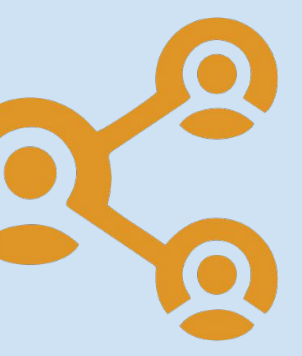


Progression of enteral feeding volumes in ELBW infants in the CONNECTION TRIAL

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IBP-9414 is a pharmaceutical grade probiotic with quality standards equivalent to all drug products. Manufacturing requires full pharmaceutical GMP (21 CFR Part 210/211) throughout the entire process from cell banking to final drug product, which includes e.g., testing for absence of a range of specified organisms and potential contaminants as well as batch control, shelf-life, and validated procedures for correct dosing of 1x10⁹ CFU. **The Connection Trial** is a placebo-controlled multicenter study under US IND and EU CTX exploring IBP-9414 in VLBW infants (ClinTrials.gov ID NCT03978000).

BACKGROUND & AIM

- Current practices on how NICUs initiate and advance enteral feedings in ELBW infants have not been detailed.
- Show current feeding progression across 80+ NICUs in 641 ELBW infants.
- Quantify the relationship of 25 clinical variables with the progression of total daily (td) enteral feeding volumes of 10, 20, 40, 80 and 120 ml/kg.

MATERIAL & METHODS

- 641 infants with mean 847g body weight and GA 27w at birth were analyzed with randomization status blinded.
- Clinical events were gathered from investigator reports and analyzed with univariable and multivariable Cox proportional hazard models. NEC relied on independent adjudication of abdominal X-rays demonstrating intestinal pneumatosis and/or portal venous gas or laparotomy or autopsy.

RESULTS

- Infants reached 10 ml/kg/day at or beyond 2 days of age with a median of 4 days. At the earliest, 120 ml/kg/day was reached on day 4 with 1/4 of infants reaching this volume at or beyond 20 days for (Fig 1).
- Daily intakes varied, increasing up to about 18 days (Fig. 2) and with substantial reduction in infants with e.g., GI perforation (Fig. 3).
- Univariable regression showed 8% to 20% increased chance of reaching the td volumes for every increase in 100 g BW, GA week and 5-min Apgar score at birth. GI serious events (SAE GI) and GI perforation associated with 38% to 78% reduced chance of attaining the td volumes; NEC, GI obstruction and abdominal signs (e.g., distension, vomiting etc) associated with 24% to 57% reductions (Table 1).
- Stepwise multivariable analysis associated 12 variables with the time to the td volumes. BW, GA and 5-min Apgar score at birth associated with increases up to 14%; GI SAEs, GI perforation, respiratory SAEs, abdominal signs and hypotension with reductions of 20%-68% (Table 2).

FIGURE 1. Time (days) to reach the td volumes of 10, 20, 40, 80 and 120 ml/kg.

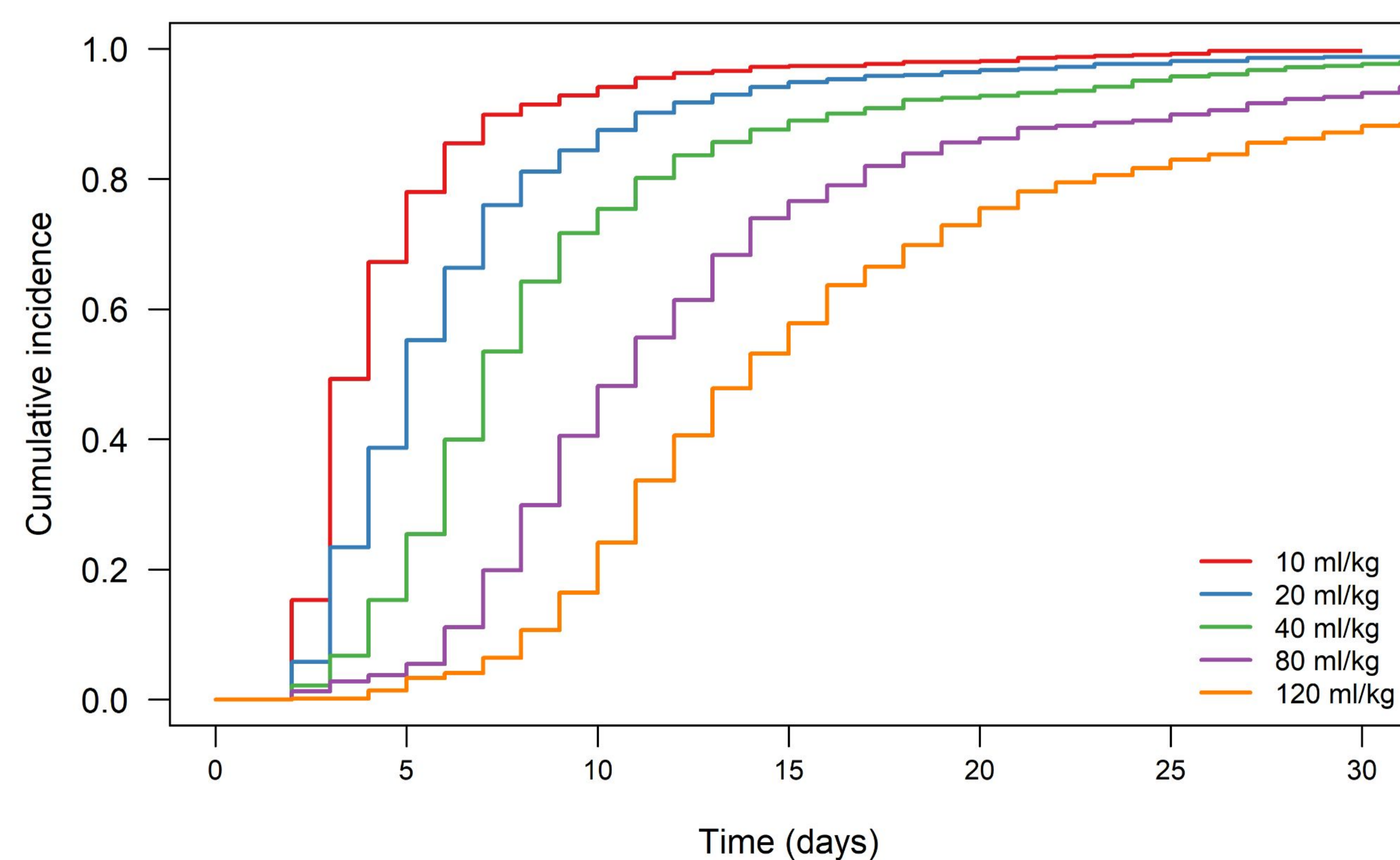


FIGURE 2. Box plot of the total daily enteral feeding volumes.

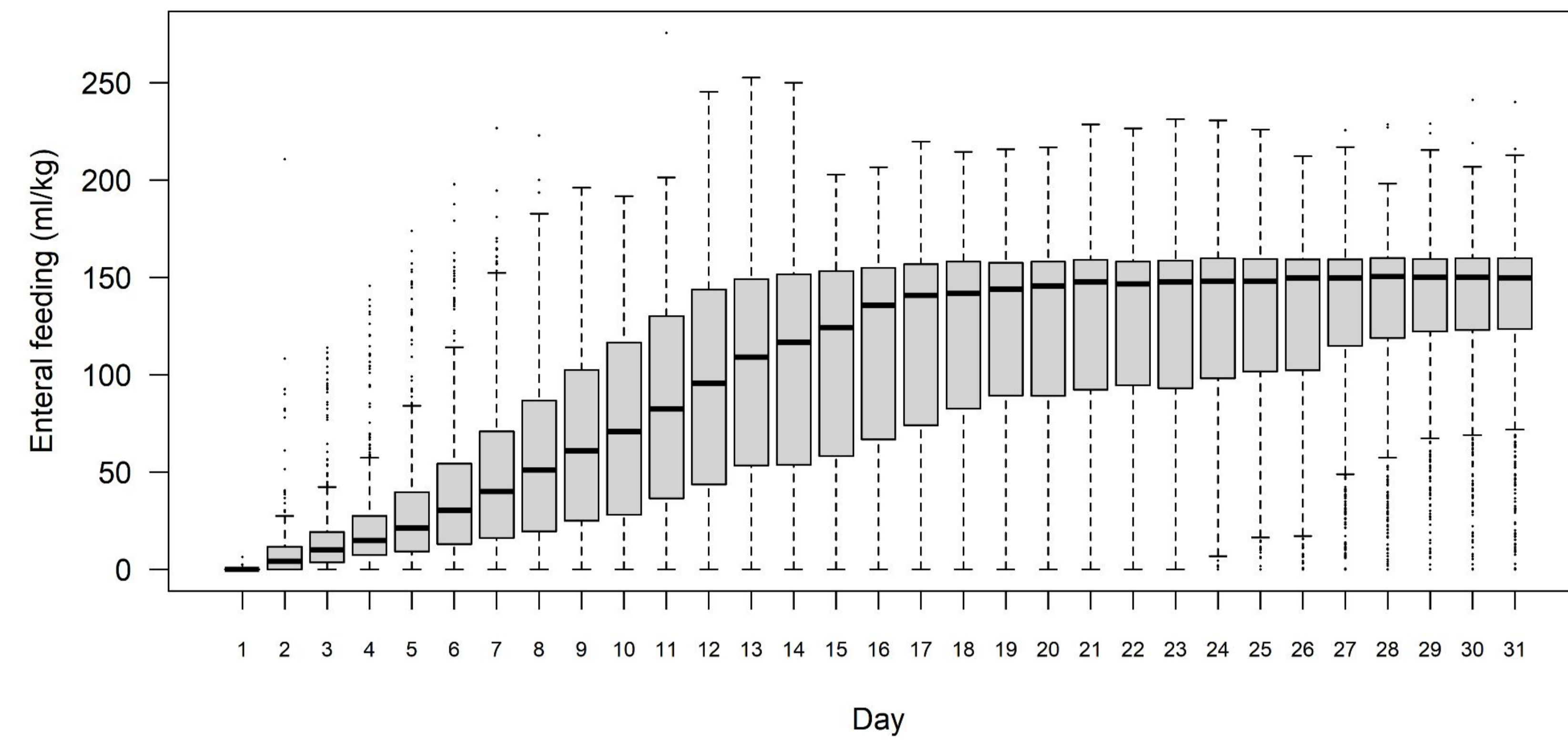


FIGURE 3. Td enteral feeding volumes for infants with (n=17) and without GI perforation.

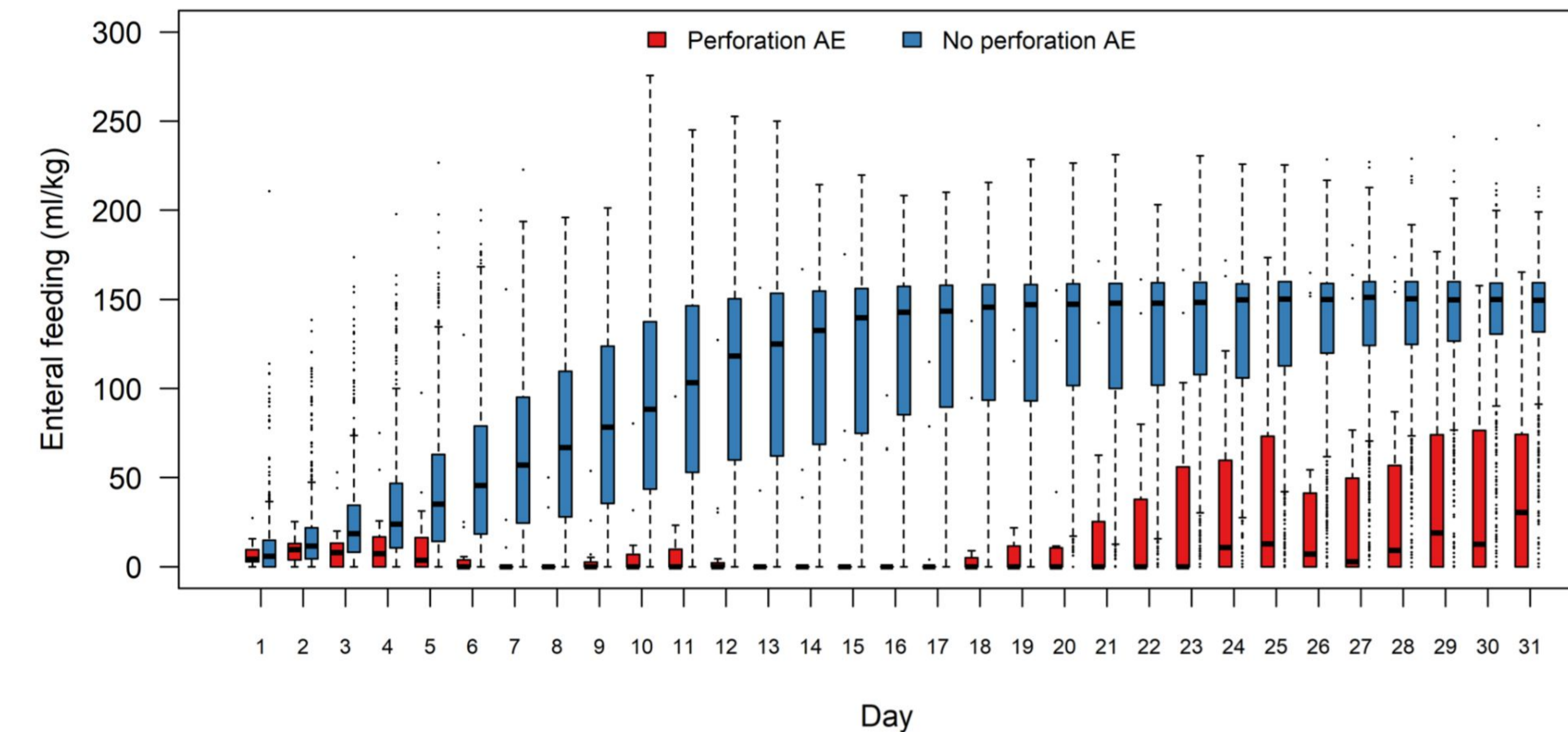


TABLE 1. Hazards ratios (HR) and color-coded statistical significance levels* in the univariable regression model for the association of clinical events with the TD volumes. For 95% confidence intervals, see the abstract print out.

Event	TD ml/kg/day	≥10	≥20	≥40	≥80	≥120	Event	TD ml/kg/day	≥10	≥20	≥40	≥80	≥120
Birthweight (100g interval)		1.13	1.15	1.20	1.18	1.20	AE clinical sepsis		1.20	0.89	0.82	0.72	0.70
GA (week)		1.10	1.15	1.16	1.15	1.17	AE los culture positive		1.17	0.93	0.87	0.73	0.68
Apgar 5-min score		1.08	1.09	1.10	1.11	1.11	Iv. antibiotic treatment (day)		0.993	0.990	0.989	0.981	0.977
In-hospital stay (day)		0.997	0.995	0.992	0.991	0.990	AE PDA		0.81	0.71	0.68	0.67	0.70
Any SAE		0.78	0.71	0.63	0.66	0.69	SAE cardiac		0.71	0.78	0.62	0.72	0.65
SAE GI		0.62	0.47	0.39	0.39	0.48	AE bradycardia		1.13	1.003	1.10	1.07	0.987
Confirmed NEC		0.89	0.77	0.72	0.73	0.70	AE hypotension		0.60	0.42	0.42	0.40	0.47
AE perforation		0.49	0.28	0.22	0.24	0.29	AE cranial bleeding		0.98	0.86	0.82	0.85	0.88
AE obstruction		0.95	0.54	0.54	0.43	0.48	AE ROP		0.87	0.78	0.76	0.85	0.86
Abdominal symptom/sign		0.84	0.76	0.76	0.74	0.74	SAE metabolic		1.07	1.39	1.27	1.58	1.63
SAE respiratory		0.63	0.65	0.68	0.70	0.65	SAE renal		0.68	0.56	0.70	0.83	0.77
AE BPD		0.90	0.91	0.90	0.91	0.86	AE renal		0.79	0.68	0.74	0.74	0.67
AE pneumonia		0.81	0.80	0.79	0.74	0.70							

*color-coded p-values: 0.001, 0.010, 0.025, 0.049, 0.100, 0.250, 0.500, 0.750, 1.000

HR refers to the chance of reaching the specific enteral feeding volume at each day related to a one-unit change in the specific event; AE, adverse event; SAE, serious adverse event defined as e.g., life-threatening, prolonging hospitalization or causing significant incapacity.

TABLE 2. Hazards ratios (HR) with color-coded statistical significance levels* in the stepwise selected multivariable model for the association of clinical events with the chance of reaching total daily enteral (TD) volumes of 10-120 ml/kg. For 95% confidence intervals, please see the abstract print out.

Event	TD ml/kg/day	≥10	≥20	≥40	≥80	≥120
BW (100g interval)		1.06		1.12	1.14	1.13
GA (week)		1.05	1.10	1.06	1.07	1.05
Apgar 5-min score		1.05		1.06	0.987	1.06
In-hospital stay (day)						0.996
SAE GI		0.70		0.64	0.54	0.71
AE perforation			0.32	0.33	0.48	0.54
Abdominal symt/sign			0.73	0.68	0.67	0.65
SAE respiratory		0.76	0.69	0.78	0.79	0.80
Iv. antibiotics (day)			0.997	0.997	0.998	0.983
AE PDA			0.85	0.82		
AE hypotension		0.73	0.51	0.54	0.56	0.66
AE renal event			0.77			

*color-coded p-values: 0.001, 0.010, 0.025, 0.049, 0.100, 0.250

HR refers to the chance of reaching the specific enteral feeding volume at each day related to a one-unit change in the specific event. Variables without HR values are those not recognized as relevant in the stepwise model analysis. AE, adverse event of any seriousness; SAE, serious adverse event defined as e.g., life-threatening, prolonging hospitalization or causing significant incapacity.

KEY CONCLUSION

- The chance of successful early enteral feeding in ELBW infants has been quantified in relation to 25 clinical variables.
- Successful enteral feeding is reduced in infants with GI complications (such as perforation, obstruction and NEC) as well as non-GI events e.g., hypotension, PDA and respiratory compromise.
- Current enteral feeding practices are more cautious than published guidelines.
- The findings lend support that overly cautious progression of enteral feedings may increase risks of serious clinical complications in ELBW infants.

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