# Gastric Residual Volume in Feeding Advancement in Preterm Infants (GRIP Study): A Randomized Trial

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**Objective** To evaluate the effect of not relying on prefeeding gastric residual volumes to guide feeding advancement on the time to reach full feeding volumes in preterm infants, compared with routine measurement of gastric residual volumes. We hypothesized that not measuring prefeeding gastric residual volumes can shorten the time to reach full feeds.

**Study design** In this single-center, randomized, controlled trial, we included gavage fed preterm infants with birth weights (BW) 1500-2000 g who were enrolled within 48 hours of birth. Exclusion criteria were major congenital malformations, asphyxia, and BW below the third percentile. In the study group, the gastric residual volume was measured only in the presence of bloody aspirates, vomiting, or an abnormal abdominal examination. In the control group, gastric residual volume was assessed routinely, and feeding advancement was based on the gastric residual volume. The primary outcome was the time to reach feeding volumes of 120 mL/kg per day. Secondary outcomes were time to regain BW, episodes of feeding interruptions, sepsis, and necrotizing enterocolitis.

**Results** Eighty-seven infants were enrolled. There were no differences between the study and control groups with respect to time to reach full feeds (6 days [95% CI, 5.5-6.5] vs 5 days [95% CI, 4.5-5.5]; $P = .82$), time to regain BW, episodes of feeding interruptions, or sepsis. Two infants in the control group developed necrotizing enterocolitis.

**Conclusions** Avoiding routine assessment of gastric residual volume before feeding advancement did not shorten the time to reach full feeds in preterm infants with BW between 1500 and 2000 g. *(J Pediatr 2018;■■:■■-■■).*

**Trial Registration** Clinicaltrials.gov NCT01337622.

One of the most challenging tasks in neonatology is to provide adequate and safe nutrition to preterm infants.[1] Despite our efforts, neonatal intensive care units (NICUs) are rarely able to replicate in utero growth rates for preterm infants.[2-7] An important intervention to achieve this goal is the establishment of early enteral nutrition.

Gastric residual volumes are frequently measured to guide enteral feeding advancement, despite no clear evidence to justify their usefulness in either improving feeding intolerance or preventing necrotizing enterocolitis (NEC).[8-11] Mihatsch et al found no relationship between the mean gastric residual volume and feeding volume achieved on day 14.[9] Shulman et al concluded that gastric residual volumes were unreliable in predicting the attainment of full enteral feedings.[12] Gastric residual volumes may not be as significant a predictor of NEC as previously thought and gastric residual volumes should not be checked routinely, at least until feeding volumes of 5 mL/kg are reached.[13,14] Despite insufficient evidence to support this practice, the presence of large or greenish gastric residual volume often triggers bedside staff to withhold or decrease the volume of subsequent feeds.[15,16] This practice results in suboptimal nutrition and poor weight gain, which may cause lasting effects on neurodevelopmental outcomes in neonates.[17] An audit at our institution identified gastric residual volume as the most common reason for nonadvancement of feeds, accounting for 71% of feed interruptions.

We hypothesized that, among preterm infants, a policy of not routinely measuring prefeed gastric residual volumes would result in a significantly shorter duration of time to reach full enteral feeds without an increase in the risk of NEC, compared with a policy of routinely measuring the prefeed gastric residual volume.

## Methods

We conducted an open-label, 2-arm randomized controlled trial from September 8, 2011, to December 2, 2013. The Research Ethics Board approved the protocol. The protocol of the study was registered with clinicaltrials.gov (NCT01337622).

| | |
|---|---|
| BW | Birth weight |
| NEC | Necrotizing enterocolitis |
| NICU | Neonatal intensive care unit |
| VLBW | Very low birth weight |

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The authors declare no conflicts of interest.

Portions of this study were presented at the 5th Congress of the European Academy of Pediatric Societies, Barcelona, Spain on October, 18th, 2014, the Canadian Neonatal Perinatal Research Meeting, Montebello, Canada on February 26th, 2015, and as a poster presentation at the Pediatric Academic Societies annual meeting, San Diego, CA, on April 27th, 2015.



https://doi.org10.1016/j.jpeds.2018.04.072

The study was conducted in the level II and level III NICU at McMaster Children's Hospital, in Hamilton, Ontario. Preterm infants were included if the birth weight (BW) was 1500-2000 g, the infant required gavage feeding, and had a postnatal age of <48 hours. Exclusion criteria were perinatal asphyxia (defined as a cord blood gas or first blood gas after birth with a pH of <7.0 or a base excess of greater than –16 mmol/L and an Apgar score of <5 at 10 minutes of age), major congenital malformations/surgical conditions that could interfere with feeding, and severe growth restriction (defined as a BW below the third percentile).[18]

All infants with a BW of 1500-2000 g admitted to the NICU were screened for eligibility. Infants were stratified by BW (1500-1750 g vs 1751-2000 g). The randomization sequence was computer generated and permuted, even numbered, randomly varying block sizes were generated with a 1:1 allocation ratio. The allocation sequence was concealed using serially numbered opaque sealed envelopes. The research personnel enrolled and randomized the babies after verification of eligibility criteria and obtaining consent. The envelopes were opened in serial order after the subject had been enrolled and the name and unique identification of the subject had been written on the envelope.

Blinding was not feasible. To minimize bias, strict guidelines were used for the volume and advancement of feedings. Feedings were started by the clinical team on day 1 or later, once the infant was hemodynamically stable. Feedings were started at 3 mL every 3 hours and increased by 3 mL every 9 hours in infants with a BW of 1500-1750 g and for infants with a BW of 1751-2000 g, they were started at 6 mL every 3 hours and increased by 3 mL every 6 hours. Infants were fed breast milk if available and preterm formula after obtaining parental consent when breast milk was not available. Feedings were fortified when enteral feeds of 150 mL/kg per day were achieved. We included algorithms with instructions for advancing or holding feeds based on clinical assessment, gastric residual volume, and its color (**Figure 1**; available at www.jpeds.com). To ensure compliance, we conducted educational sessions for healthcare providers and attached flowcharts regarding feeding guidelines to the clipboards of all enrolled patients. The outcome assessors were nonblinded; however, the outcome assessment was objective.

### Interventions

**Control Group.** As per unit policy, nurses aspirated the gastric residual volume before each feed. A comprehensive algorithm for feeding advancement was used (**Figure 1**). Intravenous access was discontinued when infants reached 120 mL/kg per day of feeds unless intravenous access was needed for another purpose, for example, giving antibiotics.

**Study Group.** A maximum of 0.5 mL of gastric contents was aspirated before feedings to confirm the tube placement and evaluate for hemorrhagic residuals. The gastric residual volume was not assessed. In the case of repeated bilious aspirates, vomiting, gastric aspirates containing frank blood, or abnormal abdominal examinations (localized or generalized tenderness, abdominal wall discoloration, or absent bowel sounds), feedings were withheld until assessment by a physician. Based on this assessment, the physician elected to continue or withhold feedings, or to order further diagnostic procedures and a note was recorded in the patients' chart.

### Outcomes

The primary outcome of the study was the time to reach full enteral feedings (120 mL/kg per day) based on BW or the actual weight if it was above the BW. Our secondary outcomes included time to regain BW, time to regain 120% of BW, the incidence of late-onset culture-proven sepsis (≥72 hours), NEC (Bell stage of ≥2), number of occasions feedings were either discontinued for >24 hours or not increased for >24 hours. NEC was defined as the presence of pneumatosis or portal gas as diagnosed by abdominal radiograph, ultrasoud examiantion, or surgical or autopsy diagnosis of NEC. The intervention was discontinued if infants were transferred to another hospital before completion of study intervention and infant data were censored at that time. However, parents were provided with data collection forms if infants were transferred after completion of the intervention, but before completion of the relevant outcome data. The form was completed by the caring physicians or nurses and parents mailed the completed forms to the study personnel.

### Statistical Analyses

Historical data from preterm infants with a BW of 1750-2000 g in our NICU showed that the time to reach full enteral feeds was normally distributed with a SD of 1.9 days. To detect a mean difference of 1.5 days between the experimental and the control groups, a sample size of 43 infants per group was required to reject the null hypothesis with a power of 0.90 and an alpha error of .05 and to adjust for a 10% dropout of patients.

Analyses were performed using IBM SPSS Statistics version 22 (SPSS Inc, Chicago, Illinois). Baseline patient characteristics were summarized using descriptive measures: expressed as mean (SD) or median (first, third quartile) for continuous and number (percent) for categorical variables. An intention-to-treat analysis was performed. The primary outcome was analyzed using survival analysis and the log-rank test. Subjects who were transferred out of the NICU or who died before attainment of full feeds, BW, or 120% of BW were censored at the time of transfer or death. We used the linear regression model to adjust the analyses of primary outcome for differences between the 2 groups. Secondary outcomes with categorical variables were analyzed using the $\chi^2$ or Fisher exact test. Continuous variables were compared using the Student *t* test. All statistical tests were performed using 2-sided tests at the .05 level of significance.

## Results

Between September 8, 2011, and December 2, 2013, there were 87 infants enrolled in the study (**Figure 2**); 45 infants were included in the study group with a gestational age of 31.9 ± 1.6



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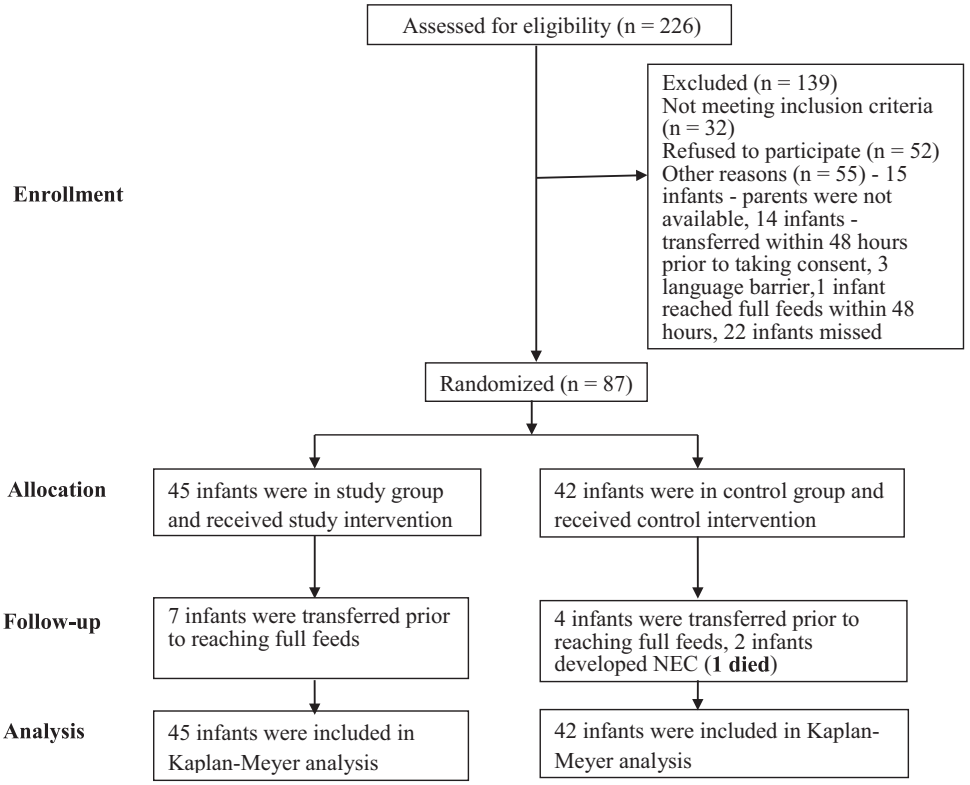


**Figure 2.** Patient flow chart.

weeks, and 42 infants were in the control group (32.3 ± 1.3 weeks). More infants in the study group received mainly breast milk as compared with the control group (**Table I**).

The Kaplan-Meier curves comparing time to reach full feedings were similar and overlapping (**Figure 3**). The median time to reach full feedings was 6 days (95%, CI 5.5-6.5) in the study group compared with 5 days (95% CI, 4.5-5.5) in the control group ($P = .82$; log-rank test). We did not find a difference in the primary outcome between the groups after adjustment for differences in breast milk intake and singletons. For the secondary outcomes, there were no differences between the groups, including the incidence of sepsis and time to regain BW (**Table II**). Two babies developed surgical NEC with intestinal perforation in the control group with no obvious risk factors for NEC. There were no adverse events noted in the study group.

**Table I. Comparison of demographic characteristics between the study and control groups**

| Characteristics | Study group (n = 45) | Control group (n= 42) | *P* value |
|---|---|---|---|
| Gestational age (wk) | 32.3 ± 1.3 | 31.9 ± 1.6 | .23 |
| BW (g) | 1750 ± 140 | 1750 ± 130 | .97 |
| Antenatal steroids (%) | 33 (73) | 31 (74) | .81 |
| Males (%) | 26 (58) | 22 (52) | .67 |
| Singleton (%) | 23 (51) | 14 (33) | .13 |
| Chorioamnionitis (%) | 5 (11) | 2 (5) | .44 |
| SGA (%) | 6 (13) | 3 (7) | .49 |
| LGA (%) | 3 (7) | 5 (12) | .48 |
| APGAR 1 minute, median (Q1, Q3) | 8 (6, 9) | 7 (6, 8) | .2 |
| Diet >80% breast milk (%) | 12 (26.7) | 4 (9.5) | .053 |
| Diet formula and breast milk (%) | 19 (42.2) | 18 (42.9) | .9 |
| Diet >80% formula (%) | 14 (31.1) | 20 (47.6) | .13 |
| PIV (%) | 38 (84.4) | 36 (88.1) | .45 |
| UVC (%) | 6 (13.3) | 5 (11.9) | .57 |

*LGA*, Large for gestational age; *PIV*, peripheral Intravenous catheter, $Q_1$ *and* $Q_3$, first and third quartiles, respectively; *SGA*, small for gestational age; *UVC*, umbilical venous catheter.

## Discussion

In this study, we did not find a difference in the primary or secondary outcomes between the study and control groups. However, our study showed that not measuring gastric residual volumes before feedings was feasible in preterm infants with BWs of 1500-2000 g. Our study showed a shorter time to reach full feeding volumes in both the groups compared with our previous experience and we suspect that this was a consequence of strict adherence to the study protocol in both groups as compared with nonrecruited patients.

Torrazza et al also looked at the effects of not measuring gastric residual volumes and included 61 babies with a BW of <1250 g.[16] Although the time to reach full feeds (150 mL/k per day) was 6 days shorter in the study group (22.3 ± 11.7 days in the study group vs 28.1 ± 3.9 days in the control group),[16] this difference did not attain statistical significance, possibly because of the small sample size. They also did not find a



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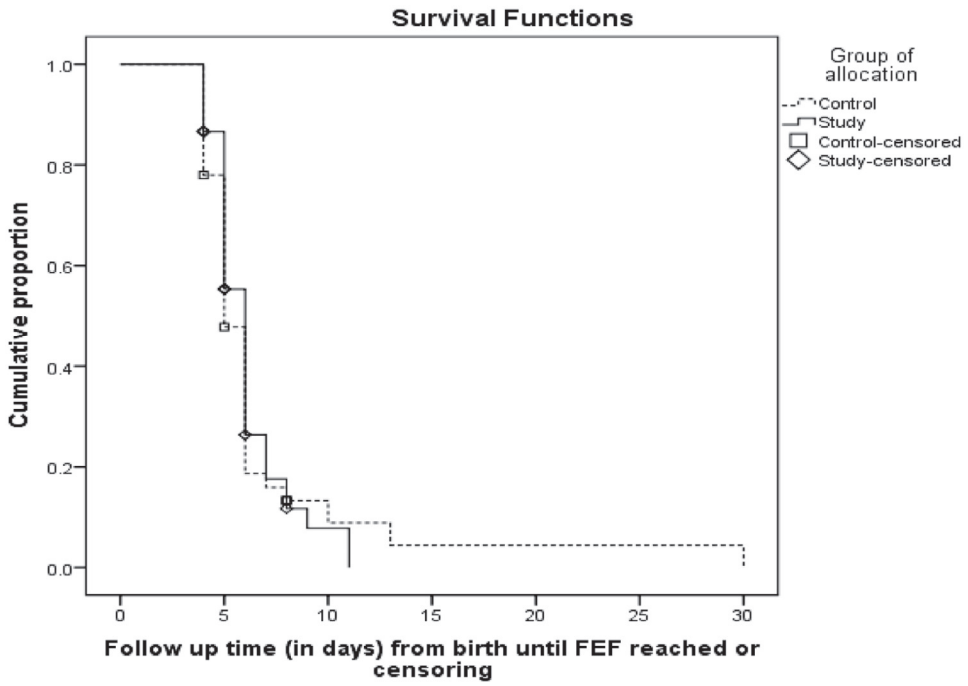


**Figure 3.** Kaplan-Meier curve. *FEF*, Full enteral feeds.

statistically significant difference in the feeding volumes at 2 and 3 weeks of age, sepsis or NEC between 2 groups. There were 4 cases of NEC (3 in the control group). A retrospective observational study by Riskin et al showed that avoiding the routine evaluation of gastric residual volume before every feeding was associated with earlier attainment of full enteral feeding without increasing the risk of NEC.[19]

Studies by Mihatsch et al and Shulman et al concluded that gastric residual volumes were unreliable predictors of feeding intolerance and the attainment of full enteral feeds.[9,12] Mihatsch et al also concluded that increased gastric residual volume is not predictive of NEC.[9] In contrast, 2 case-control studies by Cobb et al and Bertino et al suggested that increased gastric residual volumes could be associated with NEC.[20,21] However, both these studies were retrospective in nature with many confounders, and there was a considerable variation in cutoff values for significant gastric residual volumes. Although our study did not show a benefit of not measuring gastric residual volumes, we also found no evidence to support the role of assessing gastric residual volumes in preventing NEC or predicting feeding intolerance. However, we recognize that the study was not powered to assess the outcome of NEC.

In addition to the lack of significant benefits of measuring gastric residual volumes, there are a few disadvantages and risks associated with this practice. The procedure itself is time consuming,[22] and there is no accepted consensus on thresholds for significant residual volumes. Additionally, wide variation exists in the subsequent management, which depends on nurses' experience, clinicians' individual preference, and NICU protocols.[22] It is postulated that the negative pressure created by repeated aspiration of gastric contents might damage the fragile gastric mucosa, and discarding the gastric contents results in a loss of gastric enzymes and gastric acid in premature babies. Moreover, it has been shown that aspirating gastric fluid is not a reliable measurement of actual gastric content.[22] Accurate assessment of gastric residual volume depends on size and the

**Table II. Comparison of outcomes between the study and control groups**

| Outcomes | Study group | Control group | *P* value |
|---|---|---|---|
| Results from time-to-event analysis | | | |
| Time to reach enteral feeds of 120 mL/k/d (d) | 6 (5.5, 6.5) | 5.0 (4.5, 5.5) | .82 |
| Time to regain BW (d) | 11.0 (9.8, 12.2) | 12.0 (9.2, 14.9) | .53 |
| Time to regain 120% of BW (d) | 21.0 (19.5, 22.5) | 23.0 (21.1, 24.9) | .75 |
| Other results | | | |
| Incidence of late-onset sepsis | 0 | 2 (5) | .06 |
| No. of times feeding was stopped or not increased for >24 hours, median (Q1, Q3) | 0 (0, 1) | 1 (0, 2) | .75 |
| Incidence of NEC (Bell stage ≥2) | 0 | 2 (4.7) | .23 |

Data are shown as the median (95% CI) or n (%), unless otherwise noted.



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position of the nasogastric or orogastric tube,[23,24] as well as on body position.

There are a few limitations to our study. Because blinding was not feasible, to limit potential bias we conducted educational sessions for healthcare providers, used strict guidelines for feeding advancement, and objective study outcomes. More infants in the study group received mainly breast milk as compared with the control group. This factor may affect the time to reach full feeds, because breast milk is better tolerated. However, we did not see a difference in the primary outcome between the 2 groups after adjustment. Another limitation was that some neonates were transferred to other hospitals before completion of study intervention, and thus their data were censored beyond the point of transfer. To minimize the impact of the transfer of neonates during the study, we used a survival analysis (time-to-event analysis) to include available data from subjects until transfer from the unit. Furthermore, parents provided completed data collection sheets on babies' feeding and growth outcomes if they were transferred after the study intervention was completed but before completion of relevant data collection. The subjectivity in individual clinical judgment to initiate feeds could have impacted the results. However, to minimize its impact and ensure consistency, we always clarified the reason for noninitiation of feeds and any deviation from feeding guidelines with the clinical team. The frequencies of withholding feeds were not different between the 2 groups (**Table II**).

The issue of gastric residual volumes is more important in infants with a BW of <1500 g compared with bigger babies. However, it was the standard of care in our center to measure gastric residual volumes in all preterm infants (<37 weeks) who were receiving gavage feeds. In the absence of strong evidence to support not measuring gastric residual volumes, and concerns about NEC with smaller babies, this trial was designed to assess weight gain and the time to achieve full enteral feeding in slightly larger babies. The aim was to follow this study with a multicenter trial targeting a more immature and smaller patient population with a sample size powered to evaluate the risk of NEC if gastric residual volumes are not assessed. There is a need for a large, multicenter trial in extremely low BW or very low BW infants that includes the time to reach full feeds as a superiority outcome and the incidence of NEC as a noninferiority outcome. ■

Submitted for publication Jul 17, 2017; last revision received Apr 19, 2018; accepted Apr 23, 2018

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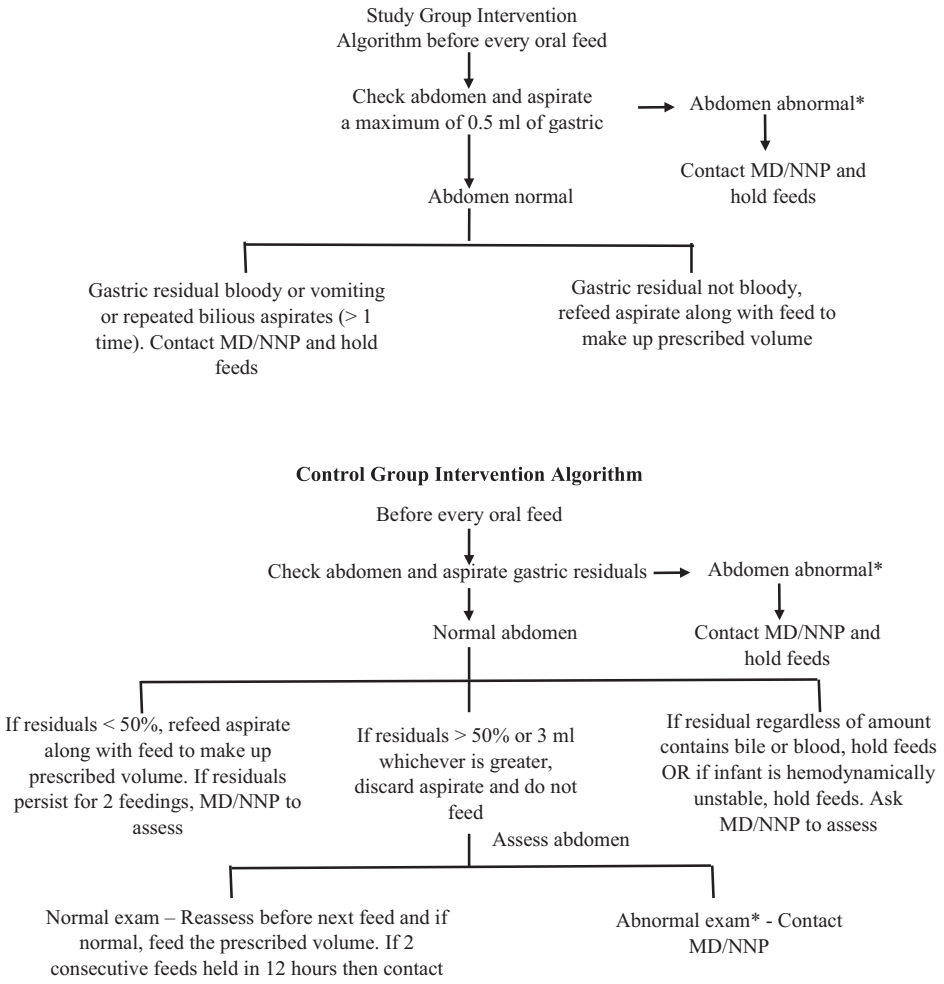


**Figure 1.** Algorithms for study and control group interventions. *Abdomen abnormal (tender, discolored, absent bowel sounds). †Always refeed residuals unless the feeding is to be held. *MD*, Medical doctor; *NNP*, Neonatal Nurse Practitioner.



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