% were full-term newborns, and 16% had intra-uterine growth retardation (IUGR). The average weight at admission was 2840 g. The average number of hospitalization days in the Neonatal Intensive Care Unit was 7 days, after which, due to early diagnosis, they were transferred to the Pediatric Surgery Department, where they further remained admitted to treat the underlying cause. Digestive malformations were classified into 3 groups: atresia, stenosis, and others. As shown in the Table 1, there were 17 cases of atresia, 19 cases of stenosis, and 15 other digestive malformations (NEC, cloaca). In 69% of the cases, breast milk (BM) was administered but it did not affect the number of days of hospitalization.

The duration of hospitalization in the case of atresia was statistically significant with a $P$ value of 0.050; their median was 6 days, while for the control group it was 10 days (Table 2).

#### Table 1. Descriptive statistics.

| Characteristic       | Overall N=51* | Atresia N=17* | Stenosis N=19* | Other N=15* | p-value**  |
|----------------------|---------------|---------------|----------------|-------------|-----------|
| Sex                  |               |               |                |             | 0.10      |
| F                    | 20 (39%)      | 4 (24%)       | 7 (37%)        | 9 (60%)     |           |
| M                    | 31 (61%)      | 13 (76%)      | 12 (63%)       | 6 (40%)     |           |
| Weight: baseline     | 2,840 (2,315, 3,295) | 3,160 (2,400, 3,400) | 2,760 (2,165, 3,325) | 3,000 (2,275, 3,060) | 0.4       |
| Weight: discharge    | 3,000 (2,595, 3,535) | 3,000 (2,750, 3,600) | 3,210 (2,260, 3,440) | 3,000 (2,620, 3,530) | 0.7       |
| Difference (weight)  | 150 (25, 320) | 110 (0, 330)  | 150 (50, 295)  | 220 (35, 415) | 0.7       |
| LOS (days)           | 7 (4, 14)     | 6 (3, 14)     | 6 (4, 14)      | 10 (7, 14)  | 0.2       |
| Gestation            |               |               |                |             | 0.2       |
| Pre-term IUGR        | 20 (39%)      | 5 (29%)       | 8 (42%)        | 7 (47%)     |           |
| Term                 | 23 (45%)      | 9 (53%)       | 6 (32%)        | 8 (53%)     |           |
| Nutrition            |               |               |                |             | 0.6       |
| BM                   | 35 (69%)      | 10 (59%)      | 14 (74%)       | 11 (73%)    |           |
| FM                   | 16 (31%)      | 7 (41%)       | 5 (26%)        | 4 (27%)     |           |
| GR                   | 28 (55%)      | 10 (59%)      | 8 (42%)        | 10 (67%)    | 0.3       |
| Vomiting             | 30 (59%)      | 13 (76%)      | 15 (79%)       | 2 (13%)     | <0.001    |
| Abdominal distension | 39 (76%)      | 13 (76%)      | 12 (63%)       | 14 (93%)    | 0.12      |

* n (%); Median (IQR); ** Pearson’s Chi-squared test; Kruskal-Wallis rank sum test; Fisher’s exact test; LOS – length of stay (days); IUGR – intra-uterine growth retardation; BM – breast milk; FM – formula milk; GR – gastric residuals.
Tolerance of Early Enteral Nutrition

During postoperative follow-up, abdominal distention was the most common observation, followed by repeated vomiting, in children who underwent surgery. Difficulties in nutritional recovery were encountered in 56.8% of cases (n=29). We also found a slow pace of nutritional recovery in all newborn cases. Poor weight recovery was present in 61.5% of the cases, 35% had malabsorption syndrome, 15% needed gastrostomy replacement, and surgery was performed in 10% of the cases. In addition to that, prolonged use of oro/nasogastric tubes accentuated pre-existing respiratory distress or produced a long-term aversion to oral food in 68.6% of the cases (n=35).

Bodyweight decreased at a rate of 15% in newborns with stoma present in the first 10 days after hospitalization. The average length of hospital stay was longer in newborns who received long-term parenteral nutrition. Furthermore, early initiation of enteral feeding (18% of newborns) was achieved at the time of resumption of intestinal transit in premature infants with a gestational age greater than 32 weeks but lesser than the normal range of 38-42 weeks of gestation, and the number of days needed to reach full enteral nutrition was longer. Return to enteral feeding after parenteral nutrition in infants with gastric malformation was usually performed around 7-10 days postoperatively. Protein intake was 2.5 g/kg/day in full-term newborns and 4.5 g/kg/day for preterm very low birth weight (VLBW) and extremely low birth weight (ELBW) infants in both groups, while the lipid dose was increased to 4 g/kg/day in the postoperative period. Glucose can be synthesized from other sources by gluconeogenesis; therefore, there was no minimum required glucose from dietary sources. The milk used was 69% breast milk together with specific formulas for premature babies, whereas extensively hydrolyzed formulas were given for the full-term newborns. Patients were given 10 ml/kg/day of formula through a nasogastric tube, divided into 8 meals, and the feeding amount was increased by 10-15 ml/kg/day increment if it was adequately tolerated. Full feed was considered when the newborn tolerated 130 ml/kg/day. In the comparison between case and control groups, control subjects were more likely to have received higher enteral total fluid volume.

Tolerance of Early Enteral Nutrition

| Characteristic                  | Overall N=51* | Atresia N=17* | Control atresia N=34* | p-value** |
|--------------------------------|--------------|--------------|-----------------------|-----------|
| Sex                            | F            | M            |                       | >0.9      |
|                                | 12 (24%)     | 39 (76%)     |                       |           |
|                                | 4 (24%)      | 13 (76%)     | 26 (76%)              |           |
| Weight: baseline               | 3,160 (2,400, 3,420) | 3,160 (2,400, 3,400) | 3,160 (2,400, 3,420) | >0.9      |
| Weight: discharge              | 3,120 (2,890, 3,645) | 3,000 (2,750, 3,600) | 3,155 (2,980, 3,675) | 0.3       |
| Difference (weight)            | 220 (90, 490) | 110 (0, 330) | 265 (102, 552)        | 0.089     |
| LOS (days)                     | 9 (5, 15)    | 6 (3, 14)    | 10 (7, 15)            | 0.050     |
| Gestation                      |              |              |                       | >0.9      |
| Preterm                        | 15 (29%)     | 5 (29%)      | 10 (29%)              |           |
| IUGR                           | 9 (18%)      | 3 (18%)      | 6 (18%)               |           |
| Term                           | 27 (53%)     | 9 (53%)      | 18 (53%)              | 0.8       |
| Nutrition                      |              |              |                       |           |
| BM                             | 31 (61%)     | 10 (59%)     | 21 (62%)              |           |
| FM                             | 20 (39%)     | 7 (41%)      | 13 (38%)              |           |
| GR                             | 21 (41%)     | 10 (59%)     | 11 (32%)              | 0.070     |
| Vomiting                       | 14 (27%)     | 13 (76%)     | 1 (2.9%)              | <0.001    |
| Abdominal distension           | 16 (31%)     | 13 (76%)     | 3 (8.8%)              | <0.001    |

* n (%); ** Median (IQR); ** Wilcoxon rank sum test; Pearson’s Chi-squared test; LOS – length of stay (days); IUGR – intra-uterine growth retardation; BM – breast milk; FM – formula milk; GR – gastric residuals.
and calories, have reached full enteral feeds (defined as enteral feeds of at least 120 cc kg⁻¹ per day with no use of parenteral nutrition), and to have fewer feeding interruptions than case patients.

### Discussion

In the neonatal period, the nutritional requirements are higher compared to other pediatric groups due to the limited energy resources, pathology, and accentuated growth rate. The nutritional needs provided by enteral nutrition are adjusted according to weight and gestational age. The guidelines set by the American Society for Parenteral and Enteral Nutrition (ASPEN), the Society of Critical Care Medicine (SCCM), and the European Society of Pediatric and Neonatal Intensive Care should be carefully followed for a better and faster recovery of patients [19-21]. However, due to limited resources, it is sometimes difficult to implement such guidelines, as happened in our study. The purpose of EN in the critical newborn is to ensure proper growth, development, and prophylaxis of complications related to nutrition. Moreover, finding a balance of appropriate nutritional intake to meet metabolic demands is frequently difficult during the perioperative period [22]. Enteral nutrition can be started early in the postoperative period in neonates [23]. During enteral nutrition, some complications can occur, such as mechanical or digestive complications leading to the interruption of enteral nutrition; these can manifest as bilious vomiting, abdominal distension, and intestinal perforation [23-25]. Nevertheless, early postoperative enteral feeding did not increase the incidence of postoperative gastrointestinal complications [7,26,27]. Gastric residue should also be checked before each feeding [28]. The rate of advancement of enteral feedings should be individualized, with careful monitoring of stool/stoma output, vomiting, and abdominal distention. Continuous enteral feeding allows complete saturation of molecules in intestinal transporters and increased absorption of lipids, proteins, calcium, zinc, and copper [29]. EN with human milk is also associated with higher survival and is associated with shorter hospital stay without

| Characteristic                   | Overall N=57* | Stenosis N=19* | Control stenosis N=38* | p-value** |
|----------------------------------|---------------|----------------|------------------------|-----------|
| Sex                              |               |                |                        | >0.9      |
| F                                | 21 (37%)      | 7 (37%)        | 14 (37%)               |           |
| M                                | 36 (63%)      | 12 (63%)       | 24 (63%)               |           |
| Weight: baseline                 | 2,750 (2,060, 3,360) | 2,760 (2,165, 3,325) | 2,750 (2,108, 3,340) | >0.9      |
| Weight: discharge                | 3,000 (2,700, 3,520) | 3,210 (2,260, 3,440) | 2,990 (2,742, 3,700) | 0.5      |
| Difference (weight)              | 220 (100, 520) | 150 (50, 295)  | 270 (138, 580)         | 0.060     |
| LOS (days)**                     | 11 (6, 18)    | 6 (4, 14)      | 14 (9, 25)             | 0.003     |
| Gestation                        |               |                |                        | >0.9      |
| Pre-term                         | 24 (42%)      | 8 (42%)        | 16 (42%)               |           |
| IUGR                             | 15 (26%)      | 5 (26%)        | 10 (26%)               |           |
| Term                             | 18 (32%)      | 6 (32%)        | 12 (32%)               |           |
| Nutrition                        |               |                |                        | >0.9      |
| BM                               | 42 (74%)      | 14 (74%)       | 28 (74%)               |           |
| FM                               | 15 (26%)      | 5 (26%)        | 10 (26%)               |           |
| GR                               | 18 (32%)      | 8 (42%)        | 10 (26%)               | 0.2       |
| Vomiting                         | 22 (39%)      | 15 (79%)       | 7 (18%)                | <0.001    |
| Abdominal distension             | 19 (33%)      | 12 (63%)       | 7 (18%)                | <0.001    |

* n (%); Median (IQR); ** Pearson’s Chi-squared test; Wilcoxon rank sum test; LOS – length of stay (days); IUGR – intra-uterine growth retardation; BM – breast milk; FM – formula milk; GR – gastric residuals.
major complications [30]. Studies on the metabolic response in infants who undergo surgery indicate that protein turnover is influenced by fat-to-carbohydrate ratio; thus, parenteral nutrition support with amino acids rather than dextrose is useful to control this state [31,32]. Furthermore, extensively or partially hydrolyzed formulas have greater digestibility with lower energy consumption of protein hydrolysates compared to whole proteins [33,34]. Recognizing the best type of formula milk to use requires extensive research; the use of Extensively Hydrolyzed Formula is justified by the increased risk of protein allergy characterizing newborns after intestinal surgery, whereas macronutrients in a complex form were found to better promote bowel adaptation. On the other hand, the use of the semi-elemental or elemental formula is suggested in those patients who have an intolerance to conventional preterm/term formulas. Our study results suggest that children should be administered enteral feed as soon as possible to avoid prolonged use of parenteral nutrition, but at the same time the tolerance to enteral feedings should be evaluated. Early diagnosis of gastrointestinal pathologies or malformations can avoid unnecessary delay in treatment and provide nutritional care to the newborns. A number of national and international guidelines are used in many countries, but, unfortunately, due to financial constraints we are not able to follow these completely. Government-funded hospitals have limitations and milk formulas provided are ever-changing depending on the budget and vendors approved, which makes it impossible for doctors to prescribe feedings meeting international norms.

Conclusions

The ideal enteral nutrition formula for neonates with gastric malformation remains controversial. Breast milk and commercially available elemental formulas are associated with a reduced duration of PN dependence. Early enteral feeding can increase survival, accelerate recovery of gastrointestinal function, and improve the nutritional status of newborns. The time of onset of enteral nutrition depends on several factors, such as gestational age, intestinal functional status, milk formula used (polymeric vs elemental), and route of administration (stomach vs jejunum). The management of a newborn with a gastrointestinal malformation necessitates qualified care for food administration in particular; slow nutritional recovery should be expected together with frequent complications. Neonatal digestive pathology remains a major cause of mortality and morbidity. Neonates should be evaluated thoroughly on a case-by-case basis to evaluate the need for parenteral nutrition and when to decide when to switch to enteral feeding. Neonates undergoing major surgeries need more attention and support; not only for healing, but also to achieve optimal growth and development. However, more studies are required to discover the optimal feeding formula and routine clinical therapy for neonates with GI malformations.

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