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Systematic review: The relation between nutrition and nosocomial pneumonia: randomized trials in critically ill patients

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Abstract

Objective: To review the effect of enteral nutrition on nosocomial pneumonia in critically ill patients as summarized in randomized clinical trials.

Study identification and selection: Studies were identified through MEDLINE, SCISEARCH, EMBASE, the Cochrane Library, bibliographies of primary and review articles, and personal files. Through duplicate independent review, we selected randomized trials evaluating approaches to nutrition and their relation to nosocomial pneumonia.

Data abstraction: In duplicate, independently, we abstracted key data on the design features, population, intervention and outcomes of the studies.

Results: We identified four trials of enteral *vs* total parenteral nutrition, one trial of early enteral nutrition *vs* delayed enteral nutrition, one trial of gastric *vs* jejunal tube feeding, one trial of intermittent *vs* continuous enteral feeding, and three trials evaluating different enteral feeding formulae. Sample sizes were small, pneumonia definitions were variable and blinded outcome assessment was infrequent. Randomized trial evidence is insufficient to draw conclusions about the relation between enteral nutrition and nosocomial pneumonia.

Conclusions: Nutritional interventions in critically ill patients appear to have a modest and inconsistent effect on nosocomial pneumonia. This body of evidence neither supports nor refutes the gastropulmonary route of infection.

enteral nutrition nosocomial pneumonia, parenteral nutrition, prevention, ventilator-associated pneumonia

Introduction

Nosocomial pneumonia is an important cause of morbidity and mortality in hospitalized patients. Diagnosis and treatment continues to challenge clinicians and stimulate investigators. Prevention of this serious infection has been the focus of numerous studies, conferences and professional documents. Nosocomial pneumonia prevention strategies may be directed at the ventilator circuit (frequency of tubing circuit changes and gas humidification strategies), the endotracheal tube (intubation orifice, secretion drainage and suctioning) or body position (kinetic bed therapy and semirecumbancy). Other nonpulmonary approaches are pharmacologic (selective digestive decontamination and stress ulcer prophylaxis) or nutritional (the type, site and timing of enteral feeds).

The largest number of published randomized trials in intensive care medicine have evaluated selective digestive decontamination and stress ulcer prophylaxis. Five meta-analyses [1-5] suggest that selective digestive decontamination confers a large, clinically important and statistically significant reduction in nosocomial pneumonia rates (common odds ratio approximately 0.30, 95% CI 0.28–0.48). Nevertheless, selective digestive decontamination is not widely used, in part due to concern about long-term microbial resistance patterns and antibiotic costs [6]. Stress ulcer prophylaxis trials have been recently summarized in a meta-analysis suggesting that sucralfate, as compared with histamine-2-receptor antagonists or antacids, is associated with a trend toward a lower rate of nosocomial pneumonia (common odds ratio 0.78, 95% CI 0.60–1.01) [7].

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Other experiments show that modifying gastric pH with acidified enteral feeds decreases gastric colonization, thereby supporting this underlying biologic rationale [8]. However, sucralfate is not considered of proven benefit due to the possibility that sucralfate confers a protective effect only when compared with gastric pH-altering drugs (which themselves are associated with a modest increase in nosocomial pneumonia compared to control) [7].

Kinetic bed therapy has been reviewed in a meta-analysis of six trials in seriously and critically ill patients, which indicated a significantly lower rate of pneumonia and atelectasis in patients receiving continuous postural oscillation [9]. A less expensive and adaptable pneumonia prevention strategy focussing on body position has been studied in three randomized trials [10-12]. Torres *et al* [10] found that after instillation of radioactive technetium sulfur colloid into the stomach, radioactive counts in endobronchial secretions were significantly higher in samples obtained while patients were supine than when they were semirecumbent. In another study, scintigraphic evidence of esophageal reflux was found in 81% of patients in the supine position compared to 64% in the semirecumbent position [11]. Orozco-Levi *et al* administered nasogastric technetium sulfur colloid and found that radioactive counts in endobronchial secretions increased over time, but were higher in the supine than the semirecumbent position [12]. Although a causal relationship between pneumonia and this secondary endpoint of aspiration of gastric contents has not been convincingly demonstrated, these trials are in keeping with the gastropulmonary route of infection.

The gastropulmonary route of infection is a concept at least two decades old [13], support for which is derived from multiple human observational studies and experimental evidence [14,15]. Enteral nutrition, compared to parenteral nutrition, is associated with decreased translocation in animals and decreased infectious morbidity in critical illness in humans [16]. Accordingly, it holds the promise of affording protection against nosocomial pneumonia. However, enterally feeding critically ill patients is often associated with intolerance, thereby predisposing them to aspiration pneumonia. The goal of this systematic review is to critically appraise and summarize the randomized trials of nutritional strategies and their influence on nosocomial pneumonia in critically ill patients.

Methods

Study identification

To identify randomized trials, we searched two computerized databases from 1980 onwards. For MEDLINE, we used the following text words and keywords: critical care, intensive care units, pneumonia, respiratory tract infection, mechanical ventilation, gastropulmonary, enteral nutrition, randomized controlled trials, prospective studies. For EMBASE, we used: pneumonia, prevention, control. Frequently cited articles were identified and SCISEARCH (Science Citation Index online) was used to locate any additional relevant randomized trials. We also used the Cochrane Library, searching the Clinical Trials Registry for randomized trials, and the Cochrane Database of Systematic Reviews (CDSR) as well as the Database of Abstracts of Reviews (DARE) for systematic reviews containing relevant primary studies. We confined our search to studies enrolling non-neutropenic adult humans without the human immunodeficiency virus. We had no language restrictions.

The titles (and the abstracts, when available) in the MEDLINE and EMBASE printouts, and the reference lists of all primary and review articles were reviewed independently in duplicate. Any additional relevant articles were thereby identified and retrieved.

Study selection

The following selection criteria were applied to the full manuscripts by two reviewers independently:

1. Population: critically ill adults, including trauma and burn patients.
2. Interventions: nutritional support.
3. Outcomes: nosocomial pneumonia.
4. Design: published randomized trials in humans.

A priori, we excluded relevant nutritional interventions in seriously but not necessarily critically ill patients, studies examining surrogate endpoints for pneumonia [8], studies which did not report how pneumonia was diagnosed [17-19], studies which evaluated or reported composite infectious outcomes [20], and duplicate publications [21].

Study characteristics and data abstraction

Two reviewers abstracted data from the randomized trials to describe the method of treatment allocation, the proportion of patients who were excluded post-randomization, whether cointerventions were described, whether the endpoints were assessed by investigators blinded to the intervention, and the outcome definitions employed. Disagreements between reviewers on design characteristics and raw data abstraction were resolved by discussion and consensus.

Analysis

We measured agreement between reviewers on the selection of articles for inclusion in the review. We standardized presentation of the randomized trial results using relative risk, and calculated 95% confidence intervals using the log transformation method. Since study questions and trial designs differed, we did not

statistically pool results of these trials, or subgroups of them, in a meta-analysis.

Results

Study identification and selection

The search yielded four trials of enteral *vs* total parenteral nutrition [22-25], one trial of early enteral nutrition *vs* delayed enteral nutrition [26], one trial of gastric *vs* jejunal tube feeding [27], one trial of intermittent *vs* continuous enteral feeding [28], and three trials evaluating different enteral feeding formulae [29-31]. Agreement was 100% for selection of these trials and systematic reviews.

Study characteristics

Study characteristics are reported in Table 1. Patients were medical or surgical ICU patients, burn, or trauma victims. Two studies were explicit about concealment of randomization using sealed envelopes [26,28]. The nature of some of these comparisons precluded blinding of patients and caregivers. Patients were unlikely to be aware of the details of their care and were not participating in assessment of the presence of nosocomial pneumonia. However, lack of blinding could have affected the care delivered by bedside nurses, respiratory therapists and intensivists, which could have affected the development of lung infection. In one trial, the neurosurgeon evaluating outcomes was blinded [22]; in another, confirmation of outcome was conducted by a second blinded surgeon [24]. Two of the three studies comparing different feeding products employed blinded outcome assessment [29,31].

Cointerventions are interventions which are unrelated to the study question, yet may impact on the outcome, and could be unequally distributed across groups. These include stress ulcer prophylaxis and selective digestive decontamination (Table 1). Other cointerventions not mentioned, but potentially important to standardize or report, might include chest physiotherapy and position of the patients.

In two trials, the pneumonia definition incorporated but did not require invasive bronchoscopic techniques [24,28]; in a third trial, a positive bronchoalveolar lavage was required for the diagnosis [31].

Study results

The results of these randomized trials are presented in Table 2. The four trials evaluating total parenteral *vs* enteral nutrition yield inconsistent results. In one, there was a trend toward a lower rate of pneumonia associated with enteral nutrition [23], in another study the pneumonia rate was significantly lower in the enteral nutrition group [24], and in the remaining two studies, the pneumonia rate was slightly higher in patients receiving enteral nutrition [22,25].

One study examined early enteral nasoduodenal nutrition begun within 24 h *vs* nasoduodenal enteral nutrition delayed for 72 h. In patients receiving early feeds, there was a trend toward increased pneumonia (8/19 *vs* 4/19, respectively) [26].

Considering the potential for enteral nutrition to cause aspiration pneumonia, one study tested the effect of proximal *vs* distal delivery sites [27]. Two cases of pneumonia were identified amongst those 19 patients receiving prepyloric gastric feeds and no cases were observed in the 19 patients receiving post-pyloric feeds through a jejunal tube.

To avoid continuous alkalinization and intragastric Gram-negative growth associated with enteral feeding, intermittent enteral nutrition was compared with continuous enteral nutrition in one trial [28]. Five of 30 patients in each group developed nosocomial pneumonia.

Three studies examined different enteral feeding formulae and their relation to lung infection. The first compared modular tube feeds (a high protein, low fat, linoleic acid-restricted formulation enhanced with arginine, cysteine, vitamin A, zinc, omega-3-polyunsaturated fatty acids, and ascorbic acid) against Osmolite and Traumacal and found a trend toward lower pneumonia rates in the modular tube feed patients [29]. There was no difference in pneumonia between trauma patients fed Immun-Aid (containing glutamine, arginine, omega-3-polyunsaturated fatty acids, nucleotides, and branched chain amino-acids) *vs* Vivonex (standard enteral formulae) [30]. In another study of trauma patients, Immun-Aid was associated with a trend toward a lower pneumonia rate than patients fed with Promote (an isonitrogenous, isocaloric diet) [31].

Discussion

The results of these 10 trials of feeding strategies, either individually or in aggregate, provide inconclusive evidence about the relation between enteral nutrition and nosocomial pneumonia. These studies enrolled a total of 582 patients and contribute 117 cases of pneumonia. The single trial showing a significantly lower pneumonia rate associated with jejunal enteral nutrition over parenteral nutrition [24] has not been translated into widespread clinical policy, perhaps due to the inconvenience and expertise required for jejunostomy tubes. Aside from concerns about type I and II error when interpreting the trials in this review, there are other relevant outcomes addressed by some, but not all of these studies, including effects on nutritional markers and adverse outcomes such as catheter sepsis and patient comfort.

Table 1 Nutrition and nosocomial pneumonia: study characteristics

Author [reference]	Intervention	Population	Allocation	Cointerventions	Exclusion post-randomization	Blinding of outcome accessor	Definition of VAP
Young *et al* [22]	Nasogastric enteral nutrition *vs* total parenteral nutrition	Head injury patients	`Was randomly assigned to'	All patients received prokinetic	7 Exclusions: 5-early death, 2 -withdrew	Neurosurgen evaluating outcomes was blinded	Infiltrate and leukocytosis premature cells, fever, positive sputum culture
Moore *et al* [23]	Enteral nutrition via needle catheter jejunostomy *vs* total parenteral nutrition	Trauma patients requiring emergency celiotomy	`Randomized by computer assignment'	Broad spectrum antibiotics to both groups	No exclusions: 4-early death, 3-reoperation, 3-chronic illness, 2-ATI> 40, 2-head injury, 1-mechanical failure, 1-transfer	Outcome assessment not blinded	New infiltrate and fever, leukocytosis and purulent sputum
Kudsk *et al* [24]	Enteral nutrition via needle jejunostomy *vs* total parenteral nutrition	Patients with blunt and penetrating abdominal trauma	`Computer generated randomization table'	NR	2 Exclusions: death within 4 days	Secondary confirmation of outcome by blinded surgeon	New infiltrate and leukocytosis, positive sputum or BAL, or purulent sputum
Borzotta *et al* [25]	Enteral nutrition via needle catheter jejunostomy *vs* total parenteral nutrition	Patients with severe closed head injury	`Computer generated random number assignment'	Jejunostomy group had gastrostomy tube drainage	NR	Outcome assessment not blinded	Infiltrate and fever, leukocytosis, leukorrhea and bacteria on Gram stain
Eyer *et al* [26]	Early (<24 h) nasoduodenal tube feeding *vs*	Patients with blunt abdominal trauma	`Randomization by card drawn from sealed envelope'	All patients received either sucralfate or antacids but group not	14 Exclusions: 3-regular diet, 3-steroids,	Outcome assessment not blinded	New infiltrate and significant growth on sputum

Table 1 Nutrition and nosocomial pneumonia: study characteristics *(Continued)*

	late (>72 h) nasoduodenal tube feeding			specified	2-no NGT, 6-miscellaneous		culture with <10 epithelial cells, >25 wbc/hpf OR purulent secretions, fever and leukocytosis
Montecalvo *et al* [27]	Gastric *vs* jejunal tube feeding	Medical and surgical ICU patients	`Randomly assigned according to computer generated random number code'	25 Patients received sucralfate; 1 H_2RA; 2 H_2RA and antacids; 8 sucralfate and either H_2RA or antacids; 1 no stress ulcer prophylaxis, but group not specified	5 Patients crossed over from jejunal to gastric group and 2 patients crossed over from gastric to jejunal group; these 7 patients were included until the day they crossed over	Cultures reviewed blinded to group assignment	New and persistent infiltrate and three of: purulent sputum with numerous bacteria, purulent sputum with nosocomial pathogen, T>38[6], or wbc >10
Bonten *et al* [28]	Intermittent enteral feeding (18 h) *vs* continuous enteral feeding (24 h)	Mixed ICU patients and cardiac surgery patients needing ventilation > 3 days	`Randomization was performed with sealed envelopes'	Intermittent: 13-antacids and 17-sucralfate; continuous: 7 - antacids and 23 - sucralfate	None	Outcome assessment not blinded	New and persistent infiltrate and 3 of: T>38 or T<35[5] OR wbc > 10 and/or left shift or wbc < 3 OR 10 wbc/hpf on ET Gram strain OR positive ET aspirate and one of these: BAL (positive if > 10^4 CFU/ml) OR PSB (positive if >10^3 CFU/ml) OR positive blood culture OR positive pleural culture

Table 1 Nutrition and nosocomial pneumonia: study characteristics *(Continued)*

Gottsschlich *et al* [29]	Modular tube feeding *vs* two standard enteral feeding (Osmolite *vs* Traumacal)	Burn patients (>10% BSA)	`Random number table stratified for age, center and burn size'	NR	NR	Physicians, nurses, technicians, clinical and research personnel were blinded	Infiltrate and positive sputum culture and systemic antibotics
Moore *et al* [30]	Early enteral immune-enhancing feeding *vs* standard enteral feeding (Vivonex)	Trauma patients	`Randomized by a computer-generated schedule'	NR	16 exclusions: 9-inappropriate randomizations, 7-drop -outs 1-early death	Outcome assessment not blinded	New and progressive infiltrate, fever, leukocytosis, positive sputum Gram stain with many polys
Kudsk *et al* [31]	Early immune-enhancing feeding via jejunostomy *vs* standard enteral feeding (Promote)	Trauma patients requiring emergency celiotomy	`Computer-generated randomization table'	Short-term broad spectrum antibiotics to both groups	NR	All caregivers blinded except nutritionist	New or changing infiltrate and fever, leukocytosis, purulent sputum underwent BAL (positive if > 10^3 CFU/hpf)

Abbreviations: ATI=acute trauma index; BAL=bronchoalveolar lavage; NGT=nasogastric tube; wbc=white blood cells; hpf=high power field; H_2RA=histamine-2-receptor antagonists; ET=endotracheal; CFU=colony forming units; BSA=body surface area; NR=not reported; VAP=ventilator-associated pneumonia; PSB=protected specimen brush.

Readers are referred to the original articles for these important details.

Factors such as cost, and ease with which the feeding strategy can be employed, are additional issues that bear on the interpretation and application of these trial results in practice. Intensivists also consider evidence from observational studies when making clinical decisions. Given these provisos, it is not surprising that definitive statements about enteral nutrition and lung infection are not forthcoming. Some guidelines from the Center for Disease Control on the prevention of nosocomial pneumonia [32] focus on gastropulmonary approaches. Stress ulcer prophylaxis with an agent that does not increase gastric pH was `suggested for implementation in many hospitals and supported by suggestive clinical and epidemiologic studies and a strong theoretical rationale'. Other interventions labelled as `unresolved for which no recommendations were made' included jejunal feeding, intermittent enteral feeding and selective digestive decontamination. In the American Thoracic Society statement on prevention of hospital-acquired pneumonia in adults [33], some prophylactic interventions were classified as having `probable effectiveness, used widely in some clinical settings', such as distal enteral nutrition, semi-erect positioning, and sucralfate. Selective digestive decontamination was considered `of unproven value used on a limited investigational or clinical basis'.

Table 2 Results of randomized trails of nutrition and nosocomial pneumonia

Intervention (author [reference])	Pneumonia rates	Relative risk (95% CI)
Nasogastric enteral nutrition *vs* parenteral nutrition (Young [22])	TPN: 6/23 (26%) EN: 9/28 (32%)	1.23 (0.51–2.95)
Jejunostomy feeding *vs* total parenteral nutrition (Moore [23])	TPN: 6/30 (20%) EN: 0/29 (0%)	Undefined
Jejunostomy feeding *vs* total parenteral nutrition (Kudsk [24])	TPN: 14/45 (31%) EN: 6/51 (12%)	0.38 (0.16–0.90)
Jejunostomy feeding *vs* total parenteral nutrition (Borzotta [25])	TPN: 9/23 (39%) EN: 15/36 (42%)	1.06 (0.56–2.02)
Early nasoduodenal *vs* late nasoduodenal feeding (Eyer [26])	Late: 4/19 (21%) Early: 8/19 (42%)	2.00 (0.72–5.54)
Jejunal *vs* gastric feeding (Montecalvo [27])	Gastric: 2/19 (11%) Jejunal: 0/19 (0%)	Undefined
Intermittent enteral feeding *vs* continuous enteral feeding (Bonten [28])	CEF: 5/30 (17%) IEF: 5/30 (17%)	1.0 (0.32–3.10)
Modular tube feeding (MTF) *vs* Osmolite *vs* Traumacal (Gottschlich [29])	Osmolite: 6/14 (43%) Traumacal: 9/19 (47%) MTF: 2/17 (12%)	0.27 (0.07–1.15)* 0.25 (0.06-0.99)†
Immun-Aid *vs* Vivonex (Moore [30])	Vivonex: 4/47 (9%) Immun-Aid: 4/51 (8%)	0.92 (0.24–3.48)
Immun-Aid *vs* Promote (Kudsk [31])	Promote: 3/17 (18%) Immun-Aid: 0/16 (0%)	Undefined

Abbreviations: EN = enteral nutrition; TPN = total parenteral nutrition; CEF = continuous enteral feeding; IEF = intermittent enteral feeding. * Osmolite compared to MTF. † Traumacal compared to MTF.

Nutrition is integral to the care of an ICU patient. The method, site and timing of enteral nutrition may have a protective or predisposing influence on the risk of nosocomial infection [34], though strong proof from experiments in humans does not currently exist. Although a meta-analysis of published and unpublished trials of general surgical and trauma patients suggested a lower pneumonia rate in patients receiving enteral nutrition *vs* total parenteral nutrition [35], published data from ventilated medical ICU patients are sparse, and generalizing to other populations may not be reasonable. Interventions requiring further investigation with large rigorous studies of ICU patients include those discussed in this review, as well as the size of feeding tubes [36], their insertion site, where the tubes are located in the gastrointestinal tract [37], feeding advancement schedules, and the effect of prokinetic drugs [38].

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