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Compatibility of rapid enteral feeding advances and noninvasive ventilation in preterm infants—An observational study

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Abstract

Aim: To evaluate safety and clinical outcome of rapid enteral feeding advances in preterm infants <1500 g birthweight (BW).

Methods: In this single-center retrospective cohort study, 293 preterm infants born during 2015–2018 were comparatively analyzed before (n = 145) and after (n = 148) the implementation of a rapid enteral feeding protocol with daily milk increments of 20–30 ml/kg of body weight. Major outcome parameters were focused toward pulmonary morbidities and nutritional variables.

Results: Preterm infants in the rapid feeding advancement group were more successfully stabilized on noninvasive ventilation (p < 0.001) never requiring mechanical ventilation. Duration of respiratory support (0.465) and frequency of bronchopulmonary dysplasia (BPD) (p = 0.341) and severe BPD (0.273) did not differ between both groups. Furthermore, patients in the rapid feeding group achieved full volume feedings faster (p < 0.001), regained BW earlier (p = 0.009), and displayed significantly improved somatic growth at 36 weeks gestational age (p < 0.001). There was no increased risk for further morbidities of prematurity including feeding intolerance, necrotizing enterocolitis (NEC), and focal intestinal perforation.

Conclusion: Rapid enteral feeding advancements in preterm infants <1500 g BW are safe and do not impede stabilization on noninvasive ventilation.

KEYWORDS

enteral feeding advancement, noninvasive ventilation, nutrition, very low birthweight infants

Abbreviations: AUC, area under the curve; BW, birthweight; BPD, bronchopulmonary dysplasia; CI, confidence interval; ELBW, extremely low birth weight; GA, gestational age; IQR, interquartile range; LISA, less invasive surfactant application; nCPAP, nasal continuous positive airway pressure; NEC, necrotizing enterocolitis; NICU, Neonatal intensive care unit; NIPPV, nasal intermittent positive pressure ventilation; PEEP, positive end-expiratory pressure; RCT, randomized controlled trial; RD, risk difference; ROC, receiver operating characteristic; RR, relative risk; STENA, standardized enteral nutritional advances; SGA, small for gestational age.

1 | INTRODUCTION

Prevention of bronchopulmonary dysplasia (BPD) and reduction of its burden for preterm infants is a primary focus of treatment in this high-risk population. Establishment of early noninvasive ventilation strategies plays a crucial role in the context of pulmonary morbidity.[1,2] Recent multicentre studies and registry analyses indicate that further improvements in the management of noninvasive respiratory support are suited to improve the pulmonary outcome in the near term while novel therapeutic strategies still await a substantiated proof of benefit.[3,4]

Enhanced energy and macronutrient intake during the first 4 weeks of life have been associated with improved somatic growth, neurodevelopmental outcomes, such as improved language scores and decreased incidence of brain lesions on magnetic resonance imaging.[5] Within the recent years, the importance of nutritional supply to reduce BPD has come into the focus of research which is best documented for the provision of breast milk supply in a recent meta-analysis.[6] Besides macronutrient content, the nonnutritive factors of breast milk including prevention of nosocomial infections are held responsible for the benefits on the pulmonary outcome. Additionally, delayed postnatal full enteral feeding is an independent risk factor of chronic lung disease, and it seems that a critical amount of protein and caloric intake is required to prevent the development of BPD.[7] The immediate period after birth seems particularly vulnerable for nutritional deficits.[8] There are wide discrepancies concerning the introduction and advancement of enteral feeds for preterm infants and standardized protocols for optimal feeding regimen differ considerably. One of the major concerns responsible for slow enteral feeding advances is the potential interference with successful stabilization of the preterm infant on noninvasive respiratory support.[9,10] Further concerns about rapid advancement of feeding volumes refer to intestinal intolerance and a potentially higher risk of focal intestinal perforation (FIP) and necrotizing enterocolitis (NEC).[11–14] However, conservative feeding regimes delay establishment of full enteral feeding and extend exposure to parenteral nutrition increasing the risk for late-onset sepsis, which in turn is a major risk factor for BPD.[15,16] The recently published Cochrane analysis of randomized controlled trials indicates no significant effects of rapid versus slow feeding advances in the risk of NEC or all-cause mortality and no difference in survival without moderate or severe neurodevelopmental disability at 24 months.[17,18] Moreover, a significant delay in establishment of full enteral feeding and regain of birthweight (BW) were reported for slow advancement. All these data are mostly based on small sample size, and definitions substantially differ between studies impeding the propagation of benefits. Avoidance of mechanical ventilation and sepsis and propagation of enteral nutrition represent key priorities of clinical research to reduce the burden of BPD in preterm infants.[1,2,6–8,15,16]

So far it remains speculative whether rapid enteral feeding advances can be successfully combined with the propagation of noninvasive respiratory support strategies and whether shorter durations of parenteral nutrition and accompanied reduced incidence of sepsis are suited to improve the pulmonary outcome. The present observational study investigated safety and effectiveness of implementing a standardized feeding protocol in 363 preterm infants <1500 g BW. Special focus was set to the respiratory management, the pulmonary outcome and somatic growth that were so far not evaluated in the consideration of treatment results. The sample size of our cohort allowed the separation into subgroups of BW ≤ 500 g, 500 g < BW ≤ 1000 g, and 1000 g < BW ≤ 1500 g that specified the outcome for extremely low birthweight (ELBW) infants at highest risk for long-term morbidities.

2 | MATERIALS AND METHODS

2.1 | Study design

This study was designed as a single-center retrospective cohort study to evaluate safety and clinical outcome parameters of implementing a rapid standardized enteral nutritional advances (STENA) protocol in preterm infants <1500 g BW. We included all preterm infants ($n = 363$) admitted to the perinatal center of the Justus-Liebig-University Giessen between 2015 and 2018. Exclusion criteria contained major congenital malformations, severe syndromal diseases, or death before 36 weeks of gestation. After the exclusion criteria were applied, we had 293 infants left in the study (Figure 1). The study collective was comparatively analyzed before ($n = 145$) and after the implementation of STENA starting 2017 ($n = 148$) with daily milk increments of 20–30 ml/kg of body weight (rapid feeding advancement) (Table S1). Furthermore, items for STENA protocol deviations were precisely defined and included the following items: gastric residuals >5 ml/bodyweight in 50% of all daily feeds, recurrent vomiting (>4×/day), bilious vomiting, focal intestinal perforation, suspected or proven necrotizing enterocolitis (NEC), sepsis, surgical procedure, respiratory instability (repeated prolonged or deep desaturations requiring stimulation at the discretion of the attending physician and nurse, while pCO_2 or the fraction of oxygen applied were not taken into account), medical abdominal abnormalities (abdominal distension with pressure pain, clinical signs of ileus, discoloration of the abdominal wall, hematochezia) or no objective reason. In case of STENA protocol deviation, feeds were either held or restarted at the same step/volume when symptoms ceased. In infants with protocol deviation, the subsequent feeding increments were scheduled as predetermined in the next STENA protocol step. Initiation of septic workup or radiologic imaging was not mandatory in case of STENA protocol deviation but was left to the discretion of the attending physician. Data were collected for the first 21 days of life (STENA observation period) and only five infants achieved full enteral feeding later on [d23, d26, d39, d42, d135]). Before standardization of our feeding protocol, we usually started enteral feeding with an amount of 10 ml/kg/day at the first day of life and increased the volume at a rate of 10–15 ml/kg/day until reaching full enteral feeds (standard feeding advancement), defined as 140–160 ml/kg/day. All feeds were given as bolus or intermittent gravity feed by a nasogastric tube over 10–30 min at the discretion of the attending nurse with intervals

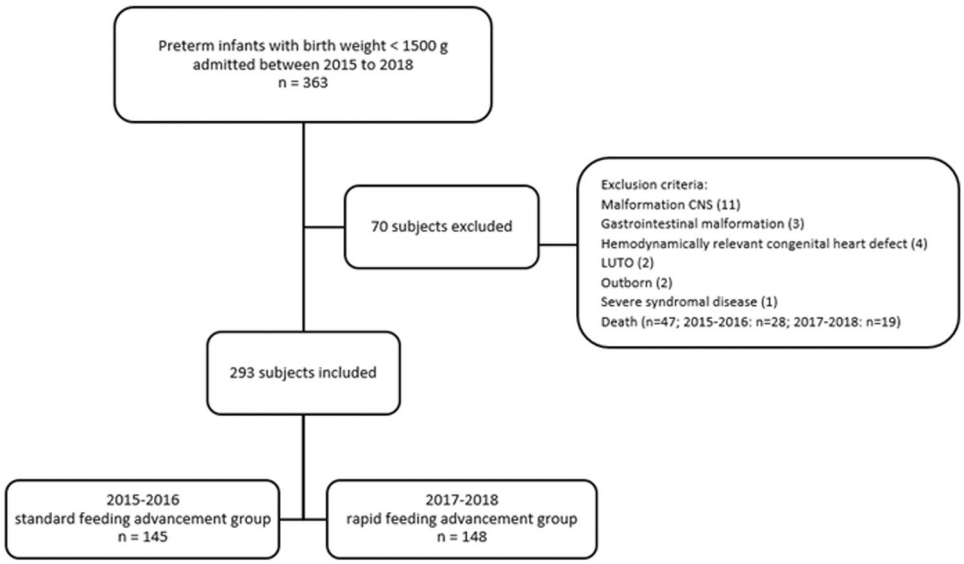

FIGURE 1 Flowchart of the study population. CNS, central nervous system; LUTO, lower urinary tract obstruct

TABLE 1 Demographics and cohort characteristics

	Standard group (2015–2016) *n* = 145	Fast group (2017–2018) *n* = 148	*p* value
Birth weight, g	1100 (800–1390)	1065 (850–1383)	0.896[a]
Gestational age, weeks	29.00 (27.00–31.14)	29.00 (27.00–31.36)	0.869[a]
z-scores at birth			
Weight	−0.73 (−1.29 to −0.14)	−0.73 (−1.41 to −0.17)	0.518[a]
Length	−0.60 (−1.09 to −0.27)	−0.63 (−1.20 to 0.19)	0.819[a]
Head circumference	−0.77 (−1.22 to −0.33)	−0.81 (−1.24 to −0.28)	0.936[a]
SGA[b]	41 (28)	45 (30)	0.689[c]
Male sex, *n* (%)	68 (47)	81 (55)	0.180[c]
Multiple birth, *n* (%)	60 (31)	58 (39)	0.702[c]
Antenatal corticosteroids, *n* (%)	134 (94)	137 (93)	0.861[c]

Note: Data shown as median (interquartile range) or *n* (%).

[a]Wilcoxon test.

[b]Small for gestational age.

[c]Pearson test.

of 2, 2.4, or 3 h (tube size Ch 5, 40 cm). In between feeds, the tube was left open and vented, active decompression of air was performed routinely during rounds and additionally between rounds in case of respiratory instability due to a gas-filled stomach. Feeding was initiated within the first 3 h of life with standard preterm formula (Nestlé® BEBA premature baby food level 1 during the observation period). The own mothers' breast milk was given when available (first feeds with crude colostrum, holder-pasteurization of breast milk to prevent postnatally acquired cytomegalovirus infection was started at Day 5 of life). Nutritional supply was provided as recommended by the ESPGHAN[19] and there was no change in nutritional aims such as type of formula, substrates, or ingredients of parenteral nutrition during the whole study period.

The study collective was divided into three weight categories (BW ≤ 500 g, 500 g < BW ≤ 1000 g, and 1000 g < BW ≤ 1500 g) for a complementary subgroup analysis (Table S3). A number of perinatal variables were retrieved from the medical notes. These included the infant's perinatal clinical characteristics, gestational age (GA), sex and somatic parameters at birth and with 36 weeks gestational age. Days to reach full enteral feeding and regain of BW were of particular interest. We also collected data on medical treatment, like antenatal and postnatal corticosteroids, surfactant use with less invasive

surfactant administration (LISA) as primary standard, medicinal treatment of apnea, diuretics, antihypertensive therapy at discharge, and inhalation therapy. Additionally, all kind of surgeries and nosocomial infections were recorded.

Regarding respiratory stabilization, the mode of ventilatory support (invasive vs. noninvasive ventilation including nasal continuous positive airway pressure (nCPAP) and nasal intermittent positive pressure ventilation [NIPPV]) and the end of oxygen therapy were recorded (Tables 1 and 2 and Table S2). Standard settings for noninvasive ventilation were equal in both periods with a positive end-expiratory pressure (PEEP) of 5–8 cmH_2O; a peak inspiratory pressure of 12–18 cm H_2O; a respiratory rate of 40–60/min; and inspiratory time of 0.3 s. Clinical criteria for intubation were primary respiratory failure in the delivery room immediately after delivery, $FiO_2 > 40\%$ after a maximum of three LISA maneuvers, pneumothorax, FIP or NEC, and severe and prolonged apnea with bradycardia under standard caffeine treatment. Severity of BPD was determined according to the most widely used NIH consensus definition.[20] To specify the PEEP level and the fraction of oxygen supplied via nasal cannula, our recently published approach was applied.[21] Further major short-term outcomes were intraventricular hemorrhage, NEC,[22] FIP, occurrence and therapy of retinopathy of prematurity and presence of a patent ductus arteriosus.

2.2 | Statistical analysis

The statistical analyses were performed using R, version 4.0.2 (R Foundation for Statistical Computing). The demographics in Table 1 are shown as medians and interquartile ranges. The absolute and relative frequencies of the parameters are given for counted data. Comparisons were carried out using the Wilcoxon rank-sum test for metric data and Pearson's χ^2 with continuity correction/Fisher's exact test for categorical data. There was no need to control for possible confounders because there were no differences regarding baseline demographic and perinatal characteristics (Table 1). For the calculation of the cutoff weight (Table S4), receiver operating characteristic (ROC) analyses were performed using R-package optimalCutpoints (Version 1.1–4). Optimal cutpoints were selected by maximum specificity. Confidence intervals in ROC analysis were calculated based on the Wald statistic. Statistical significance was defined as a p value of <0.05. Supporting information S1 provides

TABLE 2 Outcome variables in the study collective

	Standard group (2015–2016) $n = 145$	Fast group (2017–2018) $n = 148$	p value
Days to full enteral feeding	11 (8–14)	7 (6–9)	<0.001[a]
Days to regain birth weight	8 (5–11)	7 (5–9)	0.009[a]
z-scores at 36 weeks gestational age			
Weight	−1.19 (−1.67 to −0.81)	−1.03 (−1.46 to −0.52)	0.004[a]
Length	−1.69 (−2.35 to −0.92)	−1.31 (−2.08 to −0.79)	0.015[a]
Head circumference	−1.24 (−1.75 to −0.69)	−0.87 (−1.44 to −0.50)	<0.001[a]
Δz-score (weight 36 weeks gestational age-birth)	−0.54 (−0.92 to −0.24)	−0.24 (−0.58 to 0.11)	<0.001[a]
Intraventricular hemorrhage, n (%)[b]	23 (16)	14 (9)	0.134[c]
Necrotizing enterocolitis, n (%)	2 (1)	1 (1)	0.986[c]
Focal intestinal perforation, n (%)	3 (2)	6 (4)	0.518[c]
Retinopathy of prematurity, n (%)[b]	42 (29)	54 (37)	0.197[c]
Patent ductus arteriosus, n (%)	43 (30)	40 (27)	0.618[c]
Nosocomial infection	16 (11)	8 (5)	0.079[c]
Patients with surgery, n (%)	24 (17)	27 (18)	0.820[c]
Total number of surgeries, n	35	42	0.082[d]

Note: Data shown as median (interquartile range) or n (%).

[a]Wilcoxon test.

[b]Any grade.

[c]Pearson test.

[d]Fisher's exact test.

the complete statistical data, including the confidence intervals and the area under the curve.

3 | RESULTS

The subjects' demographic data are summarized in Table 1, and the total data set can be found in the supporting information (Table S2). Infant baseline demographic and perinatal characteristics were similar and statistically comparable in the two trial groups. In the standard advancement group, median GA was 29 weeks (interquartile range [IQR] 27.00–31.14) and median BW 1100 g (IQR 800–1390g). In the fast advancement group, median GA was 29 weeks (IQR 27.00–31.36) and median BW 1065 g (IQR 850–1383g) with balanced gender distribution and presence of a PDA in both groups (Table 1). Infants born small for gestational age (SGA) were equally distributed across the evaluation groups ($p = 0.689$). Postnatal treatment strategies, including the use of corticosteroids, surfactant, or medicinal treatment of apnea did not differ between both groups. In total, 60 out of 148 infants were able to adhere to the fast-feeding advancement regimen without protocol deviation. Infants who were fed and advanced at 20–30 ml/kg per day according to our STENA protocol achieved full enteral feeding (140–160 ml/kg/day) within 7 days, thus 4 days earlier than the standard advancement group ($p < 0.001$). In addition, days to regain BW were significantly reduced in the rapid group (median 7 instead of 8 days, $p = 0.009$, Table 2). Somatic growth with 36 weeks gestational age displayed by the median *z*-scores of the auxological parameters was higher in the fast group (weight $p = 0.004$, length $p = 0.015$, head circumference $p < 0.001$). Even SGA infants reached full enteral feeding 4 days earlier in the rapid group ($p = 0.006$) and Δ*z*-scores for growth at 36 weeks postmenstrual age were higher (Δ*z*-score median −0.29 to 0.04, $p < 0.001$, Table S2). Radiologic imaging and septic work-up during the first 21 days of life (STENA observation period) was performed less frequently in the STENA group than in the control group. Thereby, radiological diagnostics significantly differed for pulmonary but not abdominal X-ray examinations (Table S2).

Focusing on the parameters of respiratory support, significantly more infants in the fast advancement group were successfully stabilized on noninvasive ventilation and did never require mechanical ventilation $n = 78$ (54%) before and $n = 112$ (75%) infants after STENA implementation, $p < 0.001$). The duration of invasive mechanical ventilation and of noninvasive ventilation did not differ between both groups, as well as the end of oxygen therapy (Table 3). Within the categories of enteral feeding intolerances, recurrent vomiting (17.2%), medical abdominal abnormalities (22.3%), and no objective reasons (31.5%) were the most common reasons for feed interruption during the first 3 weeks of life in the fast advancement group. Respiratory instability accounted for 8.3% of episodes and mostly occurred within the first 3 days of life (Figure 2). The frequency of BPD and severe BPD did not differ between both groups (Table 3). Concerning the further relevant clinical outcome parameters, we detected no significant differences for FIP, NEC, intraventricular hemorrhage, and retinopathy of prematurity (Table 2). There was a trend toward a nonsignificant reduction of nosocomial infections in the rapid group and no impact on the frequency of surgeries (Table 2 and Table S2).

As BW plays a substantial role in volume-targeted enteral feeding, we also analyzed the total cohort in a ROC analysis concerning the cut-off for the strongest effect to reach full enteral feeding within one week. Before implementation of our feeding protocol the calculated BW cut-off was 910 g, afterwards it decreased to 530 g (area under the ROC curve (AUC) 0.841, Table S4). Moreover, all items were evaluated in a subgroup analysis of the three BW strata. Major outcome variables in the subgroup of ≤500 g BW had no statistical effect due to the low number of infants included in the analyses ($n = 11$). In the subgroup of 500 g < BW ≤ 1000 g ($n = 126$) all items of interest showed significant changes, by analogy with the total cohort except for days to regain BW. Infants with 1000 g < BW ≤ 1500 g

TABLE 3 Respiratory outcome

	Standard group (2015–2016) $n = 145$	Fast group (2017–2018) $n = 148$	p value
Bronchopulmonary dysplasia,[a] *n* (%)	60 (42)	54 (36)	0.405[b]
Mild	34 (24)	35 (23)	0.655[c]
Moderate	3 (2)	2 (1)	0.655[c]
Severe	23 (16)	17 (11)	0.655[c]
Mechanical ventilation, *n* (%)	66 (46)	37 (25)	<0.001[b]
Duration, days	2 (1–10)	4 (1–14)	0.226[d]
Start, day of life	1 (0–1)	1 (1–3)	<0.001[d]
Noninvasive ventilation, *n* (%)	78 (54)	112 (75)	<0.001[b]
Duration, days	25 (6–57)	29 (7.5–54.5)	0.465[d]
End of oxygen therapy, day of life	5 (1–45)	5 (1–36)	0.451[d]
Medicinal treatment of apnea, *n* (%)			
Caffeine	136 (94)	131 (89)	0.112[b]
Doxapram	10 (7)	9 (6)	0.777[b]
Surfactant, *n* (%)	80 (55)	80 (54)	0.848[b]
Inhalation therapy, *n* (%)	31 (21)	21 (14)	0.107[b]
Postnatal corticosteroids, *n* (%)	8 (6)	11 (7)	0.506[b]

Note: Data shown as median (interquartile range) or *n* (%).

[a]36 weeks gestational age.

[b]Pearson test.

[c]Fisher's exact test.

[d]Wilcoxon test.

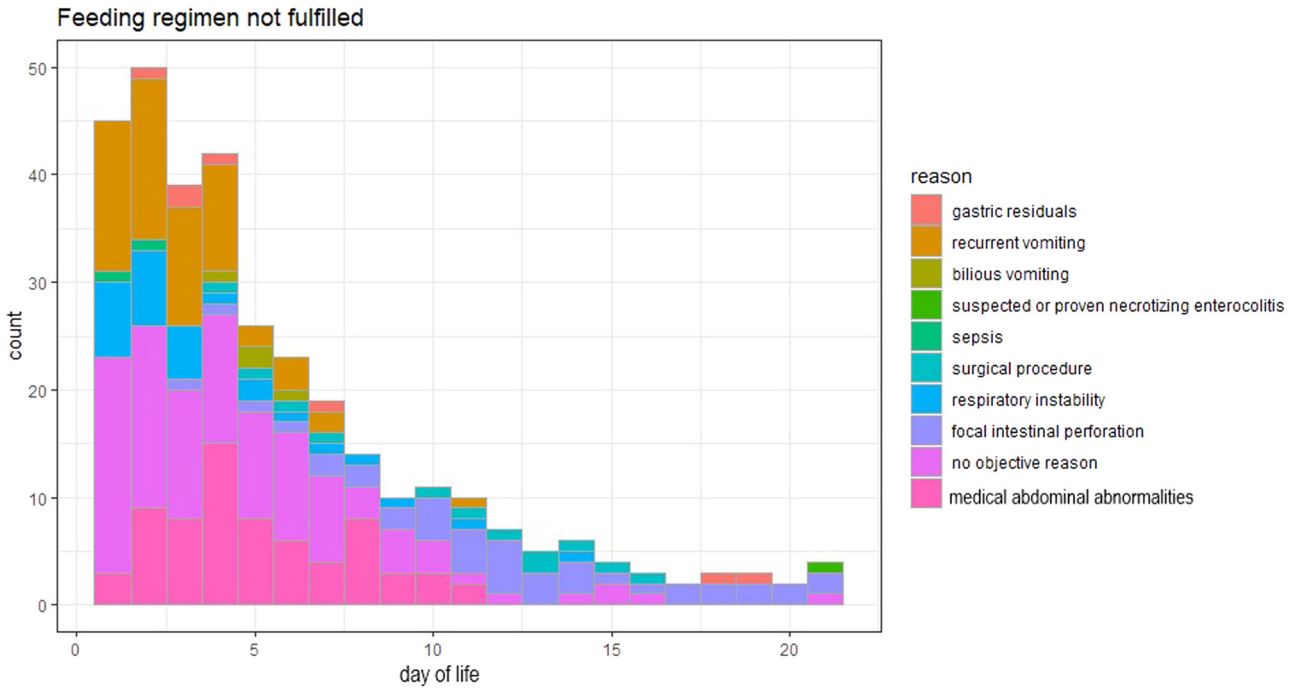

FIGURE 2 There were $n = 337$ protocol deviations (counts) within $n = 3108$ evaluation points in $n = 148$ patients treated according to STENA over the first 21 days of life. One count represents the leading cause of each infant not meeting that day's feeding regimen, whereby each day counts separately for the superordinate criterion and count is reset on the next day of life. gastric residuals ($n = 10$): >5 ml/bodyweight in 50% of all daily feeds; recurrent vomiting ($n = 58$): >4×/day; bilious vomiting ($n = 4$); FIP ($n = 41$); suspected or proven NEC ($n = 1$); sepsis ($n = 2$); surgical procedure ($n = 12$); respiratory instability ($n = 28$): repeated prolonged (>30 s) or deep desaturations (<70% of oxygen); medical abdominal abnormalities ($n = 75$): abdominal distension with pressure pain, clinical signs of ileus, discoloration of the abdominal wall, hematochezia; no objective reason ($n = 106$) [Color figure can be viewed at wileyonlinelibrary.com]

($n = 156$) achieved statistical significance for days to reach full enteral feeding and regaining of BW, as well as for the z-score of head circumference at term (Table S3). As for the total cohort, in both subgroups of 500 g < BW ≤ 1000 and 1000 g < BW ≤ 1500 g the need for invasive mechanical ventilation was significantly reduced ($p = 0.002$ and $p = 0.004$). While in the latter group, BPD was a rare event, a trend toward reduced risk for BPD and severe BPD became evident in the 500 g < BW ≤ 1000 g subgroup of infants (Table S3).

4 | DISCUSSION

Improving nutrition for very preterm infants plays a crucial role in the context of neonatal morbidity and long-term outcome. The pulmonary outcome is just emerging as another important aspect here. Enteral feeding practices have been repeatedly evaluated with the aim to implement risk-reducing strategies, but uniform international standards are lacking. Our present study on rapid enteral feeding advances in preterm infants born <1500 g BW adds the factors for successful implementation of noninvasive ventilation strategies and improved somatic growth with 36 weeks postmenstrual age during STENA to the current state of knowledge of this topic. This is of particular importance against the background that still today many neonatologists are afraid of rapid enteral feeding advances in the grounds that these are associated with an increased risk of feeding intolerance, abdominal distension and subsequent instability on noninvasive respiratory support. As there were no alterations in management of ventilatory support during the immediate postnatal period, especially no change in stabilization procedures such as noninvasive surfactant application, breast milk provision, and nutritional protocols during the total study period, our cohort is ideally suited to study the impact of introduction of a regime of rapid enteral feeding advances. The results of our detailed comparative analysis clearly indicate that rapid enteral feeding is safe and does not impede noninvasive ventilation.

Despite the reduced need of invasive mechanical ventilation, which constitutes a well-known risk factor for BPD, the incidence of BPD and severe BPD was not impacted by rapid feeding increments in our total cohort. These results are in line with other studies of similar size where strategies to reduce the need for invasive mechanical ventilation proved successful but failed to reduce the risk of BPD.[3,23] For these and our analysis, the studies were certainly underpowered to detect a statistically significant difference which can be attributed to the multifactorial origins of BPD.[24] We postulate that as for the noninvasive application of surfactant after birth, evaluation of a much larger cohort would have enabled a clearer view toward the benefits for BPD.[25] This was not possible in our cohort to avoid trade-off effects by extending the observation period. But the

separate investigation of the subgroup of infants with a BW between 500 and 999 g at highest risk for BPD points toward a trend for the rapid enteral feeding advances group.

Noninvasive ventilation can cause abdominal distension, and nCPAP decreases pre- and post-prandial intestinal blood flow in preterm infants.[26] The gaseous bowel distension due to CPAP was termed "CPAP belly syndrome"[27] and raised concerns about abdominal complications like NEC and FIP what can result in withholding feeds, prolonging the use of parenteral nutrition and constitute important risk factors for BPD. For infants born with 500–1500 g BW the mean prevalence of NEC is still unchanging and about 7% with an estimated rate of death from 20% to 30%.[28] Unfortunately, the connection between early and progressive enteral feeding and NEC incidence has resulted in prolonged duration of intravenous nutrition in infants, potentially increasing the risk of infectious complications and the length of hospitalization which in turn increases the risk for BPD.[29] A recent Cochrane analysis comparing 10 randomized controlled trials (RCTs) ($n = 3753$) did not provide evidence that slow advancements reduce the risk of NEC (typical relative risk [RR]: 1.07, 95% confidence interval [CI]: 0.83–1.39; risk difference [RD]: 0.0, 95% CI: −0.01 to 0.02) or all-cause mortality (typical RR: 1.15, 95% CI: 0.93–1.42; typical RD: 0.01, 95% CI: −0.01 to 0.03).[17] In our cohort the cumulative incidence of NEC was much lower (1.0%; $n = 2$ before and $n = 1$ after implementation of STENA) than in the before-mentioned studies but did not differ significantly before and after STENA implementation (Table 2). As well, FIP (3.1%; $n = 3$ before vs. $n = 6$ after implementation of STENA) and death rates ($n = 28$ before vs. $n = 19$ after implementation of STENA, Figure 1) were comparable in both study arms. Vice versa, a recent Cochrane review[30] comparing the rates of gastric distension, gastrointestinal perforation, and NEC with NIPPV and higher gas flows versus nCPAP found no significant difference for any variables between the groups. Our data add further evidence to both topics that both noninvasive ventilation strategies and rapid enteral feeding advances can be implemented simultaneously and successfully in preterm infants.

Our observational data showed that infants with increased daily enteral feeds had statistically significant improved somatic growth at term in all body measurements (Table 2). This is of special interest, because preterm infants accumulate significant growth deficits by the time of discharge from hospital[31,32] that persist through infancy and early childhood into adolescence.[33,34] Our subgroup analyses prevailed that ELBW and SGA infants with the highest risk for growth deviations benefited in somatic growth when their feedings are advanced rapidly using STENA. Additionally, our ROC analysis calculation indicates that standardized and progressive feeding works even for these infants at particular risk (530 g cut-off for full enteral feeding within the first week of life for the fast group, Table S4). To our knowledge, we are the first to report *z*-score differences for head circumference which can be seen as surrogate for psychomotor outcome.[35] In addition in our results, the change in *z*-score from birth to 36 weeks of gestation was lower compared to the change observed by Rochow et al.,[36] though they measured change in *z*-scores from birth to 21 postnatal days. The fact that more immature infants experience a slightly higher *z*-score difference was similar to our findings (Table S3). The association between postnatal growth failure and impaired neurocognitive development is of particular concern.[8,37] Our data on somatic growth until discharge might argue toward an additional benefit of rapid feeding increments for the lung what might be mirrored in the trend toward reduced risk for BPD in infants between 500 and 999 g of BW. In the literature, advancing the volume of enteral feeds at a slow rate resulted in several days of delay in establishing full enteral feeds, may increase the risk of invasive infection and higher risk of BPD.[17,23,38] The trend toward a reduced risk for nosocomial infections in our rapid enteral feeding advances group might have as well contributed to the trend of reduced BPD in the infants born 500–1000 g BW (Table S3).

The sample size of our cohort and demographic characteristics (Table 1) are of equal value to the published trials on this topic.[11,12,15,39] Of note, even the SIFT trial[18] only included 17 infants with BW < 500 g ($n = 7$, 0.5% of slow group and $n = 10$, 0.7% of fast group); therefore, our cohort can be regarded as representative ($n = 4$, 2.8% of standard group and $n = 7$, 4.7% of fast group; Table S3). The feeding rates in most of the before published prospective trials were 15–20 ml/kg/day in the slow advancement and 30–40 ml/kg/day in the fast advancement group, which is in agreement with our standard and rapid feeding advancement categories. The strengths of our study are its large sample size, the homogeneous baseline demographics in both groups and the short observation period. Moreover, we had no drop-outs of eligible infants in contrast to multicenter studies where an a priori parental consent is required. Another strength is the systematic record of protocol compliance with assessment of feed tolerance for the fast advancement group to evaluate the STENA protocol adherence (Figure 2). Within our cohort, primarily objective criteria led to the withholding of the next STENA step (68.55% of all protocol deviations, Figure 2). As published within a parallel analysis from our patient cohort, the nonobjectifiable protocol deviations (31.5%) as a leading event can serve as an occasion for internal team training and protocol editing in the future.[8] It was recently demonstrated that the omission of gastric residual evaluation in extremely preterm infants increased the delivery of enteral nutrition as well as improved weight gain and led to earlier hospital discharge in a recent RCT.[40] This fact might be suited to further improve the success of STENA in units with a policy of feeding interruption upon gastric residuals, although gastric residuals made up only a small percentage (3.0%) of the total protocol deviations in our cohort. This aspect might be traced back to our restrictive policy for evaluating gastric residuals (Figure 2). Another strength of our results is that STENA was not associated with increased laboratory and radiologic workups for respiratory instability, suspected abdominal complications, or clinical signs of sepsis. Whether the statistically significant reduced numbers of evaluation episodes can be ascribed to the shorter duration until reaching full enteral feeding remains speculative. Our study also had some limitations, in particular its retrospective and single-center design and the unstandardized enteral feeding advances in the slow group. But a large proportion of

our study collective were ELBW infants ($n = 137$, 46%); therefore, our results confirm the applicability of STENA to this particularly vulnerable patient cohort. Due to the retrospective character of our study, reasons for cessation of enteral feeding were not systematically documented before STENA implementation what prohibits a before after comparison. It must be noted that significantly more infants were spared from mechanical ventilation in the STENA cohort (2017–2018) than in the control group (2015–2016) ($p < 0.001$). Although there were no alterations in the general management of ventilatory support in our neonatal intensive care unit (NICU) during the 4-year study period, subtle but clinically relevant changes in noninvasive ventilation strategies and increasing team acceptance over time might have accounted for the reduction in failure rate on noninvasive ventilation during STENA. Nevertheless, it can be noted that higher daily feeding volumes do not preclude preterm infants from successful stabilization on noninvasive ventilation.

Taken together our data confirm current evidence about the safety of rapid enteral feeding advances in preterm infants. Reducing the duration of parenteral nutrition has many theoretical advantages, but besides shortening of iv access and lengths of hospital stay, little advantage has been documented despite the potentially higher risk of acquiring a severe infection.[17] In contrast, there are still major concerns of rapid feeding advances with respect to NEC and other morbidities. Our data provide novel insights that even in a situation of changing trends toward avoiding mechanical ventilation to protect the immature lung from shear stress rapid feeding advances are feasible. The question why our overall BPD rate did not decline can be answered by its multifactorial origins and that our study was not powered to detect this.[23,24] Larger, adequately powered trials probably will detect such a statistically significant reduction of BPD but the expectable effect size must be rated as moderate. Perhaps other, so far neglected aspects of nutritional supply may have a higher impact on BPD than rapid enteral feeding advances or the total caloric intake.[8] Nevertheless, the reduction of mechanical ventilation is known to be associated with a better pulmonary outcome.[25] The trend toward reduced risks for nosocomial infections in the STENA group is another indicator for a better pulmonary outcome.[41] Furthermore, better somatic growth (*z*-scores) suggests improved conditions for lung growth. Therefore, it is of utmost importance to confirm our data in larger and multicenter cohorts to document and promote the benefits of improved nutritional strategies for the pulmonary outcome.

5 | CONCLUSION

Rapid enteral feeding advancements (increments of 30 ml/kg/day) in preterm infants <1500 g BW are safe concerning major clinical short-term outcome parameters, improve somatic growth, and do not impede noninvasive respiratory support. The systematic re-evaluation of criteria to withhold rapid feeding advances in daily NICU routine should be included into future research strategies particularly in combination with approaches to further promote noninvasive respiratory support.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Judith Behnke: conceptualization (lead); writing—review and editing (equal); writing—original draft (lead). **Vanessa Estreich**: data curation (lead); writing—review and editing (equal). **Frank Oehme**: writing—review and editing (equal). **Klaus-Peter Zimmer**: writing—review and editing (equal). **Anita Windhorst**: formal analysis (lead); writing—review and editing (equal). **Harald Ehrhardt**: conceptualization (supporting); writing—original draft (supporting); writing—review and editing (equal); supervision (lead).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author.

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SUPPORTING INFORMATION

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