# Continuing versus Holding Duotube Feeds in the Peri-Extubation Period with respect to the Risk of Developing Aspiration Pneumonia: a Prospective, Randomized Trial

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## A. Study Purpose and Rationale

Nosocomial pneumonia is the second-most common hospital acquired infection in the United States and carries the highest associated morbidity and mortality[1]. One recent meta-analysis found that nosocomial pneumonia develops in 9 to 17% of all intensive care unit (ICU) patients[1]. Fagon *et al*[3] determined that while only 16.4% of ICU patients develop nosocomial pneumonia, their mortality rate is 52.4% compared to 22.4% in ICU patients without pneumonia ($p<0.001$).

Aspiration of oropharyngeal or esophagogastric contents into the lungs is thought to be one of the primary causes of ICU-acquired pneumonia[1,4]. Patients in the ICU have higher rates of aspiration and microaspiration than other hospitalized patients for many reasons: presence of nasogastric or nasoduodenal tubes, suboptimal functioning of the lower esophageal sphincter, decreased gastric motility, presence of endotracheal tubes, decreased gag and cough reflexes, and decreased level of consciousness[1]. Patients in the ICU have increased rates of aspiration both while an endotracheal tube is present and in the first few days after extubation due to impaired gag reflex, mucosal lesions from endotracheal tube damage, and altered level of consciousness[5,6,7]. Leder *et al*[6] found that up to 45% of patients who received mechanical ventilation for a period of 48 hours or more aspirate in the first 24 hours after extubation. While Barquist *et al*[7] documented much lower rates of aspiration (15%) in the first 24 hours after extubation, they found that all of these patients who aspirated went on to develop pneumonia.

Although not specifically mentioned in the 1996 American Thoracic Society consensus statement on prevention of hospital-acquired pneumonia[1], many ICU physicians routinely hold enteral feeds in the period surrounding extubation [8,9] in an attempt to minimize aspiration events during this period of increased risk for aspiration. However, no formal randomized trials have evaluated whether this practice of holding enteral feeds in the peri-extubation period actually does decrease the risk of developing aspiration pneumonia.

Meanwhile, multiple studies have documented that inadequate nutrition of critically ill patients leads to poor outcomes, including increased rates of infection and increased mortality[9,10,11]. Moreover, malnutrition can lead to decreased respiratory muscle strength and function and impaired ventilatory drive, in turn resulting in difficulty weaning patients from mechanical ventilation [10,11]. DeJonghe *et al*[9] found that up to 50% of the daily volume of enteral feeds was held on days on which extubation was attempted. Although perhaps not a significant contributor to malnutrition if the patient is successfully extubated on the first attempt, repeatedly holding the enteral feeds on successive days where extubation is anticipated but unsuccessful might contribute to significant malnutrition and its ensuing complications in a critically ill patient. Therefore, the practice of holding enteral feeds in critically ill patients on days where extubation is anticipated may not be entirely benign.

Given that holding enteral feeds may contribute to poor outcomes in critically ill patients in some cases, this study is designed to examine whether the practice of holding duotube feeds in the peri-extubation period has the benefit of decreasing the risk of aspiration pneumonia.

## B. Study Design and Statistical Analysis

There will be two study arms in this trial: one group will have enteral feeds delivered continuously via duotube throughout the period surrounding extubation and the second group will have

duotube feeds held for the three hours preceding extubation through the four hours following extubation (seven hours total surrounding extubation). Subjects will be randomly assigned to one of the two study arms by means of a computer-generated random number program. Baseline characteristics of each subject will be recorded, including age, sex, race, reason for ICU admission, Acute Physiology and Chronic Health Evaluation (APACHE) II score[14], presence or absence of diabetes mellitus (which may be associated with gastroparesis), history of prior cerebrovascular accident (which may be associated with increased rates of aspiration), and duration of mechanical ventilation.

The frequency of the primary outcome, development of pneumonia in the first 72 hours after extubation, will be compared in these two groups, as will secondary outcomes including success rate of first extubation attempt, reintubation rate, and mean change in serum albumin level (significantly correlated with decreasing percent of goal calories infused[15]). For study purposes pneumonia will be defined as the presence of a new infiltrate on chest x-ray plus two of the following three criteria: 1) temperature greater than 101 degrees Fahrenheit or less than 96 degrees Fahrenheit, 2) white blood cell count greater than 10,000/mL, 3) growth of bacteria on sputum culture. The presence of new infiltrate on chest x-ray must be confirmed by two separate attending radiologists who will be blinded to the subject's study group.

The rate of pneumonia in the first 96 hours after extubation (16%) noted by Barquist *et al*[7] will be used as the expected rate of pneumonia in the group with continuous enteral feeds. Arbitrarily, as there have not been any formal studies on the impact of holding enteral feeds on the development of pneumonia, 12% will be used as the expected rate of pneumonia in the group with interruption in enteral feeding surrounding extubation. In order to detect a 4% difference in the rates of pneumonia in the two groups at a p-value of 0.05 and power of 80%, this study will require enrollment of 1252 subjects per group (2504 subjects total). Assuming that 14 patients per week are eligible for the study at each site but that 15% of eligible patients decline to participate, it will take approximately two years to enroll enough subjects.

The chi-square test will be used to compare rates of pneumonia, reintubation, and success of first extubation attempt in the two groups, while the student's t-test will be used to compare the mean change in serum albumin in the two groups.

**C. Study Procedure and Data Collection**

Each morning at 7 a.m. the study nurse will screen all study patients for readiness for a spontaneous breathing trial, following the protocol previously described by Ely *et al*[16] (Appendix 1). If the patient meets criteria, the patient will be started on a spontaneous breathing trial of continuous positive airway pressure (CPAP) at 5 cm of water. If the patient successfully completes a thirty minute trial of spontaneous breathing as described by Ely *et al*[16] (Appendix 1). that patient's duotube feeds will either be held or continued according to the patient's assigned study group. The patient will be continued on CPAP for three additional hours. If the patient still has not failed the spontaneous breathing trial by any of the criteria laid out by Ely *et al*[16] (Appendix 1), the patient will be extubated. The group randomized to holding enteral feeds will have their feeds restarted four hours after extubation. Any decisions regarding need for reintubation will be made by the primary ICU team according to their usual practice. Any patient who fails the three hour CPAP trial will be returned to his initial ventilator settings and removed from the study protocol. Similarly, any patient who is reintubated will not be included in the study protocol for further extubation attempts.

The study will last from the morning of the day of extubation until seventy-two hours following extubation. Each morning chest x-rays will be obtained on all study subjects both to assess the presence of any new infiltrate and to evaluate the placement of the duotube. Serum albumin levels will be measured on the morning of extubation and again 72 hours after extubation.

**D. Study Drugs**

No drug is being studied.

**E. Medical Device**

No medical device is being studied.

**F. Study Questionnaires**

No questionnaire will be used.

**G. Study Subjects**

All patients in the adult intensive care units (surgical, cardiothoracic, neurological, cardiac, and medical ICUs) at the study sites who have been intubated and mechanically ventilated for at least 48 hours and who have been enterally fed through a duotube for at least 24 hours will be eligible for the study, with the exception of patients who have an abnormal chest x-ray.

**H. Recruitment of Subjects**

The study nurse will screen all patients in the ICUs each afternoon for eligibility and submit names of eligible patients to the study investigators. If an eligible patient has the mental status to understand the risks and benefits of the study and to give informed consent to participate in the study, he will be offered the opportunity to enroll in the study. For any eligible patient who does not have the mental status to consent to the study because of underlying neurologic deficits, medical illness, or excessive sedation, the patient's health care agent will be offered the opportunity to enroll the patient in the study.

**I. Confidentiality of Study Data**

All study subjects will be assigned a unique study identification number for use in data recording and processing. Only the study investigators will have access to the list which coordinates study identification numbers with patient names.

**J. Potential Conflicts of Interest**

None.

**K. Location of Study**

The study will take place in the adult intensive care units (comprising the surgical, cardiothoracic, neurologic, cardiac, and medical intensive care units) of New York-Presbyterian Hospital (both Columbia and Cornell campuses), located on Fort Washington Avenue (Columbia campus) and York Avenue (Cornell campus), New York, NY.

**L. Potential Risks**

This study seeks to identify whether enteral feeding in the period surrounding extubation of a mechanically-ventilated patient leads to an increased incidence of aspiration pneumonia, a hypothesis which is commonly held but which has never been tested. For purposes of this study, I have assumed that subjects randomized to continuous duotube feeding will have a 4% absolute increased incidence of aspiration pneumonia, although this number may well overestimate the true rate of aspiration pneumonia

in these patients. Whether aspiration pneumonia has serious morbidity and mortality has been called into question by some[15,17] , but like any infection in a critically ill patient, aspiration pneumonia could certainly contribute to or cause a patient's demise. Meanwhile, holding duotube feeds in the period surrounding extubation can contribute to malnutrition, a condition associated with increased morbidity and mortality in critically ill patients.

**M. Potential Benefits**

Individual patients may or may not benefit from enrollment in this study.

**N. Alternative Therapies**

Not applicable.

**O. Compensation to Subjects**

None.

**P. Costs to Subjects**

None.

**Q. Minors as Research Subjects**

None.

**R. Radiation or Radioactive Substances**

None.

**Appendix 1**

Criteria for Readiness for Spontaneous Breathing Trial (all 6 must be met)

pO2 / FiO2 > 200
positive end-expiratory pressure (PEEP) $\leq$ 5 cm water
intact cough during suctioning of airway
respiratory rate / tidal volume $\leq$ 105 (while on continuous positive airway pressure of 5 cm water)
no vasopressor infusion
no sedatives

Criteria for Failing Spontaneous Breathing Trial (only one positive response required)

respiratory rate >35 for $\geq$ 5 minutes
SaO2 < 90%
Heart rate > 140
Sustained change in heart rate of 20% above or below baseline
SBP > 180 mm Hg
SBP < 90 mm Hg
Increased anxiety
Diaphoresis

These criteria are taken from Ely *et al*[16].

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