Critical Analysis of the Factors Associated with Enteral Feeding in Preventing VAP: A Systematic Review

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Ventilator-associated pneumonia (VAP) is a common cause of morbidity in critically ill patients. Appropriate enteral feeding is the most important factor associated with the prevention of VAP. However, the standardization of enteral feeding methods needs clarification. The purpose of this systematic review was to synthesize the factors associated with enteral feeding in order to prevent VAP and to describe the characteristics of these factors. A comprehensive search was undertaken involving all major databases from their inception to September 2008 using medical subject heading terms associated with enteral feeding in relation to VAP. The overall reference list of identified studies was audited, and eligible studies included randomized controlled trials, controlled before-and-after (pre–post) studies and meta-analyses. To generate the characteristics of the factors associated with VAP, the reported components of these trials were pinpointed and categorized. A total of 14 papers were found that had investigated the factors linking enteral feeding and VAP. For these, 11 were randomized controlled trials, 1 was a meta-analysis and 2 were case-controlled analyses. Twelve of these 14 studies were conducted at a single institute and 2 were conducted at multiple institutes. The sample sizes varied from 10 to 2,528 subjects. Three major issues were identified based on the purpose of study interventions, and these were the effects of feeding method (continuous *vs.* intermittent), feeding site on aspiration (gastric *vs.* small bowel), and the timing of enteral feeding (early *vs.* late). The evidence suggests that a correct choice of enteral feeding method can effectively reduce complications due to aspiration. Furthermore, intermittent enteral feeding and with a small residual volume feed can reduce gastroesophageal reflux, and increased total intake volume and early feeding can reduce ICU mortality. Nonetheless, the effects of these choices on preventing VAP still need further evaluation. A set of clinical guidelines based on these evidence-based findings with respect to enteral feeding is required, particularly one that covers all aspects of the enteral feeding process. [*J Chin Med Assoc* 2009;72(4):171–178]

Key Words: enteral feeding, feeding method, feeding site, intensive care unit, ventilator-associated pneumonia

Introduction

A growing body of evidence suggests that enteral feeding is associated with aspiration pneumonia, especially among critically ill patients who are on a ventilator.[1] Critically ill patients receiving enteral feedings often have a substantial gastric volume, which may increase their risk of gastroesophageal reflux, aspiration and ventilator-associated pneumonia (VAP). The literature is unclear as to the association of VAP risk with: feeding method; feeding site; and timing of enteral feeding.

It has been reported that there are 33 potentially effective measures for preventing VAP in which nurses play an essential role.[2] However, Biancofiore et al found that only 22.6% of the nurses declared that their knowledge of VAP and the strategies used to prevent it was satisfactory.[3] In our experience, appropriate enteral feeding is one of the most effective VAP preventative strategies that are widely applied by nurses. So, it is important to ensure that nurses are involved in developing and updating feeding protocols and guidelines based on the best evidence.

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Therefore, the purpose of this systematic review was to synthesize the factors associated with enteral feeding that are important to the prevention of VAP and to characterize these factors.

Methods

Search strategy

We identified articles in the literature by performing a systematic search. A set of preliminary key words were used drawn from the natural language terms of the topic that might be found in the article titles, abstracts and subject descriptors. Articles published since the inception of the databases were searched. The databases were PubMed, PsychINFO, EMBASE, the Cochrane Library (including Cochrane DSR, DARE and CCTR), Chinese Periodicals Index, and the READncl Service System. Reference lists were created of the identified studies and review papers together with doctoral and master theses from Taiwan and proceedings of conferences from the Yahoo website. The searches were performed using the following key word groups:

1. Feeding: intermittent feeding, continuous feeding, enteral nutrition, bolus feeding, respiratory effects, delivery nutrition, nasogastric feeding, enteral nutrition, nutrition delivery;
2. Sample: mechanical-ventilated, intensive care unit;
3. Outcomes: pulmonary function, respiratory, pneumonia, respiratory effect;
4. Timing: early or no limitation.

Inclusion and exclusion criteria

The publications used in this review used the following criteria:

- Types of study review considered included randomized controlled trials (RCTs), quasi-experimental studies, meta-analyses and controlled before-and-after (pre–post) studies;
- The search was from database inception to September 2008;
- The types of article included all studies of adults on ventilators;
- The types of intervention included all studies of enteral feeding;
- The types of outcome measures included those involving the measurement of changes in patients linked to VAP and enteral feeding.

Search outcome

The searching process was carried out in 2008, and 2,196 papers were retrieved (Table 1). Of these, 2,180 papers were excluded. Among the excluded papers, 1,987 were identified as duplications or having no relevance, and this left 193 papers for further consideration. The relevance of the remaining 193 studies was audited by the author and a reviewer without blinding to authorship or journal of publication. The author and a second reviewer independently screened the remaining titles and abstracts for their eligibility. In this part of the analysis, 180 studies were excluded, with the main reasons for exclusion being that there was a lack of no intervention, that the study involved screening and diagnostic testing, there was a lack of outcome measure with respect to VAP, that the paper was pharmacologic in nature, and that the paper was related to economic evaluation. Finally, a total of 14 papers were identified as relevant, and these underwent data extraction and synthesis.

Using these 14 papers, the author and a reviewer critically appraised the quality of each eligible study using the *Critical Appraisal for Intervention Study* approach developed by the Joanna Briggs Institute.[4] Unfortunately, because of the heterogeneity of the data, no meta-analysis was possible. Study characteristics and results are reported and tabulated below and a narrative synthesis was then used to organize the data.

Table 1. Search results

Database	Time period searched	Papers retrieved	Further consideration	Relevant papers
Cochrane Library	1800–2008.10	590	71	3
CINAHL Plus Full Text	1937–2008.10	9	4	0
Ovid Full Text	1966–2008.10	773	67	4
PubMed	1966–2008.10	796	41	4
Journals of the Republic of China Index	1970–2008.10	7	3	1
Electronic theses and dissertation system	1956–2008.10	21	7	1
Total		2,196	193	13

Results

The search identified 14 studies that investigated the factors associated with enteral feeding and VAP. Overall, the quality of the evidence provided by the 14 studies was found to be relatively strong. Eleven (78.6%) of the articles described RCTs, 1 (7.1%) used meta-analysis and the other 2 (14.3%) articles described case-controlled studies. All studies were conducted in a variety of different types of ICU; among them, 78.6% were MS ICU or general ICU, 14.3% were medical ICU and 7.1% were surgical ICU. Twelve (85.7%) studies were conducted at a single institution and 2 (14.3%) involved multiple institutions. The samples sizes ranged from 10 to 2,528 subjects. All studies measured VAP in response to various issues associated with enteral feeding.

Based on the literature reviewed, 3 major issues were categorized based on the purpose of the study. These were the choice of feeding method (continuous *vs.* intermittent), the effect of feeding site on aspiration (gastric *vs.* small bowel), and the effect of the timing of enteral feeding (early *vs.* late).

Method of enteral feeding

The methods of feeding for critically ill patients on ventilators were generally assigned into intermittent enteral feeding (IEF) and continual enteral feeding (CEF). Table 2 presents the 5 studies describing the effect of the enteral feeding method on aspiration pneumonia.[5–9] The purposes of these studies focused on examining the association between the feeding method and the risk factors for VAP. The major primary outcome indicators measured for IEF and CEF

Table 2. Results for the type of enteral feeding method and its association with VAP

Trial (yr)	Study design sample	Intervention	Outcome measured	Significant results
Spilker et al (1996)[5]	• Prospective, case-controlled • MICU • $n = 13$	• > 48 hr of CEF, after samples were collected, feeding schedule was then changed to IEF	• Gastric pH • Quantitative gastric cultures	• Gastric pH not changed significantly • Existing microbial growth not cleared by IEF after CEF
Bonten et al (1995)[6]	• RCT • 2 MS ICU, 1 thoracic ICU • IEF: $n = 30$ • CEF: $n = 30$	• IEF: 18 hr/d • CEF: 24 hr/d	• 24-hr gastric pH • Upper airway colonization • VAP occurrence • Mortality rate	• IEF group: median pH decreased from 3.5 to 2.2 ($p = 0.0002$) • Other measurements were similar in both groups
Wu et al (1999)[7]	• RCT • MS ICU • Group I: $n = 5$ • Group II: $n = 5$	• Group I: NPO at 1st d, then IEF at 2nd d, NPO at 3rd d, CEF at 4th d • Group II: NPO at 1st d, CEF at 2nd d, NPO at 3rd d, IEF at 4th d • Both groups received IEF from 5th to 18th d	• GE reflux scores • Aspiration index • Wheezing index	• GE reflux scores & aspiration index were significantly higher after CEF • Wheezing index scores showed no differences after extubation
Chen et al (2006)[8]	• RCT • 1 MS ICU, 1 MICU • IEF: $n = 56$ • CEF: $n = 51$	• IEF: 250 mL 4–6 times/d, in a bolus forced by gravity • CEF: 24 hr/d via feeding pump	• Gastric emptiness index • Aspiration index • Airway status	• IEF group: had a higher total intake volume at d 7 ($p = 0.000$), extubated earlier, lower risk of aspiration pneumonia (OR = 0.146, 95% CI = 0.062–0.413, $p = 0.000$)
Chou et al (2003)[9]	• RCT • MS ICU • IEF: $n = 40$ • CEF: $n = 40$	• IEF: 250 mL, 4–6 times/d • CEF: 24 hr/d via feeding pump	• Gastric emptiness index • Aspiration index • Outcome indicators	• IEF group had lower GE reflux scores & better aspiration index scores • IEF group had higher extubation rate & shorter LOS in ICU

RCT = randomized controlled trial; MS ICU = medical surgical intensive care unit; ICU = intensive care unit; MICU = medical intensive care unit; IEF = intermittent enteral feeding; CEF = continuous enteral feeding; NPO = nothing per oral; VAP = ventilator-associated pneumonia; GE = gastroesophageal; OR = odds ratio; CI = confidence interval; LOS = length of stay.

in these 5 studies were gastric emptying and VAP occurrence, and the secondary outcomes were the length of ICU stay and hospital stay together with the mortality rate.

Four of these studies were RCTs, and the remaining 1 study used a prospective case-controlled approach to evaluate the effect of IEF on gastric pH and gastric microbial growth in mechanically-ventilated patients.[5] Bonten et al used a prospective randomized design to investigate the influence of IEF and CEF on gastric pH and oropharyngeal colonization.[6] The findings indicated that almost all patients who received enteral feeding showed colonization of the stomach with Gram-negative bacteria. IEF resulted in a slight decrease in intragastric pH, but this did not influence the rate of colonization or infection of the respiratory tract.[6] Bonten et al showed that CEF is associated with decreased gastric acidity, which stimulates gastric colonization and VAP. IEF can induce a temporary increase in gastric acidity and therefore decrease the risk of VAP.[6]

In Taiwan, Wu et al used a pre–post randomly controlled trial design and recruited 10 participants to compare the efficacy of intermittent and continuous nasogastric feeding in preventing gastroesophageal reflux in patients on ventilators.[7] The findings indicated that patients on intermittent nasogastric feeding showed less gastroesophageal reflux and had a better aspiration index than did patients on continuous nasogastric feeding; the gastroesophageal reflux score may be taken as an indirect indicator of VAP. However, the number of subjects in each group in this study was only 5.[7] This small sample size precluded the provision of statistical support for the effectiveness of interventions.

Another 2 studies used prospective RCTs to examine the effect of intermittent nasogastric feeding on preventing VAP in critically ill patients on ventilators. Both studies showed that the patients in the intermittent feeding group showed a higher total intake volume, were extubated earlier and had a lower risk of aspiration pneumonia.[8,9]

Spilker et al used a prospective case-controlled study to examine the effect of intermittent enteral feeding on gastric pH and gastric microbial growth in patients on ventilators. Thirteen patients received CEF and then were changed to IEF for 5 consecutive days. Gastric microbial growth was found in 85% of patients receiving CEF. The implementation of IEF did not clear gastric microbial growth. Furthermore, gastric pH was not decreased with the administration of IEF. The amount of microbial growth was also unchanged with IEF.[5]

In summary, IEF has been shown to decrease intragastric pH and lower the risk of aspiration pneumonia; however, IEF does not consistently minimize gastric microbial growth. When considering the above studies, the small sample size and the validity of the measurements made on the gastric juice have been criticized.

Site of enteral feeding

Table 3 shows the results of 4 studies in which the researchers examined the relationship between different enteral feeding sites and VAP.[10–13] Our review identified 4 RCT studies that examined the effect of feeding site on the risk for VAP.

Kearns et al used a prospective RCT to examine the incidence of VAP when gastric versus small intestinal feeding was compared.[10] Their findings indicated that there was no significant difference in the incidence of VAP between the 2 groups.

Kortbeek et al used a RCT design to compare the efficacy of duodenal feeding and gastric feeding in ventilated blunt trauma patients with regard to their length of stay, ventilator days in the ICU, and VAP.[11] There was no difference across all outcomes between the 2 groups. However, their other findings indicated that duodenal feeding significantly reduced the time required to achieve the targeted level of enteric nutrition.

Kostadima et al conducted an RCT to determine whether early performance of gastrostomy affects frequency of VAP in stroke or head injury patients.[12] The study results revealed that more patients with nasogastric tube developed VAP compared with subjects with early gastrostomy ($p < 0.05$). Although VAP occurred in fewer patients with gastrostomies, there were no differences in secondary outcome measures between the 2 groups.

Montejo found that nasogastrojejunal tube feeding could reduce the gastrointestinal complications rate and give a higher volume ratio on day 7 than nasogastric feeding; however, both groups had a very similar incidence of nosocomial pneumonia (40% *vs.* 32%).[13]

Four trials assessed the effect of different feeding sites on VAP. Three of the trials comparing gastric feeding to post-pylorus feeding showed no significant effect on VAP incidence between sites.[10,11,13] In these 3 trials, when a tube was inserted from patients' nasal to gastric or post-pylorus areas, the risk factor for developing VAP was still present.[14] In this review, gastrostomy feeding is considered to be beneficial to patients for reducing the rate of VAP.[12]

Timing of enteral feeding

This systematic review identified 4 studies that had examined the effect of enteral feeding timing on the risk for VAP (Table 4).[1,15–17] A meta-analysis was

Table 3. Results of enteral feeding site on risk of VAP

Trial (yr)	Study design sample	Intervention	Outcome measured	Significant results
Kearns et al (2000)[10]	• RCT • ICU • NG feeding: $n=23$ • SI feeding: $n=21$	• NG feeding: feeding tube placed in gastric area • SI feeding: feeding tube placed in small intestinal area	• VAP occurrence • Adequacy of nutrition supplementation	• VAP rates & mortality rates were not different • SI group received greater percentage of their caloric requirements ($p<0.05$).
Kortbeek et al (1999)[11]	• RCT • Trauma patients in 2 ICUs • NG feeding: $n=43$ • D feeding: $n=37$	• NG feeding: feeding tube placed in gastric area • D feeding: feeding tube placed in duodenum • Feeding initiated within 72 hr	• Nutrition assessment • Duration of ICU stay • Ventilator days • VAP occurrence • Mortality	• D feeding significantly reduced time required to achieve targeted enteric nutrition • Other measurements similar in both groups
Kostadima et al (2005)[12]	• RCT • Stroke or head injury patients in ICU • Gastro feeding: $n=20$ • NG feeding: $n=21$	• Gastro feeding: feeding via gastrostomy tube • NG feeding: feeding via NG tube • Feeding initiated within 48 hr	• VAP occurrence • Duration of ICU stay • Ventilator days • ICU mortality • ICU mortality attributed to VAP	• Gastro feeding gave significantly lower VAP rate at end of 2nd & 3rd wk • Other measurements similar in both groups
Montejo (1999)[13]	• RCT • 14 ICUs in 11 hospitals • NG feeding: $n=51$ • J feeding: $n=50$	• NG feeding: fed with NG tube • J feeding: fed in jejunum with dual-lumen NGJ tube • Feeding initiated within 36 hr	• GI complications rate • Volume ratio • VAP occurrence • Multiple organ dysfunction score	• J feeding gave lower GI complications rate ($p<0.001$) & higher volume ratio at d 7 ($p<0.03$) • No differences for other measurements

RCT = randomized controlled trial; ICU = intensive care unit; NG = nasogastric; SI = small intestine; D = duodenum; J = jejunum; Gastro = gastrostomy; NGJ = nasogastrojejunal; VAP = ventilator-associated pneumonia; GI = gastrointestinal.

conducted by Marik and Zaloga in which 15 RCTs that had investigated the effect of enteral feeding timing on surgical ICU patients were included. The findings indicated that early enteral nutrition was associated with a significantly lower incidence of infection.[15]

In contrast, Ibrahim et al used a prospective, controlled, clinical trial method to compare 2 strategies of feeding (early and late feeding).[16] Patients in the early-feeding group were scheduled to receive their estimated total daily enteral nutritional requirements starting on day 1 of mechanical ventilation. Patients in the late group were scheduled to receive 20% of their estimated daily enteral nutritional requirements during the first 4 days of mechanical ventilation, followed by their full estimated daily enteral nutritional requirements beginning on day 5 of mechanical ventilation. The results showed that patients in the early-feeding group had a statistically greater incidence of VAP (49.3% *vs.* 30.7%).

Furthermore, a prospective study was carried out to determine whether early intragastric feeding may lead to gastric intolerance and subsequent pneumonia in ventilated multiple injured patients. The study involved 2 groups of patients, randomized into either an immediate intragastric early nutrition (EN) group or a delayed intragastric EN group, who started feeding later than 24 hours after admission. The findings demonstrated that 33% of the early EN patients and 64% of the delayed EN patients met the criteria for pneumonia, which suggested that early enteral nutrition decreased the incidence of nosocomial pneumonia.[17]

Discussion

This systematic search and selection process found 14 studies in which the effects of enteral feeding on VAP were rigorously examined. Overall, the literature reviewed provides evidence that 3 aspects of enteral feeding influence VAP rates and the treatment outcomes of ICU patients on ventilators. This systematic review summarized the evidence focusing specifically on the enteral feeding process and identified that

Table 4. Results for timing of enteral feeding on risk of VAP

Trial (yr)	Study design sample	Intervention	Outcome measured	Significant results
Artinian et al (2006)[1]	• Retrospective, case-controlled study design • Large multi-institutional ICU database • Early feeding: *n* = 1,264 • Late feeding: *n* = 1,264	• Early-feeding group: fed within 48 hr of mechanical ventilation onset • Late-feeding group: remainder of patients	• ICU mortality • Hospital mortality • VAP occurrence • ICU LOS • Ventilator-free days	• After adjusting acuity, early enteral feeding significantly reduced ICU & hospital mortality • Early-feeding group associated with increased risk of VAP • Both groups had similar numbers of ventilator-free days
Marik & Zaloga (2001)[15]	• Meta-analysis • 15 RCTs • Surgical ICUs • 1966–August 2000 • *n* = 753	• Early nutrition: within 36 hr of admission to hospital or within 36 hr of surgery • Delayed nutrition: initiated after 36 hr of admission to hospital or after 36 hr of surgery	• No. of infections • Non-infectious complications • LOS in hospital • Hospital mortality	• Early nutrition: lower risk of infection (95% CI = 0.30–0.66, $p < 0.000$), shorter LOS ($p = 0.0012$) • Other measurements not significantly different
Ibrahim et al (2002)[16]	• RCT • Medical ICU • Early feeding group: *n* = 75 • Late feeding group: *n* = 75	• Early feeding: received full feeding starting on d 1 of ventilator • Late feeding: received 20% of daily requirements for 4 d, & full feeding began on d 5	• VAP occurrence • Ventilator days • ICU & hospital LOS • Hospital mortality	• Early-feeding group had greater incidence of VAP ($p = 0.02$); longer ICU ($p = 0.043$) & hospital LOS ($p = 0.023$) • Hospital mortality: no statistical difference between groups
Kompan et al (2004)[17]	• RCT • ICU • Early-feeding group: *n* = 27 • Late-feeding group: *n* = 25	• Early feeding: immediate feeding after admission • Late feeding: feeding started later than 24 hr after admission	• Upper gastric intolerance • Feeding amount • VAP occurrence	• Early-feeding group received greater amount of feeding & showed less upper gastric intolerance • Early-feeding group had fewer VAP episodes ($p = 0.05$)

ICU = intensive care unit; RCT = randomized controlled trial; VAP = ventilator-associated pneumonia; LOS = length of stay.

feeding method, feeding site and timing of feeding were risk factors for developing VAP. Enteral feeding is a necessary intervention for nutritional support in ICU patients. It is a challenge for the ICU clinician and nurses to provide optimal nutrition while minimizing the incidence of VAP.

The results of this systematic review are inconclusive. Large gastric volume is one of the risk factors for tracheobronchial aspiration by patients on ventilators.[18] However, the results of studying the enteral feeding methods (IEF *vs.* CEF) in order to decrease VAP rates are mixed, with 3 groups finding an improvement with a lowering of the risk of VAP,[7–9] while 2 studies reported no change.[5,6]

The results on timing of enteral feeding (early *vs.* late) were also equivocal; the meta-analysis and 1 RCT concluded that early feeding significantly reduced the rate of VAP,[15,17] while 2 other studies reported an increased risk of VAP. Finally, the results of trials investigating sites of enteral feeding (gastric *vs.* duodenal or jejunal) seemed to show no differences among the feeding sites.[1,16]

A number of methodologic and measurement issues within this body of evidence warrant discussion. First, the majority of studies provided no information on the statistical power or the effect sample size needed to adequately detect the effect outcomes. Furthermore, in general, there was only limited information on the study setting. Thus, the reporting format and the lack of details resulted in a general lack of clarity.

Second, the definitions for the tested interventions in the literature reviewed needed to be carefully noted. That is, by definition, IEF should stop between feedings. However, in Bonten et al's study,[6] IEF was continuous for 18 hours and stopped for 6 hours, while in Wu's group, IEF used a bolus forced by gravity over 20 minutes as the feed, and this occurred 4–6 times each day.[7–9] Specifically, the outcomes were different for these 2 types of IEF; the 18 hours of IEF had a similar effect on VAP and mortality rate as 24-hour continuous feeding, but the gravity force-feeding approach had a significantly lower risk of VAP. Therefore, clinicians and nurses need to be cautious when using these findings as a basis for developing clinical guidelines or nursing standards.

Finally, the outcome variables also differed across the studies. For example, the majority of the studies diagnosed VAP by following the guidelines for diagnosis of VAP developed by the Center for Disease Control and Prevention.[19] However, Spilker et al,[5] Bonten et al,[6] and Wu et al[7] used diagnostic criteria developed by themselves.

There are additional issues that need to be considered in relation to the prevention of VAP. Torres et al indicated several prophylactic measures that seemed to help to prevent VAP, such as medication to prevent gastric reflex.[20] The literature also suggests that aspiration of gastric contents can be reduced by positioning patients in a semi-recumbent position,[18] by checking the potency of the endotracheal tube cuff,[20] and by the aspiration of subglottic secretions.[18,21,22]

There is a need to use meta-analysis to integrate the above disparate findings in order to develop a set of evidence-based clinical guidelines for ICU patients on ventilators. These would allow the structuring of an appropriate practical feeding methodology that would improve the enteral nutrition and lower the incidence of VAP in these patients.

In conclusion, this review is relevant to evidence-based practice in critical care settings. It highlights the critical points in the feeding process and interventions to manage the risk factors in the feeding process of critically ill patients on ventilators. However, it is clear that trials with larger samples are needed to produce better evidence. Replication of some of the reported trials, using the same outcome measures and scales, would also strengthen the evidence base. Therefore, more studies using methodologically higher-quality approaches and covering the complete area of VAP and enteric feeding are needed before clinicians and nurses will be able to develop a set of evidence-based guidelines for enteral feeding.

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