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Original article

Exploring the safety of prolonging the hang time of enteral feeding systems in the intensive care unit☆

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SUMMARY

Background & aims: Prolonging the hang time (HT) of administration sets and enteral feeding containers beyond the recommended 24 h may reduce waste, decrease nursing workload and lower hospital costs. The objective of this pilot study was to explore the safety of extending the HT from 24 to 48 h by investigating its impact on the occurrence of diarrhoea and new-onset pneumonia in intensive care unit (ICU) patients.

Methods: This monocenter pilot study had a combined retrospective and prospective cohort (24 and 48-h HT, respectively) design and included ICU patients (≥ 18 years) receiving enteral nutrition for at least 48 h. The primary outcome was diarrhoea, defined as (1) ≥ 3 defecations/day with a Bristol Stool Chart score of 6 or 7, or (2) colostomy/ileostomy output ≥1.5 L/24 h. The secondary outcome was new-onset pneumonia ≥48 h after ICU admission. Associations between HT protocol and the onset of outcomes were assessed by Cox regression analyses. Additionally, retrograde bacterial growth was assessed through microbiological analysis in enteral feeding systems.

Results: A total of 102 ICU patients were included between December 16, 2023 and October 11, 2024, with 51 in each cohort. Actual median HT was 31 [27–45] hours vs. 56 [37–83] hours in the 24 and 48-h groups, respectively ($p < 0.001$). In multivariable Cox regression, no significant association was found between prolonged HT and diarrhoea-free survival (HR 0.92, 95 % CI 0.55–1.53, $p = 0.746$) and new-onset pneumonia (HR 1.33, 95 % CI 0.54–3.24, $p = 0.537$), respectively. Retrograde bacterial growth did not extend beyond the first 30 cm of the administration set and was not correlated to HT.

Conclusion: We observed no association between prolonging the HT of enteral feeding sets from 24 to 48 h and the occurrence of diarrhoea or new-onset pneumonia in ICU patients. However, a substantial, adequately powered, non-inferiority trial must be conducted prior to integrating extended hang times into clinical practice.

1. Background

There is an increasing recognition of the pivotal role that nutrition plays in critically ill patients [1]. Therefore, enteral nutrition (EN) is frequently initiated within 48 h when oral nutrition is not feasible [2,3]. The delivery of EN is facilitated by an enteral tube feeding system (ETFS) comprising a gastric feeding tube, an administration set, and a feeding container (Supplementary Fig. 1) [4]. The *Safe Practices for Enteral Nutrition Therapy* guidelines by the American Society for Parenteral and Enteral Nutrition (ASPEN) state that closed enteral feeding containers may remain used for up to 48 h. However, in practice, the

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Abbreviations:

Term	Explanation
APACHE II	Acute Physiology and Chronic Health Evaluation II
BMI	Body Mass Index
CFU	Colony forming units
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-reactive protein
ETFS	Enteral tube feeding system(s)
EN	Enteral nutrition
HR	Hazard ratio
HT	Hang time(s)
ICU	Intensive care unit
MV	Mechanical ventilation
MRSA	Methicillin-resistant Staphylococcus aureus
NICE	National Institute for Health and Care Excellence
mNUTRIC	Modified Nutritional Risk in the Critically Ill
PCA	Plate count agar
PDMS	Patient Data Management System
RR	Relative risk
SOD	Selective Oral Decontamination
SOFA	Sequential Organ Failure Assessment
VAP	Ventilator-Associated Pneumonia
VIF	Variance inflation factor

feeding container and the administration set of the ETFS are often discarded after 24 h in accordance with manufacturer recommendations to change the ETFS daily [5,6]. Extended utilisation of ETFSs may result in a substantial reduction in plastic waste, care time, and costs. For instance, extending the hang time (HT) from 24 h to 36 h can reduce formula loss by 225–450 ml per day and a corresponding decrease in the utilisation of four to nine prick sets per month [7]. This waste reduction can generate annual savings of up to $2,000 per patient for the hospital, in addition to a decrease in its environmental impact [7]. Concurrently, it has the potential to alleviate the workload burden on nurses, particularly in contexts where task fatigue is prevalent, which has been associated with an increase in nurse attrition [8,9].

However, prolonging the HT may increase the risk of microbial infections for ICU patients. Diarrhoea, for example, is a prevalent condition among critically ill patients [10,11] and may be precipitated by microbial contamination of the ETFS. In a study of ICU patients, microbial contamination was found in 4 % of the feeding bottles and in 74 % of the administration sets, with contamination of the administration sets increasing over time and at a faster rate, primarily due to retrograde growth of endogenous bacteria [12,13]. The pathogenesis of diarrhoea in critically ill patients is multifactorial and likely involves gastro-intestinal infections, high osmolality containing enteral feeding formulas, medications, and alterations in gastric acid secretion, the gut microbiome and mucosal integrity [14–16]. Prolonged HT may allow for the retrograde growth of bacteria and the formation of biofilms within the ETFS, potentially exacerbating gastrointestinal symptoms such as diarrhoea. Diarrhoea, in turn, increases the risk of further complications such as dehydration, electrolyte imbalances, malnutrition, and prolonged ICU stays, and may ultimately contribute to increased mortality and morbidity [11,14,17]. Previous work in non-critically ill patients found a lower risk of diarrhea in the 24h HT group compared to the 72/96h HT group [18]. However, this prolonged duration of HT may have been too rigorous, since previous research has shown that the average time from potential initial contamination to final culture was approximately 50 h, and the authors of that study considered an HT of up to 48 h to be safe [19].

Extended HT may also increase the risk of pneumonia, as EN has been linked to a higher incidence of pneumonia compared to other feeding methods during critical illness [20,21]. This increased risk may be attributed to EN increasing gastric pH, potentially allowing gut bacteria to translocate and infect the lungs [22]. However, the effect of prolonging the HT of ETFS on the development of pneumonia is unknown.

Therefore, the primary aim of this pilot study was to investigate the effect of prolonging the HT of ETFSs from 24 h to 48 h on the occurrence and duration of diarrhoea in ICU patients. Additionally, we assessed the effect of the prolonged HT protocol on the occurrence of new-onset pneumonia and investigated retrograde microbiological growth in gastric feeding tubes and administration sets to gain insight into the safety of prolonging HT in the ICU.

2. Method

2.1. Study design

This monocenter pilot study was conducted in a combined retrospective and prospective cohort. The prospective cohort commenced on April 12, 2024, when the HT of the ETFS was increased from 24 h to 48 h, and continued until October 11, 2024 (a 6-month screening period). The retrospective cohort included an equal number of patients, screened starting from April 7, 2024, going back to those admitted as early as December 16, 2023, when the HT of the ETFS was 24 h. We adopted a retrospective–prospective design since our ICU had already implemented the 48-h hang time, making this the most feasible and valid method to evaluate the intervention. Moreover, a randomized trial could have introduced bias, as knowledge of group allocation might have influenced nursing practices.

2.2. Study participants

Consecutive adult patients (≥18 years) who received ≥48 h of enteral tube (pre- and post-pyloric) feeding during their ICU stay were included in this study. All patients who likely suffered from diarrhoea due to known underlying comorbidities, such as inflammatory bowel disease, chronic pancreatitis, pancreatic exocrine insufficiency, intestinal ischemia, prior bariatric surgery, and bowel motility disorder, were excluded from the study. In addition, patients with gastroenteritis or high colostomy output at ICU admission were excluded.

2.3. Data Collection

Collected characteristics at ICU admission included age, sex, anthropometric measurements (admission weight, height, Body Mass Index (BMI)), substance usage (smoking, alcohol, drugs), comorbidities and type of ICU admission [23]. Other collected data included the Acute Physiology and Chronic Health Evaluation (APACHE) II and IV scores, the Sequential Organ Failure Assessment (SOFA) score, the Barthel Index for Activities of Daily Living (Barthel) score, the Rockwood Clinical Frailty score, and modified Nutritional Risk in the Critically Ill (mNUTRIC) score. Pneumonia was diagnosed based on physician clinical suspicion, which included the presence of new, progressive, or persistent chest infiltrates and microbiological confirmation when available, as outlined in the international guidelines [24]. In addition, influenza (PCR confirmed), and sepsis (according to the Sepsis-3 criteria) were recorded [25]. During the ICU stay, the length of stay, duration of mechanical ventilation (both invasive and non-invasive), and ICU mortality were recorded.

The tube feeding formula was calculated automatically by the patient data monitoring system (PDMS, MetaVision system (iMDsoft, Tel Aviv, Israel)) based on the patient's energy and protein requirements. The available enteral feeding formulas in our ICU included Jevity (1.2 kcal, Plus, Plus HP, 1.5 kcal), Nutrison Protein Intense, Nepro HP 1.8 kcal, and Peptamen (including Peptamen HN). All formulas were commercially prepared, sterile products. At our ICU, patients started at 25 % of the calculated protein and energy target, which was then increased by 25 % each day to reach the full target after four days. In addition, the time to initiation of tube feeding after ICU admission, the average daily volume of tube feeding, the duration of gastric tube placement, and the average HT of the feeding container and administration set were recorded. The HT of the feeding containers was recorded during the first 96 h of the ICU stay when EN was gradually increased, and throughout the entire ICU stay. The incidence of gastric residual volume >500 ml (measured three times a day), use of medications during ICU stay that could influence diarrhoea (antibiotics, laxatives, constipating medications, gastric acid suppressants, and electrolyte supplements [26,27]) and microbiological PCR testing of faeces were also recorded. Routine stress ulcer prophylaxis was administered to all invasively mechanically ventilated patients, in line with current international recommendations, and continued in those already using proton pump inhibitors at home [28]. Our ICU implements selective oral decontamination for mechanically ventilated patients, but selective digestive decontamination is not used. Faecal cultures were obtained based on the attending physician's clinical judgment in cases of suspected infectious diarrhoea.

All parameters were collected as part of standard hospital care from the ICU's PDMS (MetaVision; iMDsoft, Tel Aviv, Israel) and hospital electronic medical records (NEXUS EPD; Nexus, Vianen, the Netherlands). Patients were followed for a maximum of 30 days or until discharge from the ICU.

2.4. Microbiological investigation

Concurrent with the implementation of the prospective cohort, both gastric tubes and administration sets were collected for study purposes when removed by nursing staff during tube replacement or patient discharge. The gastric tubes and administration sets were stored in a freezer at −20 °C to prevent further bacterial growth. After collection, retrograde growth was analysed according to the laboratory protocol in Supplementary Information 1. The administration sets were cut into 20 cm pieces, swabbed and plated on Plate Count Agar (PCA) plates. After three days of incubation at 30 °C, the plates were examined for bacterial growth (in terms of the average number of colony-forming units (CFU)) and the extent of retrograde bacterial progression. Undesirable contamination was defined as greater than 10,000 CFU per PCA and marginal contamination between 1,000 and 10,000 [29]. For the ETFS collected, the length of time (h) the feeding set was used, the number of times it was aspirated and the volume aspirated were recorded. In addition, bacterial growth was determined by microscopic inspection, catalase and oxidase tests and Gram staining, which allowed the identification of genera but not specific bacterial species.

2.5. Study outcomes

The occurrence of diarrhoea was the primary outcome of this study and was defined in this study as three or more loose or liquid evacuations, a Bristol stool chart of six or seven per calendar day or a high colostomy or ileostomy output (1.5 L per 24 h), according to the World Health Organisation definitions [10,30,31]. To account for the effects of an enema, any evacuation occurring within an hour of enema use was excluded from the scoring of diarrhoea occurrence. To investigate the effect of a prolonged HT on diarrhoea occurrence, the following primary outcome measures were gathered: the occurrence of diarrhoea, the number of days between ICU admission and the onset of diarrhoea, and the number of days with diarrhoea. The number of (positive) faecal cultures performed was also collected for both groups.

The secondary outcome was the occurrence of new-onset pneumonia, which was scored in case of a pneumonia occurring ≥48 h after ICU admission, including ventilator-associated pneumonia (VAP) in patients receiving invasive mechanical ventilation ≥48 h [32] and at clinical suspicion of the treating physician. In addition, the number of days between start of EN and the occurrence of new-onset pneumonia was recorded. Patients with pneumonia at ICU admission were excluded from this analysis.

The tertiary outcomes were retrograde bacterial growth in the gastric tubes and administration sets, which were defined as the maximal distance in cm from the patient's side of the gastric tube and administration set, and the average bacteria count, which was calculated by dividing the CFU of all the plates by the number of plates upon which bacteria grew.

2.6. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 29 and R version 4.4.1. Categorical data was presented as counts alongside percentages. Continuous data was presented as either mean with standard deviation or median with interquartile range [IQR] in case of non-normal distribution. Baseline and outcome differences were compared using the Chi-Square or Fisher exact test for categorical variables, independent sample t-test for normally distributed continuous data, and Mann–Whitney U test for continuous data with non-normal distributions.

Cumulative diarrhoea-free and new-onset pneumonia-free survival data were presented in Kaplan–Meier curves. Multivariable Cox regression models were constructed to determine associations between the HT protocol and the development of diarrhoea and new-onset pneumonia. Only covariates with less than 10 % missing data were considered for inclusion in the models. Candidate variables for the multivariable model were selected if they showed an association with the outcome at $p < 0.20$ in univariate Cox regression analysis. Based on prior literature, two risk factors, receipt of enteral feeding formulas with high osmolarity [10,33] (defined as receiving at least one of the formulas Nepro HP 1.8 kcal, Jevity 1.5 kcal, or Jevity Plus during ICU stay) and higher age [34,35], were also included as covariates in the multivariable model for diarrhoea. For the analysis of new-onset pneumonia, which was conducted as a subanalysis in a smaller subset, no risk factors were forced into the model by default. Instead, all candidate risk factors, including ventilator treatment (a risk factor for pneumonia [36,37]), were considered for inclusion through the stepwise selection process. To avoid overfitting, the number of covariates was restricted according to the one-in-ten rule. Covariates suggestive of multicollinearity (Variance Inflation Factor >5), or violating the proportional hazards assumption (as assessed by Schoenfeld residuals), were excluded from the models. Stepwise selection was used to identify the final set of covariates for inclusion in the multivariable model.

Spearman correlation tests investigated correlations between retrograde growth, average bacteria counts, time spent in situ of the gastric tube, HT of the administration sets, the number of times siphoned, and the total volume siphoned. A significance level of $p < 0.05$ was considered statistically significant for all statistical tests performed.

As this was a pilot study, it was pre-specified that a sample size calculation for a non-inferiority study would be performed using a non-inferiority margin of 10 %, an alpha of 0.05, and a beta of 0.20 (corresponding to 80 % power). This calculation was conducted in R (version 4.4.1).

3. Results

A total of 550 ICU patients who received enteral feeding were screened, 276 retrospectively and 274 prospectively (Fig. 1). Ultimately, 51 patients in each group met the inclusion and exclusion criteria within the study's timeframe (Fig. 1).

There were no differences between the two groups regarding demographic and laboratory parameters at baseline (see Table 1). However, patients in the 24-h HT group compared to the 48-h HT group had more pneumonia (28 patients (55 %) vs. 14 patients (28 %), $\boldsymbol{p} = \mathbf{0.009}$) and influenza positive PCR (11 patients (22 %) vs. 2 patients (4 %), $\boldsymbol{p} = \mathbf{0.015}$) at ICU admission.

Both groups had similar ICU length of stay, with a median of 7 days [5–12] in the 24-h HT group and 7 days [5–11] in the 48-h HT group ($p = 0.833$) (see Table 2). While patients in the 24-h HT group more often received invasive mechanical ventilation than those in the 48-h HT group (54.9 % vs. 35.3 %, $p = 0.016$), patients in the 48-h HT group more often received non-invasive mechanical ventilation than those in the 24-h HT group (54.9 % vs. 35.3 %, $p = 0.047$).

The HT of the administration sets was shorter in the 24-h HT group compared to the 48-h HT group (median 31 h [27–45] vs. median 56 h [38–83], $p < 0.001$). However, there was no difference between the groups in the HT of the feeding containers over the entire ICU stay or during the first 96 h of ICU admission.

3.1. Diarrhoea occurrence

There was no significant difference in diarrhoea occurrence between the 24h and 48 ETFS HT groups (33 patients (64.7 %) vs. 37 patients (72.5 %), $p = 0.393$), as shown in Table 3. There was no significant difference in time to diarrhea onset between the 24-h versus 48-h group (median 3 [3–5] vs. 5 [3–6] days, $p = 0.269$), nor in the total number of diarrhoea days between groups (2 [1–4] vs. 2 [1–4], $p = 0.624$). Comparison of Kaplan–Meier curves between the 24-h and 48-h HT groups revealed no difference in diarrhoea-free survival between the prolonged HT groups (log-rank test, $p = 0.979$; see Supplementary Fig. 2). In addition, multivariable Cox regression analysis showed no significant association between prolonged HT and diarrhoea-free survival (HR 0.92, 95 % CI 0.55–1.53, $p = 0.746$) after adjustment for the covariates age, BMI, pneumonia, immunological insufficiency at baseline, and EN formula with high osmolality (Fig. 2, Supplementary Table 1). There was no difference in the number of positive microbiological tests in faecal samples between the 24 and 48h HT group (1 vs 1, respectively, $p = 1.000$). In both groups, there was one patient who was a methicillin-resistant Staphylococcus aureus (MRSA) carrier; neither received additional antibiotics for this.

3.2. New-onset pneumonia

There was no significant difference in the occurrence of new-onset pneumonia between the 24 and 48-h HT groups (9/28 patients (32.1 %) vs. 12/38 patients (31.6 %), $p = 0.961$; Table 3). However, pneumonia occurred significantly earlier after the start of EN in the 48-h HT group than in the 24-h HT group (median 2 [1–3] vs. 4 [3–9] days, $p = 0.018$). There was no significant difference between the groups in the incidence of VAP, which occurred in 6/23 (26.1 %) of patients in the 24-h group and 9/25 (36.0 %) in the 48-h group ($p = 0.232$). Kaplan–Meier curves for new-onset pneumonia-free survival were not statistically different between the 24h and 48h HT group; see Supplementary Fig. 3 (log-rank test, $p = 0.741$). Furthermore, after adjustment for the covariate renal insufficiency, multivariable Cox regression analysis showed no significant association between prolonged HT and new-onset pneumonia-free survival (HR 1.33, 95 % CI 0.54–3.24, $p = 0.537$) (Supplementary Table 2, Supplementary Fig. 4).

3.3. Microbiological investigation

A total of eight gastric tubes were collected (Supplementary Table 3). Bacterial growth was observed in all gastric tubes left

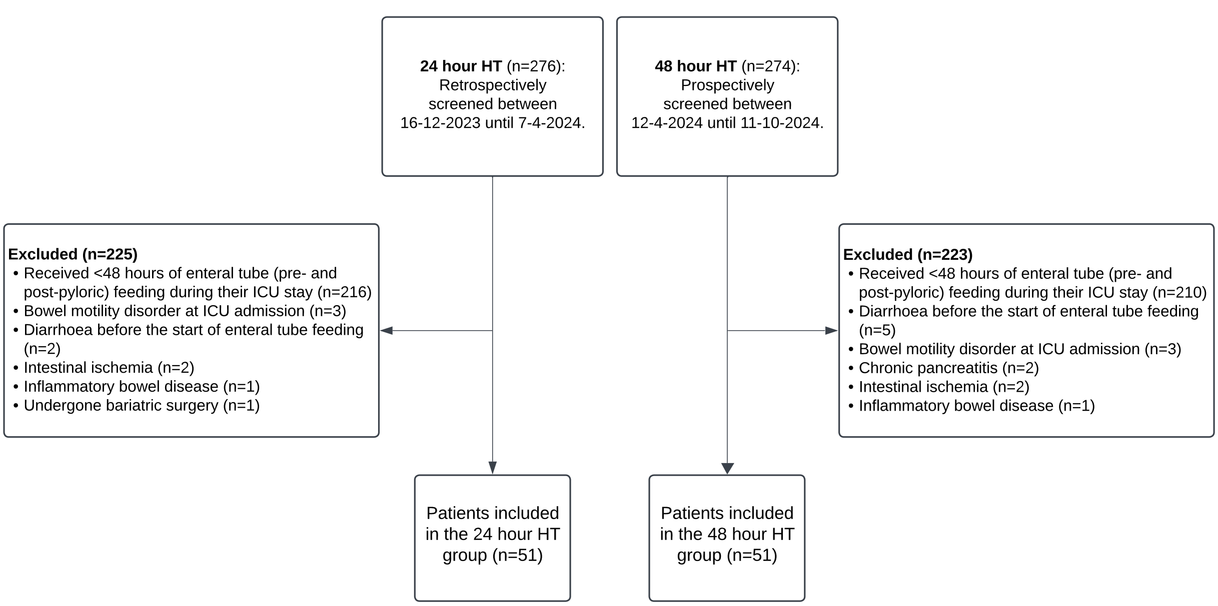

Fig. 1. Flow chart.

Table 1
Baseline characteristics of both groups at ICU admission.

Characteristic	24-h HT (n = 51)	48-h HT (n = 51)	p-value
Demographics			
Age, years	70 [65–76]	66 [56–75]	0.186
BMI, kg/m^2	27.1 [24.4–29.7]	27.1 [23.5–31.7]	0.802
Sex, male	27 (52.9 %)	32 (62.7 %)	0.423
Substance usage[a]			
Alcohol	29/49 (59.2 %)	14/31 (45.2 %)	0.225
Smoking	12/47 (25.5 %)	9/36 (25.0 %)	1.000
Drugs	1/50 (2.0 %)	3/30 (10.0 %)	0.291
Comorbidities			
Metastatic cancer	4 (7.8 %)	2 (3.9 %)	0.678
Hematologic cancer	2 (3.9 %)	1 (2.0 %)	1.000
Diabetes	17 (33.3 %)	12 (23.5 %)	0.380
COPD	14 (27.5 %)	9 (17.6 %)	0.343
Chronic cardiovascular insufficiency	8 (15.7 %)	9 (17.6 %)	1.000
Immunological insufficiency	12 (23.5 %)	4 (7.8 %)	0.054
Chronic renal insufficiency	2 (3.9 %)	5 (9.8 %)	0.436
Colostomy	1 (2.0 %)	4 (7.8 %)	0.362
Reason for ICU admission			0.486
Medical	42 (82.4 %)	45 (88.2 %)	
Elective surgery	2 (3.9 %)	3 (5.9 %)	
Emergency surgery	7 (13.7 %)	3 (5.9 %)	
Diagnosis at ICU admission			
Pneumonia	28 (54.9 %)	14 (27.5 %)	**0.009**
Sepsis	33 (64.7 %)	23 (45.1 %)	0.073
Influenza PCR positive	11 (21.6 %)	2 (3.9 %)	**0.015**
Clinical characteristics			
mNUTRIC score ($n = 98$)	5 ± 2	5 ± 2	0.905
APACHE II score ($n = 101$)	23 [17–30]	24 [19–31]	0.582
APACHE IV score ($n = 101$)	80 [62–106]	80 [68–98]	0.744
SOFA score	8 ± 4	8 ± 4	0.893
Barthel index ($n = 98$)	20 [19–20]	20 [18–20]	0.340
Clinical frailty score ($n = 70$)	3 [2–7]	5 [2–6]	0.525
Lab values			
Creatinine, μmol/L	83 [58–134]	85 [62–147]	0.581
CRP, mg/L	92 [14–198]	19 [4–152]	0.129
WBC count, x10^9	13.4 [8.7–17.5]	12.5 [9.1–16.7]	0.971

Data are presented as mean ± SD, median [IQR], or number (%), as appropriate. Abbreviations: Body mass index (BMI), Chronic Obstructive Pulmonary Disease (COPD), modified Nutrition Risk in the Critically Ill score (mNUTRIC score), Acute Physiologic assessment and Chronic Health Evaluation (APACHE), Sequential Organ Failure Assessment (SOFA), C-Reactive Protein (CRP), White Blood Cell (WBC). Reason ICU admission and Comorbidities diagnoses were made based on the guidelines of the National Institute for Health and Care Excellence (NICE).

[a] Data on alcohol use were missing for 22 patients (2 in the retrospective cohort and 20 in the prospective cohort), smoking status was missing for 19 patients (4 retrospective, 15 prospective), and drug use data were missing for 22 patients (1 retrospective, 21 prospective).

in situ for more than 48 h ($n = 6$), whereas no bacterial growth was detected in gastric tubes left in situ for shorter periods ($n = 2$). HT was positively correlated with retrograde growth (r = 0.764, p = 0.027) and average bacterial count (r = 0.826, p = 0.011) in the gastric tubes. The most common bacterial genera found in the gastric tubes were *Staphylococcus* ($n = 6$) and *Streptococcus* ($n = 3$).

Six administration sets were collected (Supplementary Table 4). In all administration sets, retrograde growth did not extend beyond the first 30 cm of the administration set (on the distal side), regardless of HT. The most common bacterium found in the administration sets was *Staphylococcus* ($n = 4$). A wide range of bacterial counts was observed, from no growth to over 300 CFU. However, no correlation was found between HT or total volume given over administration sets, and retrograde growth, or the average bacterial count.

4. Discussion

In this monocenter pilot study combining both retrospective and prospective cohort data of enterally tube-fed ICU patients, we explored the safety of extending the HT of ETFS from 24 h to 48 h by investigating the incidence and duration of diarrhoea and hospital-acquired pneumonia. Our results showed no significant difference between prolonged HT and the occurrence of diarrhoea and new-onset pneumonia. In microbiological analysis, the duration of the gastric tube in situ, but not the HT of the administration set, was positively correlated to retrograde growth in the materials.

4.1. Diarrhoea

Manufacturers typically recommend a 24-h HT for ETFS. While extending hang time may carry potential sustainability benefits, its safety must be established before such benefits can be realized. Diarrhoea remains a key concern, as it can offset these benefits by increasing morbidity, prolonging ICU stays, and adding to the overall healthcare burden [11,14,17]. In our sample of enterally fed critically ill patients, we found a high occurrence rate of diarrhoea of 69 %, which is in line with a previous observation in the ICU [33]. However, there was no significant difference in the occurrence rate of diarrhoea between the conventional and extended HT of ETFS, nor a significant association between diarrhoea-free survival and prolonged HT. A study by Arevalo-Manso et al. found that a shorter HT of 24 h (n = 103), compared to 72–96 h (n = 72), was associated with a lower frequency of diarrhoea (13.6 % vs. 34.7 %, RR: 0.39, 95 % CI: 0.22–0.70, p = 0.001), lower incidence (RR = 0.37, 95 % CI: 0.19–0.72, p = 0.004), and longer diarrhoea-free survival (HR = 0.27, 95 % CI: 0.12–0.61, p = 0.002) in hospitalised, non-

Table 2
ICU stay characteristics and outcomes of study groups.

Outcome	24-h HT (n = 51)	48-h HT (n = 51)	p-value
Medication use, n (%)			
Macrogol (polyethylene glycol)	50 (98.0 %)	50 (98.0 %)	1.000
Lactulose	0 (0.0 %)	2 (4.0 %)	0.495
Phosphate drink	35 (68.06 %)	34 (63.3 %)	0.832
Antibiotics	48 (94.1 %)	48 (94.1 %)	1.000
SOD mouth paste	38 (74.5 %)	31 (60.8 %)	0.138
Proton pump inhibitors	50 (98.0 %)	47 (92.2 %)	0.362
H2 inhibitors	2 (4.0 %)	0 (0.0 %)	0.495
Sodium sulphate	1 (2.0 %)	2 (3.9 %)	1.000
Enteral feeding			
Prepyloric feeding	50 (98.0 %)	50 (98.0 %)	1.000
Postpyloric feeding	2 (3.9 %)	1 (2.0 %)	1.000
Time to enteral feeding, hours	13 [6–23]	15 [5–28]	0.497
Daily enteral feeding volume, ml	874 ± 316	775 ± 321	0.119
High osmolality nutrition, n (%)	35 (68.6 %)	24 (47.1 %)	**0.044**
GRV >500 ml**, n (%)**	6 (11.8 %)	8 (15.7 %)	0.565
Gastric tube in SITU, hours	152 [103–282]	141 [93–242]	0.232
Feeding container HT, hours	14 [12–16]	14 [12–17]	0.416
Feeding container HT in the first 96 h of enteral feeding, hours	16 [14–19]	16 [14–19]	0.269
Administration system HT, hours	31 [27–45]	56 [37–83]	**<0.001**
Faecal cultures, n (%)	9 (17.6 %)	11 (21.6 %)	0.804
Positive faecal cultures	1/9 positive for Norovirus (11.1 %)	1/11 positive for *Campylobacter* (9.1 %)	1.000
MV			
Non-invasive MV**, n (%)**	18 (35.3 %)	28 (54.9 %)	**0.047**
Duration, hours	12 [44–68]	34 [11–83]	0.118
Invasive MV**, n (%)**	42 (82.3 %)	31 (60.8 %)	**0.016**
Duration, hours	119 [44–241]	91 [35–172]	0.269
LOS			
Length of ICU stay, days	7 [5–12]	7 [5–11]	0.883
Mortality			
Mortality ICU**, n (%)**	13 (25.5 %)	8 (15.7 %)	0.221

Data are presented as mean ± SD, median [IQR], or number (%), as appropriate. Abbreviations: hang time (HT), high protein (HP), Intensive Care Unit (ICU), Gastric Residual Volume (GRV), in place (in SITU), mechanical ventilation (MV), selective oral decontamination (SOD).

Table 3
Clinical outcomes in 24-h and 48-h HT groups.

Outcome	24-h HT	48-h HT	p-value
Diarrhoea	n = 51	n = 51	
Diarrhoea occurrence	33 (64.7 %)	37 (72.5 %)	0.393
Diarrhoea rate per 1,000 ICU days[a]	66	80	
Days between ICU admission and occurrence of diarrhoea (n = 70)	3 [3–5]	5 [3–6]	0.269
Diarrhoea duration, days (n = 70)	2 [1–4]	2 [1–4]	0.624
Occurrence of new-onset pneumonia[b]	**n = 28**	**n = 38**	
New-onset pneumonia	9 (32.1 %)	12 (31.6 %)	0.961
New-onset pneumonia rate per 1,000 ICU days[a]	35	35	
VAP[c]	6/23 (26.1 %)	9/25 (36.0 %)	0.232
VAP rate per 1,000 IMV days[d]	34	52	
Days between start of enteral feeding and occurrence of pneumonia (n = 21)	4 [3–9]	2 [1–3]	**0.018**

Data are presented as median [IQR], or number (%), as appropriate. Abbreviations: Intensive Care Unit (ICU), Invasive Mechanical Ventilation (IMV), Ventilator-acquired pneumonia (VAP). For all patients who developed diarrhoea, the number of days between ICU admission and the onset of diarrhoea and the duration of diarrhoea in days were recorded.

[a] Diarrhoea rate and new-onset pneumonia rate were calculated by dividing the number of patients experiencing the event by the total number of ICU days in the respective cohort, and then multiplying by 1,000 to express the rate per 1,000 patient-days.

[b] Patients with baseline pneumonia were excluded from the pneumonia outcome unless it was explicitly documented that the baseline pneumonia had been fully treated and the patient had developed new hospital-acquired pneumonia, resulting in 28 patients being included in the 24-h hang time group and 38 in the 48-h group for this analysis.

[c] Ventilator-associated pneumonia was only recorded if invasive mechanical ventilation was used, which applied to 23 patients in the 24-h hang time group and 25 patients in the 48-h hang time group. The number of days between the start of enteral feeding and the occurrence of pneumonia was only recorded for patients who developed pneumonia.

[d] VAP rate was calculated by dividing the number of patients with ventilator-associated pneumonia by the total number of days on invasive mechanical ventilation in the respective cohort, and then multiplying by 1,000 to express the rate per 1,000 IMV days.

critically ill patients [18]. A study by Luft et al. found that hospitalised adult patients with lower adherence to the recommended 24-h administration set replacement protocol (adherence ≤75 % of days during follow-up) had a higher incidence of diarrhoea compared to those with higher adherence (>75 %), but this was near significant (19.8 % vs. 5.9 %, $p = 0.05$) [34]. However, the difference in the mean HT of administration sets between groups was not reported. The higher incidence of diarrhoea in our cohort compared to previous studies in non-ICU patients may be attributed to differences in the study population. Critically ill patients

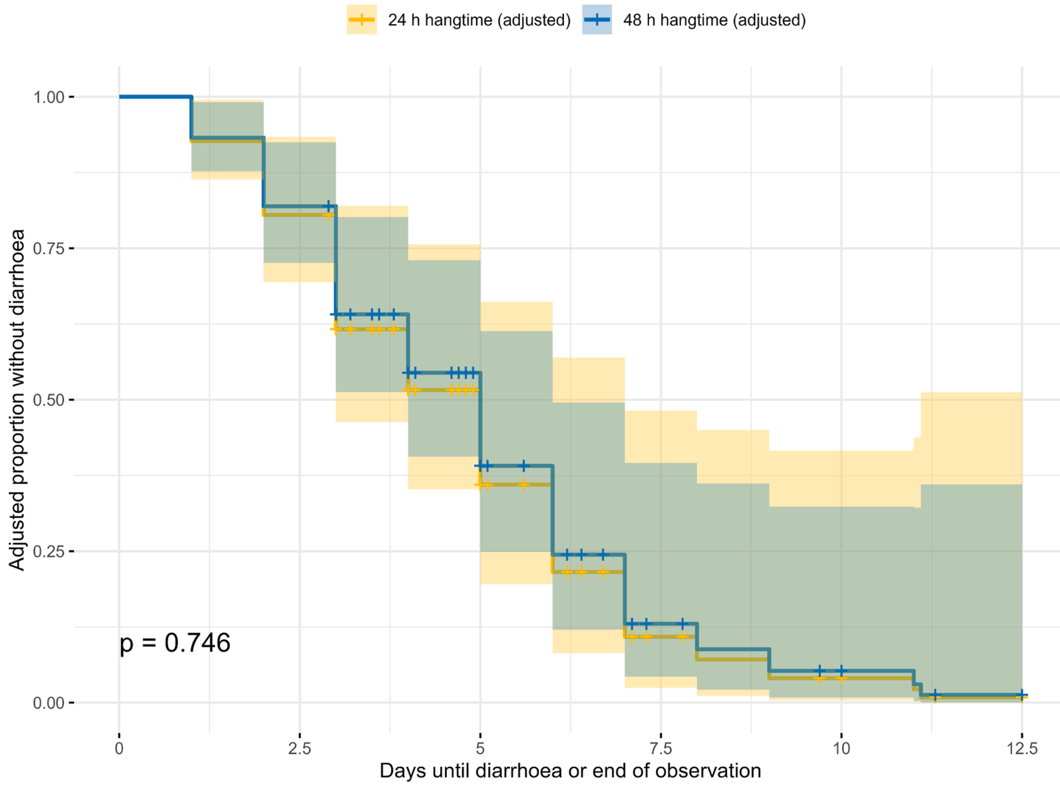

Fig. 2. Cumulative Diarrhoea-Free Survival Curve Adjusted for Cox Proportional Hazards Model in 24-Hour vs. 48-Hour Hangtime Groups
Cumulative diarrhoea-free survival curve adjusted for the Cox proportional hazards model comparing the risk between 24-h (n = 51) and 48-h (n = 51) hangtime groups. Covariates included in the model are listed in Supplementary Table 1.

are more vulnerable to develop diarrhoea due to factors such as medication exposure (e.g., antibiotics and laxatives), systemic inflammation, and gut-related organ dysfunction [10,17,38,39], which limits the extrapolation of our results to other hospital settings. Multivariable Cox regression analysis also showed that immunological insufficiency was a significant covariate for the development of diarrhoea, which is consistent with the known increased risk of severe gastrointestinal infections in immunocompromised patients [40]. However, even in these patients, it may be possible to extend the HT to 48 h, as research in immunocompromised patients found that a HT of up to 48 h, which in practice ranged from 10 to 35 h within that study, did not result in bacterial growth or nosocomial infections associated with contamination of ETFS [41]. Of note, in both cohorts the median actual HT of the administration sets exceeded the protocol of 24 and 48h (31h [IQR 27–45] and (56h [IQR 38–83], respectively). However, these findings align with clinical practice and the actual HT was significantly longer in the prospective cohort.

4.2. New-onset pneumonia

In the subset of patients that were admitted to the ICU without pneumonia, we observed new-onset pneumonia in 32 %, with the majority being potentially ventilator-associated. VAP occurs in approximately one-third of mechanically ventilated ICU patients and is associated with prolonged mechanical ventilation and ICU stay [42]. Risk factors for new-onset pneumonia during an ICU stay include elevated gastric pH related to continuous nasogastric nutrition [22], which may facilitate the translocation of intestinal bacteria. Bacterial overgrowth in gastric feeding administration sets could exacerbate this phenomenon. However, we found no significant difference between prolonging the delivery set HT from 24 to 48 h and the incidence of new-onset pneumonia. Remarkably, the prolonged HT group developed new-onset pneumonia sooner after the start of EN than the conventional HT group. A possible explanation could be that the prolonged HT increases exposure to pathogens in the gastrointestinal tract, which, upon aspiration, leads to an earlier onset of pneumonia.

4.3. Microbiological investigation

This study also examined microbial contamination of the feeding system, as prolonged HT may promote endogenous bacterial growth and biofilm formation within delivery sets. Research has shown that biofilms can form on nasogastric tubes within one day [43,44]. These biofilm-associated organisms can become detached from the nasogastric tube, potentially leading to symptoms such as diarrhoea or even systemic infection [45]. The genera detected in microbiological analysis include pathogenic organisms, suggesting potential biofilm formation, which can serve as a reservoir for infection. Nevertheless, retrograde growth in the gastric tubes extended throughout the entire tube length (120 cm), whereas contamination in the administration sets was confined to the first 30 cm adjacent to the gastric tubes. Given the total administration set length of 210 cm, this finding indicates that contamination is not in close proximity to the feeding container. Furthermore, five out of six average CFU counts in the administration sets were ≤100 CFU, which is well below the unacceptable CFU limit of 10^4 CFU/g per food product [46,47]. This study found no correlation between administration set HT and retrograde growth or CFU count, consistent with previous observations. A study performed by Vanek et al. found that all 14 closed system feeding bags with HT ranging from 22 to 47 h were sterile, except for one bag, which was likely contaminated due to the addition of methylene blue dye used for detecting aspiration [48]. Similarly, a lab-based study by Moffitt et al. found no contamination beyond the drip chamber in administration sets with an hangtime of 36–48 h [7]. These findings support the safety of current closed enteral feeding practices and suggest that observed contamination likely arises from a patient-derived retrograde flow rather than a systemic failure of feeding systems or prolonged HT.

4.4. Strengths & limitations

Our study was the first pilot study to compare a 24-h and 48-h ETFS HT protocol in critically ill patients. One strength of this study is its comprehensive scope of outcome measures, including both diarrhoea and new-onset pneumonia. Additionally, collecting gastric tubes and administration sets provided valuable insight into bacterial growth, offering a microbiological perspective that strengthens the clinical findings. However, this study has several limitations. First, this study was conducted in a small, monocenter-derived sample, which limits statistical power and generalizability. Second, using two consecutive cohorts rather than a randomised controlled design introduces a risk of bias, particularly due to potential seasonal effects. These baseline imbalances may have introduced residual confounding, underscoring the need for a randomized controlled trial to confirm these findings. Microbiological analyses were limited by the small number of collected ETFS, the absence of a negative control, and identification restricted to the genus level. These limitations prevented a comprehensive statistical assessment and hindered distinction between endogenous (patient-derived) and exogenous (environmental) sources.

4.5. Future recommendations

Based on the findings of this pilot study, a large, well-powered, multicentre non-inferiority trial is warranted to evaluate the safety of prolonging hang time in ICU patients. Assuming a non-inferiority margin of 10 %, $\alpha = 0.05$ and 80 % power, at least 5,465 patients per group would be required. Future studies should also investigate the full range of potential implications of extending enteral feeding hang time, including effects on nursing workload, healthcare costs, and overall patient care. Importantly, microbiological analyses with species-level identification and negative controls are strongly recommended to better establish contamination sources and assess potential risks of extended hang time, such as biofilm formation in gastric tubes and administration sets. Finally, studies should evaluate the safety and outcomes of extended hang time in other patient populations.

5. Conclusion

In conclusion, in this pilot study involving enterally fed ICU patients, extending HT of ETFS from 24 to 48 h was not associated with an increased risk of diarrhoea or new-onset pneumonia. Microbiological analysis revealed minimal contamination and no evidence of a link between HT and retrograde bacterial growth in the administration sets. Our findings support the safety of further investigating prolonged hang times in ICU patients on a larger scale. Potential sustainability benefits, although suggested in earlier research [7], were not evaluated here.

Author contributions

MCP: Conceptualisation, Methodology, Formal analysis, Writing – original draft/review. MM: Conceptualisation, Methodology, Formal analysis, Writing – review. TdR: Methodology, Data Collection, Formal Analysis. MR: Methodology, Data Collection. MHZ: Methodology, Writing - review. ARHvZ: Conceptualisation, Methodology, Writing – review. All authors read and approved the final manuscript.

Ethical statement

The Institutional Review Board of Hospital Gelderse Vallei granted permission for the study (file number 2403-021). In the prospective cohort, patients or their families were provided with an information leaflet at the time of ICU admission, and they had the option to opt out by submitting a form. The ethics committee granted the retrospective cohort a waiver, as retrospective consent was deemed infeasible, thus enabling retrospective enrollment and pseudo-anonymisation.

Data sharing statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Funding statement

Not applicable.

Conflict of interest

Prof. dr Van Zanten reported receiving honoraria for advisory board meetings, lectures, research, and travel expenses from Abbott, AOP Pharma, Baxter, Cardinal Health, Danone-Nutricia, Fresenius Kabi, GE Healthcare, InBody, and Rousselot. Prof. dr Zwietering is food safety advisor of Friesland Campina. The other authors have no declarations to make.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2025.10.013.

References

[1] Viner Smith E, Lambell K, Tatucu-Babet OA, Ridley E, Chapple LA. Nutrition considerations for patients with persistent critical illness: a narrative review. J Parenter Enteral Nutr 2024;48(6):658–66. https://doi.org/10.1002/jpen.2623.

[2] Preiser JC, Arabi YM, Berger MM, Casaer M, McClave S, Montejo-González JC, et al. A guide to enteral nutrition in intensive care units: 10 expert tips for the daily practice. Crit Care 2021;25(1):424. https://doi.org/10.1186/s13054-021-03847-4.

[3] Singer P, Blaser AR, Berger MM, Calder PC, Casaer M, Hiesmayr M, et al. ESPEN practical and partially revised guideline: clinical nutrition in the intensive

care unit. Clin Nutr 2023;42(9):1671–89. https://doi.org/10.1016/j.clnu.2023.07.011.
[4] Wireko BM, Bowling T. Enteral tube feeding. Clin Med 2010;10(6):616–9. https://doi.org/10.7861/clinmedicine.10-6-616.
[5] Boullata JI, Carrera AL, Harvey L, Escuro AA, Hudson L, Mays A, et al. ASPEN safe practices for enteral nutrition therapy. J Parenter Enteral Nutr 2017;41(1):15–103. https://doi.org/10.1177/0148607116673053 [Formula: see text].
[6] Sinha S, Lath G, Rao S. Safety of enteral nutrition practices: overcoming the contamination challenges. Indian J Crit Care Med 2020;24(8):709–12. https://doi.org/10.5005/jp-journals-10071-23530.
[7] Moffitt SK, Gohman SM, Sass KM, Faucher KJ. Clinical and laboratory evaluation of a closed enteral feeding system under cyclic feeding conditions: a microbial and cost evaluation. Nutrition 1997;13(7–8):622–8. https://doi.org/10.1016/s0899-9007(97)83002-x.
[8] Ramirez-Elvira S, Romero-Bejar JL, Suleiman-Martos N, Gomez-Urquiza JL, Monsalve-Reyes C, Canadas-De la Fuente GA, et al. Prevalence, risk factors and burnout levels in intensive care unit nurses: a systematic review and meta-analysis. Int J Environ Res Publ Health 2021;18(21). https://doi.org/10.3390/ijerph182111432.
[9] Vogt KS, Simms-Ellis R, Grange A, Griffiths ME, Coleman R, Harrison R, et al. Critical care nursing workforce in crisis: a discussion paper examining contributing factors, the impact of the COVID-19 pandemic and potential solutions. J Clin Nurs 2023;32(19–20):7125–34. https://doi.org/10.1111/jocn.16642.
[10] Dionne JC, Mbuagbaw L. Diarrhea in the critically ill: definitions, epidemiology, risk factors and outcomes. Curr Opin Crit Care 2023;29(2):138–44. https://doi.org/10.1097/MCC.0000000000001024.
[11] Tirlapur N, Puthucheary ZA, Cooper JA, Sanders J, Coen PG, Moonesinghe SR, et al. Diarrhoea in the critically ill is common, associated with poor outcome, and rarely due to Clostridium difficile. Sci Rep 2016;6:24691. https://doi.org/10.1038/srep24691.
[12] Mathus-Vliegen LM, Binnekade JM, de Haan RJ. Bacterial contamination of ready-to-use 1-L feeding bottles and administration sets in severely compromised intensive care patients. Crit Care Med 2000;28(1):67–73. https://doi.org/10.1097/00003246-200001000-00011.
[13] Mathus-Vliegen EM, Bredius MW, Binnekade JM. Analysis of sites of bacterial contamination in an enteral feeding system. J Parenter Enteral Nutr 2006;30(6):519–25. https://doi.org/10.1177/0148607106030006519.
[14] Murali M, Ly C, Tirlapur N, Montgomery HE, Cooper JA, Wilson AP. Diarrhoea in critical care is rarely infective in origin, associated with increased length of stay and higher mortality. J Intensive Care Soc 2020;21(1):72–8. https://doi.org/10.1177/1751143719843423.
[15] Thorens J, Froehlich F, Schwizer W, Saraga E, Bille J, Gyr K, et al. Bacterial overgrowth during treatment with omeprazole compared with cimetidine: a prospective randomised double blind study. Gut 1996;39(1):54–9. https://doi.org/10.1136/gut.39.1.54.
[16] Buendgens L, Bruensing J, Matthes M, Dückers H, Luedde T, Trautwein C, et al. Administration of proton pump inhibitors in critically ill medical patients is associated with increased risk of developing clostridium difficile-associated diarrhea. J Crit Care 2014;29(4):696.e11–5. https://doi.org/10.1016/j.jcrc.2014.03.002.
[17] Reintam Blaser A, Deane AM, Fruhwald S. Diarrhoea in the critically ill. Curr Opin Crit Care 2015;21(2):142–53. https://doi.org/10.1097/mcc.0000000000000188.
[18] Arevalo-Manso JJ, Martinez-Sanchez P, Juarez-Martin B, Fuentes B, Ruiz-Ares G, Sanz-Cuesta BE, et al. Preventing diarrhoea in enteral nutrition: the impact of the delivery set hang time. Int J Clin Pract 2015;69(8):900–8. https://doi.org/10.1111/ijcp.12645.
[19] Wagner DR, Elmore MF, Knoll DM. Evaluation of "closed" vs "open" systems for the delivery of peptide-based enteral diets. J Parenter Enteral Nutr 1994;18(5):453–7. https://doi.org/10.1177/0148607194018005453.
[20] Kogo M, Nagata K, Morimoto T, Ito J, Sato Y, Teraoka S, et al. Enteral nutrition is a risk factor for airway complications in subjects undergoing noninvasive ventilation for acute respiratory failure. Respir Care 2017;62(4):459–67. https://doi.org/10.4187/respcare.05003.
[21] Gaitanidis A, Breen K, Mendoza A, Fawley J, Lee J, Parks J, et al. Enteral nutrition is associated with high rates of pneumonia in intensive care unit (ICU) patients with acute pancreatitis. J Crit Care 2022;69:154012. https://doi.org/10.1016/j.jcrc.2022.154012.
[22] Jacobs S, Chang RW, Lee B, Bartlett FW. Continuous enteral feeding: a major cause of pneumonia among ventilated intensive care unit patients. J Parenter Enteral Nutr 1990;14(4):353–6. https://doi.org/10.1177/0148607190014004353.
[23] National Institute for Health and Care Excellence (NICE). Conditions and diseases [Internet]. London: National Institute for Health and Care Excellence; 2024 [cited 2024 Dec 13]. Available from: https://www.nice.org.uk/guidance/conditions-and-diseases.
[24] Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). Eur Respir J 2017;50(3). https://doi.org/10.1183/13993003.00582-2017.
[25] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315(8):801–10. https://doi.org/10.1001/jama.2016.0287.
[26] Chassany O, Michaux A, Bergmann JF. Drug-induced diarrhoea. Drug Saf 2000;22(1):53–72. https://doi.org/10.2165/00002018-200022010-00005.
[27] Wei L, Ratnayake L, Phillips G, McGuigan CC, Morant SV, Flynn RW, et al. Acid-suppression medications and bacterial gastroenteritis: a population-based cohort study. Br J Clin Pharmacol 2017;83(6):1298–308. https://doi.org/10.1111/bcp.13205.
[28] Cook D, Deane A, Lauzier F, Zytaruk N, Guyatt G, Saunders L, et al. Stress ulcer prophylaxis during invasive mechanical ventilation. N Engl J Med 2024;391(1):9–20. https://doi.org/10.1056/NEJMoa2404245.
[29] U.S. Food and Drug Administration. Compliance program guidance manual: medical foods program – import and domestic (FY 06/07/08) (Program 7321.002, chapter 21 – food composition, standards, labeling and economics) [Internet]. U.S. Department of Health and Human Services; 2006 [cited 2025 Jun 15]. Available from: https://www.fda.gov/media/71685/download.
[30] World Health Organization. The treatment of diarrhoea: a manual for physicians and other senior health workers [Internet]. Geneva: World Health Organization; 2005 [cited 2025 Jun 1]. Available from: https://apps.who.int/iris/bitstream/handle/10665/43209/9241593180.pdf.
[31] Nightingale JMD. How to manage a high-output stoma. Frontline Gastroenterol 2022;13(2):140–51. https://doi.org/10.1136/flgastro-2018-101108.
[32] Spalding MC, Cripps MW, Minshall CT. Ventilator-Associated pneumonia: new definitions. Crit Care Clin 2017;33(2):277–92. https://doi.org/10.1016/j.ccc.2016.12.009.
[33] Dionne JC, Mbuagbaw L, Devlin JW, Duprey MS, Cartin-Ceba R, Tsang J, et al. Diarrhea during critical illness: a multicenter cohort study. Intensive Care Med 2022;48(5):570–9. https://doi.org/10.1007/s00134-022-06663-8.
[34] Luft VC, Beghetto MG, de Mello ED, Polanczyk CA. Role of enteral nutrition in the incidence of diarrhea among hospitalized adult patients. Nutrition 2008;24(6):528–35. https://doi.org/10.1016/j.nut.2008.02.004.
[35] McFarland LV. Epidemiology of infectious and iatrogenic nosocomial diarrhea in a cohort of general medicine patients. Am J Infect Control 1995;23(5):295–305. https://doi.org/10.1016/0196-6553(95)90060-8.
[36] Chevret S, Hemmer M, Carlet J, Langer M. Incidence and risk factors of pneumonia acquired in intensive care units. Results from a multicenter prospective study on 996 patients. European cooperative group on nosocomial pneumonia. Intensive Care Med 1993;19(5):256–64. https://doi.org/10.1007/BF01690545.
[37] Wolkewitz M, Vonberg RP, Grundmann H, Beyersmann J, Gastmeier P, Barwolff S, et al. Risk factors for the development of nosocomial pneumonia and mortality on intensive care units: application of competing risks models. Crit Care 2008;12(2):R44. https://doi.org/10.1186/cc6852.
[38] Chen W, Wang H, Chen Y, Yuan D, Chen R. The independent risk factors of early diarrhoea in enteral nutrition for ICU patients. J Int Med Res 2019;47(10):4929–39. https://doi.org/10.1177/0300060519868340.
[39] Reintam Blaser A, Padar M, Mändul M, Elke G, Engel C, Fischer K, et al. Development of the gastrointestinal dysfunction score (GIDS) for critically ill patients - a prospective multicenter observational study (iSOFA study). Clin Nutr 2021;40(8):4932–40. https://doi.org/10.1016/j.clnu.2021.07.015.
[40] Krones E, Högenauer C. Diarrhea in the immunocompromised patient. Gastroenterol Clin N Am 2012;41(3):677–701. https://doi.org/10.1016/j.gtc.2012.06.009.
[41] Rupp ME, Weseman RA, Marion N, Iwen PC. Evaluation of bacterial contamination of a sterile, non-air-dependent enteral feeding system in immunocompromised patients. J Parenter Enteral Nutr 1999;14(3). https://doi.org/10.1177/088453369901400309.
[42] Li W, Cai J, Ding L, Chen Y, Wang X, Xu H. Incidence and risk factors of ventilator-associated pneumonia in the intensive care unit: a systematic review and meta-analysis. J Thorac Dis 2024;16(9):5518–28. https://doi.org/10.21037/jtd-24-150.
[43] Misra T, Tare M, Jha PN. Insights into the dynamics and composition of biofilm formed by environmental isolate of Enterobacter cloacae. Front Microbiol 2022;13:877060. https://doi.org/10.3389/fmicb.2022.877060.
[44] Leibovitz A, Baumoehl Y, Steinberg D, Segal R. Biodynamics of biofilm formation on nasogastric tubes in elderly patients. Isr Med Assoc J 2005;7(7):428–30.
[45] Donlan RM. Biofilm formation: a clinically relevant microbiological process. Clin Infect Dis 2001;33(8):1387–92. https://doi.org/10.1086/322972.
[46] Ojo O, Adegboye ARA, Ojo OO, Wang X, Brooke J. The microbial quality and safety of blenderised enteral nutrition formula: a systematic review. Int J Environ Res Publ Health 2020;17(24). https://doi.org/10.3390/ijerph17249563.
[47] Institute of Medicine (US), National Research Council (US). Committee on the review of the use of scientific criteria and performance standards for safe food. Scientific criteria to ensure safe food [Internet]. Washington (DC): National Academies Press (US); 2003 [cited 2025 Jun 2]. Appendix E, International microbiological criteria. Available from: https://www.ncbi.nlm.nih.gov/books/NBK221566/.
[48] Vanek V. Closed versus open enteral delivery systems: a quality improvement study. Nutr Clin Pract 2000;15:234–43. https://doi.org/10.1177/088453360001500506.