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# Enteral Nutrition and Acid-Suppressive Therapy in the Pediatric Intensive Care Unit: Impact on the Risk of Ventilator-Associated Pneumonia

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## Abstract

**Objective—**Enteral nutrition (EN) has been implicated as a risk factor for ventilator-associated pneumonia (VAP). We explored the incidence of VAP and its association with clinical and nutrition-related therapies in mechanically ventilated children.

**Design—**Prospective, multicenter, cohort study.

**Setting—**59 Pediatric intensive Care Units in 15 countries.

**Patients—**Children < 18 years of age, mechanically ventilated >48 hours.

**Interventions—**None. Multivariable logistic regression to determine factors associated with VAP.

**Measurements and Major Results—**Data are presented as median (IQR) or counts (%). We enrolled 1245 subjects (45% female, 42% surgical), age 20 (4, 84) months and duration of mechanical ventilation 7 days (3, 13). Culture-positive VAP was diagnosed in 80 (6.4%) patients; duration of mechanical ventilation for this subgroup was 17 days (8, 39). Enteral nutrition was delivered in 985 (79%) patients, initiated within 48 hours in 592 (60%) patients, and via post-pyloric route in 354 (36%) patients. Acid-suppressive agents were used in 763 (61%) patients. The duration of EN ($p = 0.21$), route (gastric vs. postpyloric) of delivery ($p = 0.94$), severity of illness ($p = 0.17$), and diagnostic category on admission ($p = 0.31$) were not associated with VAP. After adjusting for EN days, illness severity, and site; VAP was significantly associated with mechanical

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ventilation >10 days (OR 3.7, 95% CI: 2.2-6.5, $p < 0.001$), PICU length of stay >10 days (OR 1.8, 95% CI: 1.1-3.1, $p = 0.029$), and use of acid-suppressive medication (OR 2.0, 95% CI: 1.2-3.6, $p = 0.011$).

**Conclusions—**VAP was diagnosed in 6.5% of mechanically ventilated children in a heterogeneous multicenter cohort. We did not find a link between enteral nutrition duration or route of delivery and VAP. In addition to duration of mechanical ventilation and length of PICU stay; the use of acid-suppressive therapy independently increased the likelihood of developing VAP in this population. This association must be further explored in clinical trials.

### Keywords

Enteral feeding; antacid; mechanical ventilation; pneumonia; hospital-acquired infection

## Introduction

The importance of enteral nutrition (EN) in critically ill children has become increasingly recognized. Recent reports have described significant associations between higher adequacy of EN delivery and improved clinical outcomes (1). However, concerns about the safety of EN delivery have impeded efforts to optimize nutrient delivery in the pediatric intensive care unit (PICU). Enteral nutrient delivery has been linked to an increased risk of ventilator-associated pneumonia (VAP) (2-5). Safety concerns often result in a delay in the initiation of EN and subsequently failure to achieve the prescribed nutrition goals in critically ill patients (6).

The prevalence of ventilator-associated pneumonia in a recent study of 2,082 mechanically ventilated children was 5.2% (7). VAP may prolong recovery and is associated with higher mortality, longer duration of mechanical ventilation, and PICU stay (7). The economic burden of pediatric VAP has been reported to be approximately $50,000 in additional hospital costs per episode (8). Determination of factors associated with VAP would improve our understanding of the etiology of this condition and help direct interventions in vulnerable patients. Furthermore, identification of potential interactions between nutritional variables and VAP will elucidate the safety profile of enteral nutrient delivery in the PICU population. In this study, we aimed to examine the incidence of VAP in critically ill children worldwide using an international, multicenter, prospectively collected database of mechanically ventilated children. We aimed to identify factors associated with the development of VAP in this cohort. In particular, we examined the link between VAP and nutritional therapies such as the duration of EN delivery, gastric or post pyloric route of EN delivery, and the use of EN adjuncts. We hypothesized that VAP is not independently associated with enteral feeding.

## Materials and Methods

Approval for this study was obtained from the Institutional Review Board of Boston Children's Hospital and at each participating site. This study was registered at clinicaltrials.gov as NCT02354521. Data were prospectively collected as part of the second Pediatric International Nutrition Study (PINS2) with VAP as an *a priori* identified outcome.

Participation, recruitment and data collection methods for the PINS2 study have been previously reported (9). In brief, participating sites recruited consecutive subjects, age 1 month to 18 years, who required mechanical ventilation and had an anticipated PICU stay >48 hours. Children who were not mechanically ventilated in the first 48 hours, those receiving compassionate end-of-life care, or those who were enrolled in any other interventional nutrition study were excluded.

The primary outcome of our current study was the development of VAP. The principal investigator (PI) at each site verified the presence of a confirmed VAP diagnosed according to the CDC guidelines (10, 11). A study manual with details of the definition and illustrations of VAP was provided and site investigators participated in online simulated data entry prior to patient enrolment. Direct communication with the study PI and coordinator allowed resolution of any questions and data entry checks allowed detection and reconciliation of erroneous entries. A dietician entered data for each site. The endpoint for nutritional data collection was 10 days or discharge from the PICU, whichever was sooner. All subjects were followed from PICU admission through 60 days post admission, for outcome variables. Descriptive characteristics of subjects recorded included age, weight, height, gender, diagnosis at admission, severity of illness, length of PICU stay, and mechanical ventilator days. Details of nutritional practices such as initiation, duration, route of enteral nutrition (gastric vs. postpyloric), and acid-suppressive therapy use were also recorded daily using a web-based data collection tool. The number and the type of acid-suppressive medications, including proton pump inhibitor (PPI) and histamine-2 ($H_2$) receptor antagonists, were recorded.

Since Pediatric Risk of Mortality II, Pediatric Risk of Mortality III, and Pediatric Index of Mortality scores were used at different sites to indicate severity of illness, we defined severity of illness scores as levels 1 to 4, corresponding to quartiles of the given score for the cohort. Thus, a patient was considered Level 4 if their score was in the highest $4^{th}$ quartile of the group of patients who used the same scoring system. In the rare case where more than one scoring system was recorded for a patient, we used the lowest score. Patients without a recorded severity of illness score were categorized as ‘unknown’ severity of illness.

## Statistical Analysis

Continuous variables were summarized by the median and interquartile range (IQR) and compared using the Mann-Whitney *U*-test. Differences in proportions and categorical data were assessed by chi-square analysis. Univariate analysis included comparison of patients with and without ventilator-associated pneumonia (VAP) with respect to demographics (age, gender, BMI Z-score, medical or surgical diagnosis, severity of illness based on PIM and PRISM score quartiles), and management variables (length of PICU stay, days on mechanical ventilator, duration of enteral nutrition, gastric vs. postpyloric enteral route for nutrient delivery, use of acid-suppressive agents). Since univariate analysis revealed that patients who developed VAP had significantly longer time in the PICU and more days on the ventilator, we applied receiver-operating characteristic (ROC) curve analysis to identify the optimal cut-off values in days for differentiating between patients with and without VAP with the Youden J-index (12). Based on the results of the univariate analysis and the goal of

adjusting for possible confounders, nine candidate predictors of VAP were included in the multivariable logistic regression analysis with the likelihood ratio test used for assessing significance and the odds ratio and 95% confidence interval (CI) constructed (13). The optimal cut-off values of >10 days were utilized for time in the PICU and duration of ventilator therapy to improve prognostic accuracy. Maximum likelihood estimation in logistic regression was used to determine the probability of VAP with 95% CI according to each combination of the significant multivariable predictors (14). All tests were two-tailed with values of $p < 0.05$ considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics (version 23.0, IBM, Armonk, NY). The cohort sample size of 1245 patients including the 80 patients who developed VAP provided 80% statistical power to detect an odds ratio of 2.0 (considered a clinically meaningful effect size for possible factors associated with VAP) for each of the clinical and management variables evaluated (version 7.0, nQuery Advisor, Statistical Solutions, Cork, Ireland).

## Results

Data from 1245 eligible subjects from 59 PICU's in 15 countries were included in the analyses. No eligible patients were excluded. Sites from the United States (U.S.) comprised 58% of the cohort. The remaining sites were from the U.K., Ireland, Spain, Italy, Switzerland, Russia, Australia, New Zealand, Canada, Argentina, Venezuela, Chile, Peru and Brazil. **Table 1** describes demographic characteristics. EN was administered in 985/1245 (79%) patients in this cohort and it was initiated within 48 hours of admission in 591/985 (60%) patients. Enteral nutrition was delivered via the post-pyloric route in 354/985 (36%) patients. Trophic feeding was recorded in 160 (16%) of the patients and in 10% of those diagnosed with VAP. During the study period, the median (IQR) percentage of prescribed enteral intake adequacy was 42% (18, 68) for protein and 41% (18, 69) for energy delivery. Parenteral nutrition was used in 29% of the cohort and 22% of those diagnosed with VAP.

Acid-suppressive agents were employed in 763 (61%) patients. Of these patients, 634 (83%) received one agent, while 129 (17%) received a second agent, and 15 (2%) a third agent. The most common agent used was an $H_2$-antagonist in 431 (57%) patients. A PPI was used in 88 (12%) patients. For 158 (21%) patients, the acid suppressive agent was not specified. Three patients remained NPO throughout the study period. Acid-suppressant therapy was continued in 145 patients who were on trophic feeding. In the remaining 615 patients on acid-suppressant therapy, EN was initiated and advanced during the course of the PICU stay.

A total of 80 patients were diagnosed with VAP during the study period, as defined by the Centers for Disease Control and Prevention (CDC) criteria. Incidence of VAP in this cohort was 6.4%. VAP was diagnosed within the first 7 days of mechanical ventilation in 46 (57%) patients. **Table 2** depicts the results of the univariate analysis to determine independent factors associated with VAP. Demographic variables, route of EN delivery (gastric vs. postpyloric), and severity of illness were not significantly associated with VAP. Significant variables based on univariate analysis, as well as other variables such as site, severity of illness, and enteral nutrition duration were included in the multivariate regression analysis to determine risk factors independently associated with VAP (**Table 3)**. Duration of EN ($p =$

0.21), severity of illness ($p = 0.17$), and diagnostic category ($p = 0.31$) were not associated with VAP. After adjusting for EN days, illness severity, and site; VAP was significantly associated with mechanical ventilation >10 days (OR 3.7, 95% CI: 2.2-6.5, $p < 0.001$), PICU length of stay >10 days (OR 1.8, 95% CI: 1.1-3.1, $p = 0.029$), and use of acid-suppressive medication (OR 2.0, 95% CI: 1.2-3.6, $p = 0.011$).

In 437 patients with mechanical ventilation duration >10 days, 57 (13%) were diagnosed with VAP, while in 808 patients with ventilator duration <10 days, the incidence of VAP was 2.8%. **Table 4** describes the combined estimated probabilities of developing VAP based on combinations of the three independent risk factors; ventilation days >10 days, PICU stay >10 days, and acid-suppressive agent use. A significantly incremental increase in the probability (95% CI) of VAP was detected; ranging from 1% (0-3%) when none of the factors were present, 4% (2-5%) with the use of acid-suppressive therapy, to 20% (14-28%) when all 3 risk factors were present.

## Discussion

Ventilator-associated pneumonia is one of the leading hospital-acquired infections of critically ill patients associated with increased morbidity, healthcare costs, and mortality (3). The incidence of VAP in our large cohort of mechanically ventilated children is consistent with preceding literature, including two international studies reporting a VAP incidence of 10.2 and 6.5%; respectively, a study from Greece reporting an incidence of 11%, and several studies in the U.S. with incidence at approximately 5% (2, 7, 11, 15, 16). In these reports, as in our current report, the duration of mechanical ventilation was the strongest predictor of VAP in the PICU population (3, 7). Optimizing sedation and ventilator weaning protocols, with the goal of shortening the duration of mechanical ventilation, are important interventions that have been shown to have a beneficial effect when bundled together as part of routine patient care (8). In addition to duration of mechanical ventilation, duration of PICU stay was significantly associated with VAP in our current study. These two variables are likely collinear and therefore we did not expect them to be retained in the final multivariable regression model. Factors other than mechanical ventilation might be independently responsible for VAP development in patients with prolonged PICU stay. Furthermore, the relationship between these two timed variables and VAP is likely bidirectional. Patients with VAP are expected to have prolonged mechanical ventilation and longer stay in the PICU. The probability of VAP in our cohort increased to 20% when acid suppressive therapy was used in addition to the length of PICU stay and MV. **(Table 4)** This combination might allow for early identification of patients at increased risk of VAP development, therefore facilitating focused strategies in addition to the current bundled elements of care.

The increased risk of VAP in patients receiving acid-suppressive therapy in this study may have theoretical plausibility based on the potential impact of acid-suppressive therapies on the microbiome of the gastrointestinal tract (17). Mechanical ventilation is one of the few indications for stress ulcer prophylaxis and acid-suppressive therapy is expected to reduce the incidence of gastrointestinal bleeding (18). The effect of mechanical ventilation on splanchnic blood flow coupled with the presence of gastric acid has been thought to increase

the frequency of ulcerating lesions in the stomach (19, 20). Several adult studies have demonstrated that mechanically ventilated adults receiving pantoprazole have a higher incidence of VAP than patients receiving ranitidine (21-23). A meta-analysis of adult studies questioned the need for acid-suppressive therapies in the ICU, particularly in patients who were on full enteral nutrition (24). In a single-center retrospective study, there were no differences in the rate of upper airway colonization with gram-negative organisms, between patients receiving ranitidine, sucralfate or no stress ulcer prophylaxis (25). Recently, acid-suppression therapy was associated with statistically significant increased risk of developing *Clostridium difficile* infections among children in the United Kingdom (26). Acid-suppressive medications were used in patients who were on trophic feeding and those that were advancing EN intake in our cohort. Based on these reports and in light of the association with VAP in our current study, the rationale and practice of acid-suppression in the PICU population must be further examined.

Nutrient intake adequacy has been associated with improved outcomes in single and multicenter observational studies in critically ill children (1, 27). The enteral route is the preferred mode of nutrient delivery in this population and recent reports have shown that early EN is feasible during critical illness. Although EN has been postulated as a risk factor for the development of VAP in some studies, our findings suggest that enteral feeding is not a significant risk factor for VAP in mechanically ventilated children (28, 29). Appropriate patient selection, stepwise advancement, and vigilance for intolerance might allow safe EN delivery during acute critical illness in eligible patients.

The main limitation of this study is its observational design. Our data were collected prospectively and therefore the study has an advantage over retrospective chart review. However, the lack of association between nutrition-related factors and VAP in an observational study should not be taken as proof of lack of causation. Similarly, the association between VAP and acid-suppressive therapy highlighted in our study merely generates hypothesis. Our results should prompt further controlled trials examining the impact of acid suppression on VAP. Another limitation is the accuracy of the clinical diagnosis of VAP according to CDC criteria. Prior to patient enrollment, we disseminated a study manual to each participating site. The manual consisted of description and illustration of the diagnosis of VAP. A period of online simulated data entry was provided for investigators to practice the data entry procedures prior to patient enrollment. However, inter-rater validation of the diagnoses in cases across the sites was beyond the scope of our study. The lack of consensus in defining this condition across the world might introduce error in the accurate estimation of VAP incidence (30). Due to variable practices around surveillance and definition of VAP, we cannot be certain of the accurate time of VAP development. Hence it is unclear if MV duration >10 days includes the period prior to development of VAP. The association between mechanical ventilation duration and VAP in our study is likely bidirectional. Indeed patients who develop VAP may require prolonged MV as a consequence. Lastly, this study was not designed to differentiate risk based upon different classes of acid-suppressive therapy, which needs to be better explored in future controlled studies.

## Conclusions

VAP was diagnosed in 6.5% of mechanically ventilated children in a large heterogeneous multicenter cohort. We did not find a link between enteral nutrition duration or route of delivery and VAP. In addition to duration of mechanical ventilation and length of PICU stay; the use of acid-suppressive therapy independently increased the likelihood of developing VAP in this population. This association must be further explored in clinical trials.

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## Table 1

Demographic, anthropometric and clinical characteristics on admission for mechanically ventilated children (N=1245)

| Variable | Median (IQR) |
|---|---|
| **Age (months)** | 20.4 (4, 84.0)[1] |
| **Sex** | |
| Female | 549 (44%) |
| **Height (cm)** | 82 (60, 118) |
| **Weight (kg)** | 11.2 (5.8, 23.2) |
| **Weight-for-age *Z*-score** | −0.60 (−2.01, 0.57) |
| **BMI** | 16.2 (14.3, 18.7) |
| **BMI *Z* score** | −0.12 (−1.47, −1.08) |
| **Admission category (%)** | |
| Medical | 726 (58%) |
| Surgical | 519 (42%) |
| **Co-morbidities**[2] | |
| Congenital Heart Disease | 165 (14.4%) |
| Hematology/Oncology/HSCT | 30 (2.6%) |
| Infectious disease | 66 (5.8%) |
| Neurologic disease | 149 (13%) |
| Other cardiac disease | 48 (4.2%) |
| Renal or Endocrine condition | 15 (1.3%) |
| Respiratory condition | 427 (37.3%) |
| Trauma/Orthopedic injury | 74 (6.5%) |
| Miscellaneous | 169 (14.8%) |
| **Severity of illness (level)**[3] | |
| 1 | 304 (24%) |
| 2 | 290 (23%) |
| 3 | 330 (27%) |
| 4 | 275 (22%) |
| Unknown | 46 (4%) |
| **Region of origin; subjects** | |
| U.S.A. | 723 (58.2%) |
| Europe | 223 (17.8%) |
| South America | 202 (16.2%) |
| Oceania | 62 (5%) |
| Canada | 35 (2.8%) |

BMI = body mass index.

[1] Median; IQR in parentheses (all such values)

[2] Complete data on diagnostic category were available for 1146 patients

[3]Severity of illness levels were corresponding to the quartiles of the Pediatric Index of Mortality (PIM) scores or Pediatric Risk of Mortality (PRISM) score for the cohort. A patient was considered Level 4 if his/her score was in the highest 4th quartile of the group of patients who used the same scoring system.

## Table 2

Univariate Analysis: Factors associated with ventilator-Associated pneumonia (VAP) in mechanically ventilated children (Total N=1245)

| Variable | VAP (*n* = 80) | No VAP (*n* = 1165) | *p* |
|---|---|---|---|
| Age, months | 16 (6, 70) | 21 (5, 84) | 0.62 |
| BMI *Z*-score | −0.2 (−2.1, 1.6) | −0.1 (−1.5, 1.1) | 0.83 |
| Gender | | | 0.73 |
| Male | 43 (54%) | 653 (56%) | |
| Female | 37 (46%) | 512 (44%) | |
| Diagnosis | | | 0.02 |
| Medical | 57 (71%) | 669 (57%) | |
| Surgical | 23 (29%) | 496 (43%) | |
| Severity Level[¶] | | | 0.17 |
| 1 | 19 (24%) | 285 (25%) | |
| 2 | 26 (32%) | 264 (23%) | |
| 3 | 15 (19%) | 315 (27%) | |
| 4 | 19 (24%) | 256 (22%) | |
| Days on Mechanical Ventilation | 17 (8, 39) | 6 (3, 12) | <0.001* |
| Mechanical Ventilation >10 days | 57 (71%) | 380 (33%) | <0.001* |
| Days in PICU | 21 (10, 45) | 10 (6, 18) | <0.001* |
| Acid-suppressive Therapy | 64 (80%) | 699 (60%) | <0.001* |
| Enteral Nutrition Days[¶¶] (N=985) | 10 (10, 10) | 10 (6, 10) | <0.001* |
| Enteral Nutrition Route | | | 0.94 |
| Gastric | 49 (65%) | 582 (64%) | |
| Postpyloric | 27 (35%) | 327 (36%) | |

Data are median (interquartile range) or number (%)

*Statistically significant

¶Severity of illness levels were corresponding to the quartiles of the Pediatric Index of Mortality (PIM) scores or Pediatric Risk of Mortality (PRISM) score for the cohort. A patient was considered Level 4 if his/her score was in the highest 4th quartile of the group of patients who used the same scoring system.

¶¶EN days are censored at 10 days, duration of study.

## Table 3

Multivariable Logistic Regression Analysis: Factors associated with ventilator-associated pneumonia (VAP) in mechanically ventilated children (N=1245)

| Variable | Odds Ratio | 95% CI | *p* |
|---|---|---|---|
| Age, months | 1.00 | 0.96 - 1.01 | 0.99 |
| BMI *Z*-score | 0.99 | 0.90 - 1.12 | 0.94 |
| Gender | | | |
| Male | 1.13 | 0.72 - 1.81 | 0.59 |
| Female | Ref. | | |
| Diagnosis | | | |
| Medical | 1.31 | 0.77 - 2.21 | 0.31 |
| Surgical | Ref. | | |
| Severity Level[¶] | 1.52 | 0.86 - 2.67 | 0.17 |
| Mechanical Ventilation >10 days | 3.70 | 2.15 - 6.42 | <0.001[*] |
| PICU >10 days | 1.93 | 1.13 - 3.30 | 0.019[*] |
| Acid-suppressive Therapy | 2.14 | 1.20 - 3.85 | 0.008[*] |
| Enteral Nutrition, days | 1.12 | 0.95 - 1.32 | 0.21 |

PICU = pediatric intensive care unit, CI = confidence interval

[3]Severity of illness levels were corresponding to the quartiles of the Pediatric Index of Mortality (PIM) scores or Pediatric Risk of Mortality (PRISM) score for the cohort. A patient was considered Level 4 if his/her score was in the highest 4$^{th}$ quartile of the group of patients who used the same scoring system.

[*]statistically significant

[¶]Severity level 4 vs. other grades.

**Table 4**

Combined estimated probability of ventilator-associated pneumonia (VAP) in mechanically ventilated children based on Logistic Regression*

| Mechanical Ventilation >10 Days | PICU Stay >10 Days | Acid-suppressive Therapy Use | Probability of VAP | 95% CI |
|---|---|---|---|---|
| Yes | Yes | Yes | 20% | 14% - 28% |
| Yes | No | Yes | 12% | 8% - 18% |
| Yes | Yes | No | 11% | 6% - 17% |
| Yes | No | No | 7% | 4% - 11% |
| No | Yes | Yes | 6% | 3% - 10% |
| No | No | Yes | 4% | 2% - 5% |
| No | Yes | No | 3% | 1% - 5% |
| No | No | No | 1% | 0% - 3% |

PICU = pediatric intensive care unit; VAP = ventilator-associated pneumonia; CI = confidence interval.

*Adjusted for diagnosis, days on enteral nutrition, illness severity, and participating site