

GASTRIC REFLUX IN MECHANICALLY VENTILATED GASTRIC FED ICU PATIENTS

BY

MARILYN SCHALLOM

Submitted to the Graduate Degree Program in Nursing and the
Graduate Faculty of the University of Kansas in partial fulfillment of the
requirements for the degree of Doctor of Philosophy

Chairperson: Janet Pierce DSN, APRN, CCRN, FAAN

Kelly Kramer-Jackman PhD, APRN, FNP-BC

Norma Metheny PhD, RN, FAAN

James Orr PhD

Moya Peterson PhD, RN, CPNP, APRN

Date Defended: June 11, 2013

The Dissertation Committee for MARILYN SCHALLOM certifies that this is the approved version of the following dissertation:

GASTRIC REFLUX IN MECHANICALLY VENTILATED GASTRIC FED ICU PATIENTS

Chairperson: Janet Pierce DSN, APRN, CCRN, FAAN

Date approved: June 16, 2013

ABSTRACT

Background: Reflux of gastric contents in gastric fed patients is a contributor to pulmonary aspiration. Aspiration events are reported in approximately 50-75% of patients with endotracheal tubes. Aspiration of oral and gastric secretions in ventilated patients is a major cause of ventilator associated pneumonia (VAP). Guidelines that recommend head of bed (HOB) elevation greater than 30° to prevent reflux, aspiration and VAP conflict with guidelines to prevent pressure ulcers which recommend HOB elevation no greater than 30°. Studies are lacking on direct comparison of HOB elevation at 30° and 45° for reflux, aspiration and pressure ulcer outcomes simultaneously. Esophageal probe pH measures are used to detect reflux. No studies have examined the predictive relationship of reflux and aspiration in mechanically ventilated gastric fed patients or the role of pH measurement at the bedside with pH paper to detect gastric reflux.

Purpose: This study had 6 aims: 1) To describe the frequency and duration to which patients' HOB angles are temporarily lowered for treatment purposes below 30° or below 45°, 2) To describe the occurrence of reflux (pepsin-positive oral secretions) and aspiration (pepsin-positive tracheal secretions) with HOB elevation at 30° and 45°, 3) To determine the association between reflux and aspiration with the 2 different HOB elevations in adult intensive care unit (ICU) mechanically ventilated gastric fed patients, 4) To determine the association between a temporarily lowered HOB position for treatment purposes and reflux of gastric contents, 5) To determine the association between 7 patient characteristics (gender, age, body mass index, gastric residual volume, sedation level, disease severity, and use of prokinetic agents) and reflux, 6) To determine the association between the pH (range 0-14) of oral secretions and pepsin presence in oral secretions.

Methodology: Human Research Protection Office approval was obtained. Consent was acquired from patient surrogates the day prior to enrollment in the study. A randomized 2-day crossover trial was conducted in a surgical and medical ICU. Mechanically ventilated gastric fed subjects were randomly assigned to 1 of the 2 HOB elevation sequences, HOB 30° for 12 hours (hrs) on day 1 and 45° for 12 hrs on day 2 or HOB at 45° for 12 hrs on day 1 and 30° for 12 hrs on day 2. A HOB measurement device stored HOB angles every 30 seconds over the 36 hrs. Subject preferences for positioning for comfort were considered and HOB was lowered at any time by clinicians as the clinical situation warranted or during procedures and diagnostic tests. Usual care for the elevation of the HOB was considered 30° and experimental was 45°. Oral secretions were obtained hourly or as needed and tracheal secretions every 2 hrs or as needed. All samples of oral secretions were examined for the presence of pepsin and pH measurement. Subjects were repositioned every 2 hrs as their condition allowed. Skin assessment of sacral/coccyx and greater trochanter areas were assessed for pressure ulcers every 2 hrs with each reposition. Data were analyzed using Wilcoxon Signed Rank Tests, Friedman tests for repeated measures and Kendall's tau correlations.

Results: Fifteen subjects were enrolled; 11 subjects completed both days, 4 subjects had partial data collection due to endotracheal tube removal. The total number of hrs was 150 hrs at 30° and 160 hrs at 45°. No subjects developed pressure ulcers per National Pressure Ulcer Advisory Panel staging guidelines. Subjects were maintained at 30° for 96% of possible minutes and at 45° for 77% of possible minutes ($p = .035$). The mean HOB angle when lowered was 8.2° in the 30° condition and 19.4° in the 45° condition ($p = .008$). Subjects' HOB angles were lowered 66 times (mean = 4.7/patient) in the 30° hrs and 76 times (mean = 5/patient) in the 45° hrs. Overall mean angle for HOB was 30° for usual care hrs and 39° for the experimental hrs. A total

of 188 oral secretions were obtained, 106 (56%) were pepsin-negative and 82 (44%) were pepsin-positive. A total of 174 tracheal secretions were obtained, 66 (38%) were pepsin-negative and 108 (62%) were pepsin-positive. No significant association was found with the minutes the HOB was lowered or the mean angle when lowered and percent pepsin-positive oral secretions. Mean HOB angle on each day was significantly negatively correlated with percent pepsin-positive oral secretions. The mean percent of pepsin-positive oral secretions was not significantly higher ($p=.108$) at 30° HOB elevation (48.4 ± 31.3) compared to 45° HOB elevation (32.3 ± 33.2). The mean percent of pepsin-positive tracheal secretions was not significantly higher ($p = .366$) at 30° HOB elevation (69.4 ± 33.8) than 45° HOB elevation (62.5 ± 34.5). The median frequency that oral secretions were obtained, (mean, SD, median) 8.5 ± 3.6 , 9.5 at 30° and 5.7 ± 3.2 , 5 , at 45° , was significantly lower at 45° ($p = .035$). The only significant patient characteristic in relationship to the percent of pepsin-positive oral secretions was deeper sedation. No relationship between reflux and aspiration or pH measures and reflux were found.

Conclusions: With the cross over design of 15 subjects, the number of oral and tracheal specimens collected provided over 360 samples. Lower mean HOB angles as well as deeper sedation levels were associated with a significantly higher frequency of reflux. Results of this study provide evidence that HOB positioning $> 30^\circ$ is feasible and superior to HOB $\leq 30^\circ$ in mechanically ventilated gastric fed ICU patients to reduce reflux and aspiration without development of pressure ulcers.

ACKNOWLEDGEMENTS

I would like to thank all those who helped me complete this amazing doctoral education journey. Dr. Pierce as my academic advisor and dissertation chair has provided me immense support, guidance and expert advice. Thank You! I'd also like to thank Dr. Metheny who has mentored me for over 20 years in research, writing and now my dissertation work. I'd also like to thank Dr. Orr for serving as my minor advisor and committee member. Your feedback always provided great improvements. Thanks to Dr. Kramer-Jackman and Dr. Peterson for sharing your clinical expertise and your support as committee members. To all the nurses at Barnes-Jewish Hospital in the MICU and SICU, a deep and everlasting gratitude for all your encouragement, assistance in finding patients and families, and assistance with data collection. I would like to thank Betsy Dykeman for her support and work on the study. I couldn't have done this study without support from nursing leaders Jennifer Aycock, Michelle Gatzert, Carrie Sona, Donna Prentice and the dietitians Beth Taylor and Lisa Mehringer. I extend a big thanks to Dr. John Kirby and Dr. John Mazuski for their support on the study, Dr. Robert Southard for opening his lab to me and Dr. Chang and Mark Woerner for work on the specimen pepsin tests.

The study is dedicated to my amazing family and friends. My deepest appreciation is extended to my mom and dad, John and Marge Maurer, my siblings, friends and co-workers. Thanks for always motivating me with your support. Words can't begin to express my appreciation to my husband Roger and our amazing children, Danie, Megan and David. You have done more to help me than you will ever know and I will forever be grateful.

Lastly for so many who have said prayers for me, especially during the dissertation process, I am most grateful. I felt God's guiding hand was with me. I am blessed beyond words and am forever grateful for His grace, the gift of faith and all my professors, family and friends.

TABLE OF CONTENTS

ABSTRACT	iii
ACKNOWLEDGEMENTS	vi
LIST OF ABBREVIATIONS	x
LIST OF FIGURES	xii
LIST OF TABLES	xiii
CHAPTER I INTRODUCTION	1
Gastric Reflux and Aspiration	2
Statement of Problem	4
Significance	4
Aims and Research Questions	5
Definition of Terms	7
Conceptual Model	10
Assumptions	11
CHAPTER II REVIEW OF THE LITERATURE	13
Anatomy and Physiology of Normal Food Passage Through the Upper Gastrointestinal Tract	14
<i>Swallowing</i>	14
<i>Esophagus</i>	14
<i>Esophageal Sphincters</i>	15
<i>Stomach</i>	17
<i>Duodenum</i>	19
Anti-reflux Mechanisms	19
<i>Anti-reflux Barriers</i>	20
<i>Esophageal Acid Clearance</i>	20
<i>Tissue Resistance</i>	21
Injury Secondary to Gastric Reflux	22
<i>Inflammatory Response</i>	22
<i>Pepsin Induced Injury</i>	23
Factors Increasing Reflux	23
<i>Transient Lower Esophageal Sphincter Relaxations</i>	23
<i>Gastric Factors</i>	24
<i>Risk Factors for Gastroesophageal Reflux</i>	24
Reflux in Critically Ill Patients	25
<i>Mechanism of Reflux</i>	25
<i>Gastric Tubes</i>	26
<i>Gastric Motility</i>	28
<i>Duodenogastric Reflux and Esophageal Damage</i>	29
Pulmonary Aspiration of Gastric Contents	29
<i>Risk Factors for Aspiration</i>	30
<i>Airway and Lung Injury Associated with Aspiration</i>	31

<i>Additional Risk Factors for Reflux and Aspiration in ICU Patients</i>	32
Interventions to Reduce Reflux and Aspiration	33
<i>Head of Bed Positioning</i>	33
<i>Gastric Residual Volume Monitoring</i>	37
<i>Gastric or Small Bowel Tube Location</i>	38
<i>Feeding Method</i>	39
<i>Prokinetics</i>	40
<i>Subglottic Secretion Drainage</i>	42
Measures to Detect Reflux and Aspiration	42
<i>Esophageal pH Monitoring for Reflux</i>	42
<i>Methods to Detect Aspiration</i>	43
<i>Pepsin Assay</i>	43
Conclusion	47
CHAPTER III METHODOLOGY	49
Research Design	50
<i>Setting</i>	51
<i>Sample</i>	51
<i>Randomization</i>	53
Data Collection and Procedures	54
Study Variables and Measurements	57
<i>HOB Elevation</i>	57
<i>Pepsin Analysis for Reflux and Aspiration</i>	58
<i>Age and Gender</i>	60
<i>Gastric Residual Volume</i>	61
<i>Richmond Agitation-Sedation Scale (RASS)</i>	61
<i>Acute Physiology and Chronic Health Evaluation (APACHE II)</i>	62
<i>Body Mass Index (BMI)</i>	63
<i>Prokinetics</i>	63
Sample Size and Data Analysis	64
Ethical Considerations	66
CHAPTER IV RESULTS	69
Sample	70
<i>Screening and Enrollment</i>	70
<i>Baseline Characteristics</i>	73
Description of HOB Maintenance at Usual and Experimental Level	76
Description of Reflux and Aspiration Occurrence	83
Association between Reflux and Aspiration	85
Lowered HOB and Reflux	88
Association of Subject Characteristics and Reflux	89
Oral Secretion pH and Pepsin Measurements to Detect Reflux	91
CHAPTER V DISCUSSION, IMPLICATIONS, CONCLUSION	93
HOB Elevation	94

Description of Reflux and Aspiration Occurrence	100
Association between Reflux and Aspiration	104
Effect of Lowered HOB on Reflux and Aspiration	106
Association of Subject Characteristics and Reflux	107
Oral Secretion pH and Pepsin Measurements to Detect Reflux	110
Limitations of the Study	111
Implications for Practice and Future Research Directions	112
Conclusions	115
Appendix A Subject Screening Form	117
Appendix B Subject Demographic Form	118
Appendix C pH Measurements.....	119
Appendix D Data Collection Sheet.....	120
References	121

LIST OF ABBREVIATIONS

- Acute Physiology and Chronic Health Evaluation (APACHE II)
- American Association of Critical Care Nurses (AACN)
- American Society for Parenteral and Enteral Nutrition (ASPEN)
- Body Mass Index (BMI)
- Centers for Disease Control (CDC)
- Electronic Medical Record (EMR)
- Enzyme-Linked Immunosorbent Assay (ELISA)
- Extraesophageal Reflux (EER)
- Gastric Residual Volume (GRV)
- Gastroesophageal Reflux (GER)
- Gastroesophageal Reflux Disease (GERD)
- Head of Bed (HOB)
- Histamine (H₂)
- Hour (hr)
- Intensive Care Unit (ICU)
- Interleukin (IL)
- Lower Esophageal Sphincter (LES)
- Microgram (mcg)
- Migrating Motor Complex (MMC)
- Milliliter (ml)
- Nasogastric (NG)
- Percutaneous Endoscopic Gastric (PEG) Tube

- Platelet Activating Factor (PAF)
- Phosphate Buffered Saline with Tween (PBST)
- Principal Investigator (PI)
- Reactive Oxygen Species (ROS)
- Richmond Agitation-Sedation Scale (RASS)
- Simplified Acute Physiology Score (SAPS II)
- Society of Critical Care Medicine (SCCM)
- Subglottic Secretion Drainage (SSD)
- Transient LES Relaxations (tLESRs)
- Upper Esophageal Sphincter (UES)
- Ventilator Associated Pneumonia (VAP)

LIST OF FIGURES

Figure	Page
1. Conceptual Model of Variables Thought to be Associated with Reflux and Aspiration.....	11
2. Reflux into Oral Cavity, Pharynx and Larynx.....	16
3. Endotracheal Tube in the Airway.....	17
4. Esophageal Orientation in the Semi-recumbent Compared to Supine Position.....	34
5. Patient Enrollment, Randomization and Disposition.....	72
6. Total Minutes the HOB was Lowered for Each HOB Assignment.....	77
7. Mean HOB When Lowered Less Than Assigned.....	77
8. Overall Mean of the HOB.....	78
9. Boxplots of Percent of Pepsin-Positive Oral Secretions at Both HOB Elevations	84
10. Boxplots of Percent of Pepsin-Positive Tracheal Secretions at Both HOB Elevations.....	85
11. Frequency of Gastric Residual Volume (GRV) in Categories.....	90

LIST OF TABLES

Table	Page
1. Randomized Crossover Design.....	51
2. Summary of Measurements.....	57
3. Richmond Agitation-Sedation Scale.....	62
4. Subject and Baseline Characteristics.....	75
5. Reasons and Frequencies the HOB was Lowered for Other than Repositioning.....	81
6. Hours HOB was Lowered for Patient Intolerance.....	81
7. Results of Paired Oral and Tracheal Samples.....	86
8. Specimen Results Log for One Subject with Observed Reflux.....	87
9. Specimen Results Log for Second Subject with Observed Reflux.....	88
10. Correlations of Minutes and Mean Less than HOB Assignments and Overall Mean at each HOB Elevation and Percent of Pepsin-Positive Oral Secretions.....	89
11. Correlations of Subject's Characteristics and Percent of Pepsin-Positive Oral Secretions...	91
12. pH Measurements and Associated Oral Secretions Pepsin Results.....	92

CHAPTER I
INTRODUCTION

Gastric Reflux and Aspiration

As a result of their primary illness or injury and need for mechanical ventilation, intensive care unit (ICU) patients often cannot consume nutritional requirements by mouth. Therefore, many patients require feeding tubes for nutrition and hydration. Gastric feeding is used most frequently as the initial site for feeding, although it is associated with a greater risk for gastroesophageal reflux (GER) of gastric contents. GER is associated with tube feedings for a variety of reasons such as gastric distention, and tubes traversing the esophageal sphincters. In addition, pulmonary aspiration of gastric content can lead to pneumonia.¹

GER refers to the passage of gastric contents into the esophagus. In most people, GER is a normal physiologic process occurring a few times a day. In contrast, patients with gastroesophageal reflux disease (GERD) experience frequent and abnormal amounts of GER which can lead to esophageal mucosal injury. Additionally, long term GERD is associated with Barrett esophagus which increases the risk of esophageal cancer.² Extraesophageal reflux (EER) refers to the passage of gastric contents in extraesophageal areas including the pharynx, oral cavity, larynx and upper airway above the vocal cords.³ EER is linked to asthma, posterior laryngitis, chronic coughing, pharyngitis,⁴⁻⁵ and middle ear and upper respiratory tract infection.⁶⁻
⁷ In the ICU setting, GER and EER are generally not measured or detected unless large amounts of gastric secretions are visualized in the oral cavity by health care providers.

Aspiration represents inhalation of material (oral or gastric) into the airway below the level of the vocal cords. Aspiration is the leading cause of pneumonia and results in significant morbidity and mortality across a variety of settings.⁸ Pulmonary aspiration of gastric secretions resulting in aspiration pneumonia and aspiration pneumonitis have been reported in the community setting,⁸ in pre-hospital emergency situations,⁹ in a variety of hospitalized patients on

medical-surgical divisions,¹⁰ in critically ill neonate, pediatric^{4, 11-12} and adult patients¹³⁻¹⁴ and in anesthesia situations.¹⁵

Critically ill patients often have a decreased level of consciousness which impairs the gag reflex and leads to pooling of oral secretions in the posterior oropharynx. In patients with an endotracheal tube, a direct pathway is available for these secretions to enter the lungs.¹⁶ Aspiration events are reported in approximately 50-75% of patients with endotracheal tubes.¹⁰ Aspiration of oral and gastric secretions in ventilated patients is a major cause of ventilator associated pneumonia (VAP).¹⁴ VAP is one of the most common hospital-acquired infection in critically ill patients with a reported incidence of 10-40%.¹⁷⁻¹⁸ VAP is associated with an increased length of mechanical ventilation, ICU and hospital length of stay as well as increased mortality. Each case of VAP is estimated to increase hospital costs by \$40,000-\$50,000.¹⁸

Critical care nurses provide interventions to prevent complications. However, at times nurses must balance the prevention of one potential complication against the prevention of other complications.¹⁹⁻²⁰ Several guidelines aim to reduce the complications of reflux, aspiration and VAP. Generally, VAP prevention interventions include recommendations for the head of bed (HOB) elevation to be maintained greater than 30 degrees (°) and as high as 45° when possible. Organizations recommending HOB elevation greater than 30° include: 1) the Centers for Disease Control (CDC),²¹ 2) the American Association of Critical Care Nurses (AACN),²² 3) American Society for Parenteral and Enteral Nutrition (ASPEN),¹ 4) Canadian Critical Care Trials Group,²³ and 5) a joint guideline from ASPEN and the Society of Critical Care Medicine (SCCM).²⁴

Conversely, risk of pressure ulcer development increases with HOB elevation above 30° due to increased pressure load to the sacral area in semi-recumbent and lateral positioning.²⁵⁻²⁶ Clinical practice guidelines on pressure ulcer reduction encourage limitation of HOB elevation in

semi-recumbent or side lying positions.²⁷⁻²⁸ In addition, many factors such as patient hemodynamic instability, patient comfort, and patient surgical or medical history may preclude the ability to maintain 30-45° HOB elevation.

Statement of Problem

Large-volume aspirations following vomiting occur infrequently and are often unwitnessed by clinicians.²⁹ However, microaspirations occur frequently in gastric fed patients.¹⁴ Nurses are often not aware that a patient is experiencing reflux thus increasing the risk for aspiration. No studies have examined the predictive relationship of reflux and aspiration in mechanically ventilated gastric fed patients. Additionally, guidelines that recommend HOB elevation greater than 30° to prevent reflux and aspiration conflict with guidelines to prevent pressure ulcers which recommend HOB elevation no greater than 30°. Therefore, research is needed to study the difference in the incidence of GER with 30° compared to 45° HOB elevations. Obtaining oral secretions is easier and less stressful for the patient than obtaining tracheal secretions. A simple pH measurement of oral secretions has not been studied in the mechanically ventilated gastric fed patient as a potential marker for reflux in this population. If reflux episodes could be detected, association with aspiration determined and risk factors identified, nurses could be better informed to make HOB position decisions.

Significance

With the high incidence of aspiration in critically ill mechanically ventilated gastric fed patients, interventions to reduce the incidence of aspiration could lead to a significant decrease in VAP. Elimination or reduction of hospital acquired infections such as VAP is a priority of the CDC,²¹ the Institute of Medicine,³⁰ and the Joint Commission.³¹ Critical care nurses can play a crucial role in the identification of patients at risk for GER and aspiration and intervene to reduce

the patient's risk with interventions such as positioning the HOB.

Research is needed to understand the relationship of reflux and aspiration in ICU patients and to further explore risk factors of reflux associated with subsequent aspiration. With identification of these risk factors for reflux and aspiration, nurse researchers can develop and study new therapies to reduce the risk of aspiration and therefore prevent airway and lung injury. Complications associated with aspiration could be greatly reduced with clinician implementation of best practices to reduce aspiration and VAP. These interventions could lead to reduced mortality for ICU patients, fewer ventilator days, fewer ICU and hospital days, significantly less suffering for patients and significant health care cost savings. Lastly, research on this topic may also provide evidence for interventions related to reflux for high risk patients in the peri-operative, long-term care and out-patient settings.

Aims and Research Questions

Below are the 6 aims for this study with one research question associated with each aim.

1) To describe the frequency and duration to which patients' HOB angles are temporarily lowered for treatment purposes below 30° or below 45°. What is the frequency and extent to which the patient's HOB is temporarily lowered for treatment purposes below 30° or below 45° and overall mean HOB elevation in adult mechanically ventilated gastric fed ICU patients?

2) To describe the occurrence of reflux (pepsin-positive oral secretions) and aspiration (pepsin-positive tracheal secretions) with HOB elevation at 30° and 45°. How often does reflux (pepsin positive oral secretions) and pulmonary aspiration of gastric contents (pepsin positive tracheal secretions) occur with HOB elevation at 30° and 45° in adult mechanically ventilated gastric fed ICU patients?

3) To determine the association between reflux and aspiration with the 2 different HOB

elevations in adult ICU mechanically ventilated gastric fed patients. What is the association between reflux (pepsin positive oral secretions) and aspiration (pepsin positive tracheal secretions) with HOB elevation at 30° and 45° in adult mechanically ventilated gastric fed ICU patients?

4) To determine the association between a temporarily lowered HOB position for treatment purposes and reflux of gastric contents. What is the association between a temporarily lowered HOB position for treatment purposes (minutes lowered, mean when lowered and overall mean) and reflux (pepsin positive oral secretions) in adult mechanically ventilated gastric fed ICU patients?

5) To determine the association between 7 patient characteristics (gender, age, body mass index, gastric residual volume, sedation level, disease severity, and use of prokinetic agents) and reflux. What is the association between the following variables and reflux in adult mechanically ventilated gastric fed ICU patients?

- Gender
- Age
- Body Mass Index (BMI)
- Gastric residual volumes (GRV)
- Sedation levels (Richmond-Agitation Sedation Scale)
- Disease severity (APACHE II)
- Prokinetic agents

6) To determine the association between the pH (range 0-14) of oral secretions and pepsin presence in oral secretions (the gold standard measure of reflux). What is the association between the pH (range 0-14) of oral secretions and presence/absence of pepsin in oral secretions

in adult mechanically ventilated gastric fed ICU patients?

Definition of Terms

The conceptual and operational definitions used in this proposal are listed below.

Gastroesophageal Reflux (GER)

Conceptual Definition: Gastroesophageal reflux is the movement of gastric contents into the esophagus.⁴

Operational Definition: Pepsin positive oral secretions obtained with a Yankauer suction device inserted into the oral cavity of ventilated ICU patients.

Extraesophageal Reflux (EER)

Conceptual Definition: Extraesophageal reflux is the retrograde flow of gastric contents to the pharynx, larynx and airway above the vocal cords.³

Operational Definition: Pepsin positive oral secretions obtained with a Yankauer suction device inserted into the oral cavity of the subjects.

Reflux

Conceptual Definition: Reflux encompasses the movement of gastric contents either to the esophagus or extraesophageal regions.

Operational Definition: Pepsin positive oral secretions obtained with a Yankauer suction device inserted into the oral cavity of the subjects.

Aspiration

Conceptual Definition: Aspiration is the inhalation of material (oral or gastric) into the airway below the level of the true vocal cords.¹

Operational Definition: Pepsin positive tracheal secretions obtained via endotracheal tube suctioning with a suction catheter advanced down the artificial airway.

Microaspiration

Conceptual Definition: Microaspiration is the aspiration of a small volume of gastric or oral material that is generally not detected clinically.¹

Operational Definition: Pepsin positive tracheal secretions obtained via endotracheal tube suctioning with a suction catheter.

Macroaspiration

Conceptual Definition: Aspiration of a large volume of material that is generally detected clinically represents macroaspiration.¹

Operational Definition: Witnessed vomiting of gastric contents by subjects or gastric contents observed in oral cavity of subjects which leads to pepsin positive tracheal secretions.

Head of Bed Elevation (HOB)

Conceptual Definition: HOB elevation is the extent to which the top portion of a hospital bed is elevated above or below zero degrees.

Operational Definition: Degrees of elevation of the HOB above or below zero obtained from a calibrated electronic gauge placed on the bed frame of the subjects in the ICU.

pH

Conceptual Definition: A measure of the acidity or basicity of a solution

Operational Definition: The pH of oral secretions measured with pH Hydrion paper with a range of 0-14.

Gastric Residual Volume (GRV)

Conceptual Definition: GRV is the volume in the stomach prior to the next bolus tube feeding or the amount in the stomach measured every 4 hrs with continuous gastric feeding.

Operational Definition: The amount of gastric secretions removed from the subjects after

instillation of 30 ml of air into the irrigation port of the gastric feeding tube with a 60 ml catheter tipped syringe and application of negative pressure to the syringe until no further aspirate can be obtained.¹⁴

Body Mass Index (BMI)

Conceptual Definition: Calculated from a patient's weight and height, BMI is a reliable indicator of a level of fatness for most people. BMI places patients in various weight categories such as normal, under or overweight using a simple number.

Operational Definition: Body weight in kilograms divided by the square of height in meters (kg/m^2).

Prokinetics

Conceptual Definition: Prokinetics are medications that stimulate gastrointestinal smooth muscle contractions.²⁴

Operational Definition: Medications, metoclopramide and erythromycin, which stimulate gastric contractions and enhance gastric emptying.

Yankauer suction device

Conceptual Definition: A Yankauer suction device is a suction device with a tip that has large openings surrounded by a bulbous head which is designed to allow effective suction of the oropharyngeal areas without damaging surrounding tissue.

Operational Definition: An oral suctioning tool used by clinicians to suction oropharyngeal secretions in order to prevent aspiration.

Washout Period

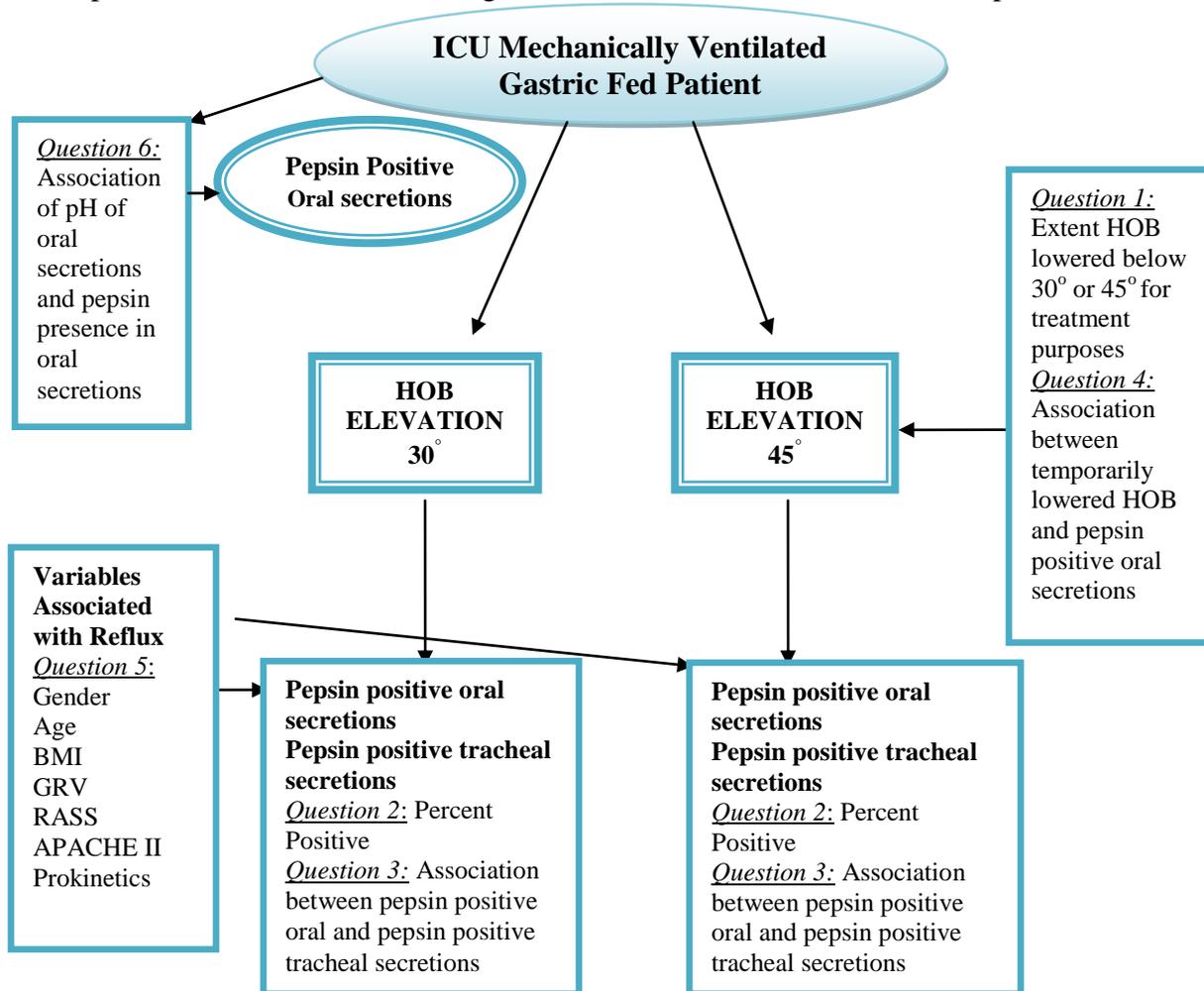
Conceptual Definition: A washout period is the time between treatment periods in a crossover design study used to minimize carry over effects from the first treatment .

Operational Definition: Night time 12-hr period between day 1 and day 2 of data collection during which the subject's bedside nurse determined HOB angle and positioning.

Conceptual Model

A conceptual schema was designed to provide a framework for this study. Variables for the study were identified in the literature review and will be discussed in Chapter II. Figure 1 depicts the independent variables of the two different HOB elevations and association with the dependent variables, reflux and aspiration, as detected by pepsin positive oral or tracheal secretions. HOB elevation of 30° and 45° was studied to describe the extent of reflux and aspiration and to determine the association between reflux and aspiration at the two different HOB elevations. In addition, variables associated with reflux, decreased HOB for treatment purposes and the patient variables identified in the literature review (age, gender, gastric residual volume, sedation level, disease severity and use of prokinetics) are presented in relationship to the different HOB elevations. The association of these variables with reflux was examined in this study. In addition, Figure 1 illustrates the study of the association of pH of oral secretions and pepsin presence in oral secretions. This study examined the association between pH of oral secretions and pepsin presence in oral secretions to determine the utility of pH measurement as a marker of reflux in the ICU mechanically ventilated gastric fed patient.

Figure 1
Conceptual Model of Variables Thought to be Associated with Reflux and Aspiration



Assumptions

1. Pepsin was measured in a quantifiable way that was accurate and reproducible when using a western blot analysis.
2. Western blot immunoassay is susceptible to pre-analytical and analytical variations. Thus, all oral and tracheal secretions were measured after careful calibration and quality control measures of the Criterion PAGE gel apparatus (Bio-Rad Labs; Hercules, CA) and the blotting apparatus (Thermo Scientific Owl; Asheville, NC), per manufacturer recommendations.

3. All collectors and processors of oral and tracheal secretions obtained, stored and prepared the specimens using an established standard protocol.
4. Measurement of pH was measured on calibrated pH paper and all readers had the ability to visualize the full range of the color spectrum from a pH of 0 through a pH of 14.
5. Measurement of the HOB elevation was conducted with a calibrated and accurate gauge that ranges from -20 to + 90 degrees placed on the bed frame.
6. Measurement of sedation with the RASS sedation scale by ICU nurses was reliable with acceptable nurse-nurse inter-rater reliability.
7. Measurement of gastric residual volume was performed by all data collectors using an established study protocol.
8. Participants who were enrolled in the study represented the general population of adult critically ill mechanically ventilated gastric fed patients.
9. Demographic (age, gender, admitting diagnosis) and APACHE II score variables derived from the EMR (EMR) were accurate.

CHAPTER II
REVIEW OF THE LITERATURE

Anatomy and Physiology of Normal Food Passage Through the Upper Gastrointestinal Tract

Swallowing

In the mouth, the digestion of food begins with mechanical breakdown from chewing and initial enzymatic digestion with salivary secretion. Saliva is comprised of a serous and a mucus portion. The serous secretion contains ptyalin an α -amylase. Mucus lubricates the food and protects surfaces of the oral cavity.³³ Mucus lubrication of the food facilitates swallowing.³⁴ The oral cavity, pharynx, and larynx transfer food from the palate to the esophagus. Muscle groups of the soft palate, tongue and pharynx participate in swallowing while extrinsic muscles of the pharynx elevate and pull the pharynx forward to seal the laryngeal inlet during swallowing. Laryngeal movement during swallowing is essential to the swallowing mechanics necessary to close the airway as the food bolus moves from the pharynx to the esophagus.³⁵

Esophagus

Anatomical features of the esophagus distinguish it from the remainder of the gastrointestinal tract. As a continuation of the oropharynx, the upper esophageal sphincter (UES) and upper 5% of the esophagus is composed of striated muscle and is under control of the cerebral cortex and medulla. The middle 35-40% of the esophagus is a combination of striated and smooth muscle with the smooth muscle proportion increasing distally. The distal 50-60% of the esophagus is entirely smooth muscle under the control of the vagus nerve and the enteric nervous system. The normal esophagus demonstrates no spontaneous contraction at rest with a pressure reflecting pleural pressure. The intensity and progression of esophageal peristalsis occurs in distinct zones because of the anatomical muscular pattern of the esophagus. Primary peristalsis of the esophagus begins with swallowing while secondary peristalsis can be initiated in response to esophageal distention with air or fluid. Low peristaltic amplitude, slight delay in

progression and an increased chance of failed transmission of peristalsis is found at the transition zone between the striated and smooth muscle segments.³⁵

Esophageal Sphincters

When closed, the upper esophageal sphincter (UES) has a slit-like configuration. The UES must maintain closure to prevent refluxed material from reaching the pharynx. UES closure also prevents air from entering the esophagus during inspiration. The UES opens when swallowing or belching is required.³⁶⁻³⁷

The lower esophageal sphincter (LES) and the diaphragm create a zone of high pressure between the low pressure esophagus and the low pressure stomach. The LES is a high pressure, 3-4 cm segment of tonically contracted smooth muscle at the distal end of the esophagus. The crural diaphragm surrounds the LES and contributes to the high pressure of the LES. Both the LES and the crural diaphragm contribute to the physiologic function of the gastroesophageal junction. Resting LES pressure ranges from 10-30 mm Hg however, can reach > 80 mm Hg with enteric migrating motor complexes. LES pressure is affected by myogenic factors, intra-abdominal pressure, gastric distention, peptides, hormones, various foods and many medications.³⁵

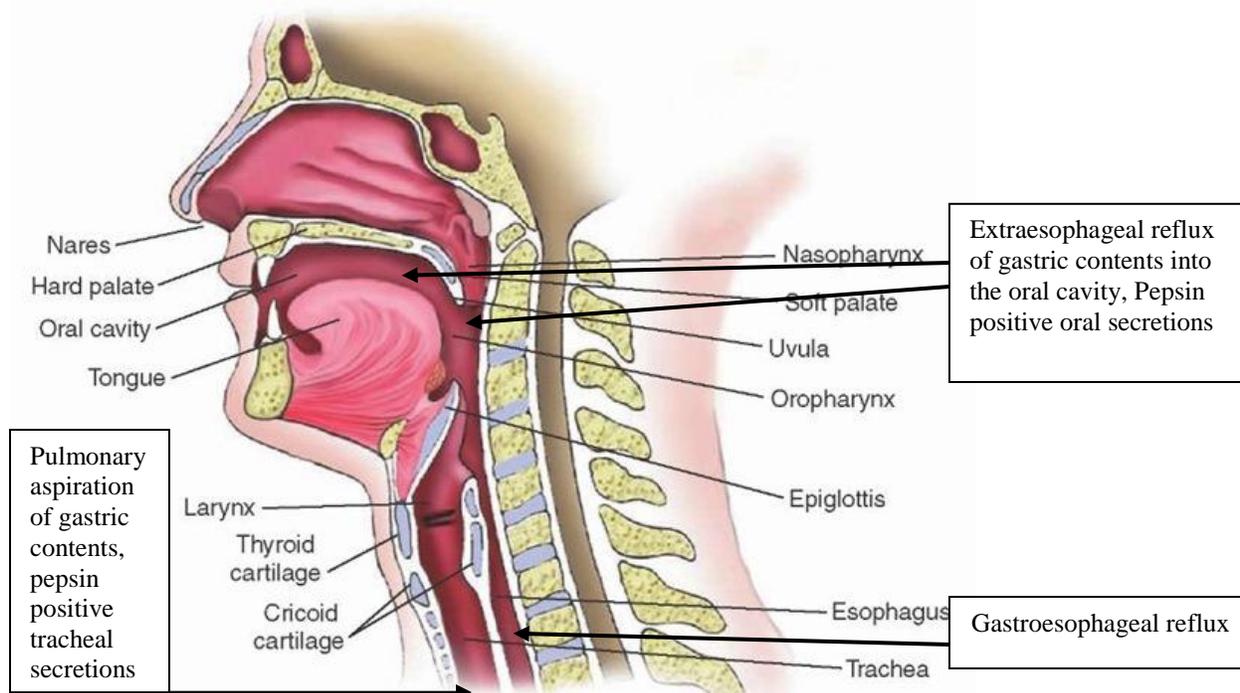
The LES opens in both an antegrade and a retrograde manner. Movement of an ingested food bolus across the esophagogastric junction is facilitated by LES relaxation. The LES relaxes to similar pressures of the stomach and esophagus within 1 second of swallowing. Thus, when the food reaches the LES, the LES is relaxed but closed. The pressure generated by the food bolus, with the aid of peristalsis, forces the LES to open and the bolus to move across the esophagogastric junction. After 5-7 seconds of relaxation, the LES recovers its initial pressure.³⁵

As gastric contents reflux into the esophagus, GER, some volume may reach the pharynx

and oral cavity, EER. If the refluxed material is not swallowed, the contents can pool in the oral cavity. Saliva and refluxed material can be suctioned and analyzed for pH and pepsin.

Alternatively, some of the reflux can enter the larynx and be aspirated below the vocal cords into the tracheobronchial tree and lungs. Figure 2 demonstrates the location of GER and EER, collection of secretions and measurement of pepsin as an indicator of reflux. This figure also illustrates aspiration of EER below the larynx and into the upper airways and measurement of pepsin in tracheal secretions as an indicator of aspiration.

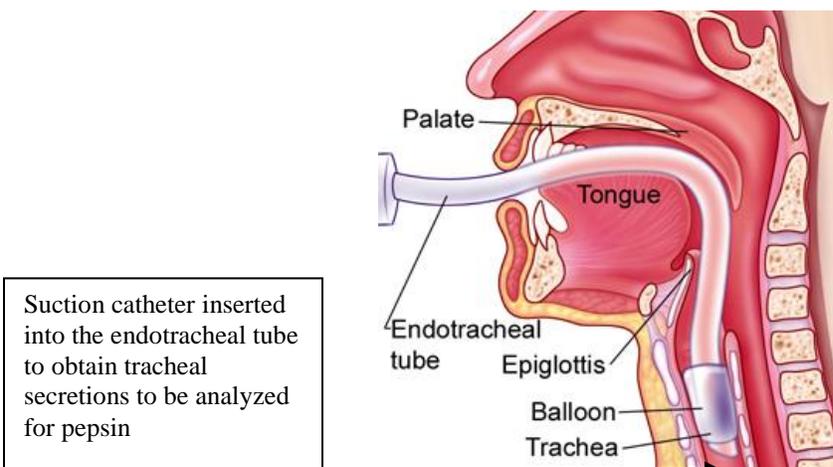
Figure 2
Reflux into Oral Cavity, Pharynx and Larynx³⁸



Reflux in the extraesophageal regions of the oral cavity, pharynx and larynx can lead to aspiration of the gastric contents below the level of the true vocal cords. In mechanically ventilated patients, the endotracheal tube traverses the vocal cords and ends in the trachea. Aspirated material, gastric contents or saliva, can be suctioned from the endotracheal tube. The tracheal secretions can then be analyzed for pepsin to detect aspiration of gastric contents as

described later in this chapter. Figure 3 demonstrates the positioning of the endotracheal tube and suction catheter placement for obtainment of tracheal secretions.

Figure 3
Endotracheal tube in the airway³⁹



Stomach

The lateral wall of the esophagus joins the stomach at an acute angle. As food moves into the stomach, gastric motility is induced within 5-10 minutes of eating and persists for the time that food remains in the stomach.⁴⁰ Intermittent phasic contractions occur with antral contractions propelling the gastric contents distally only to be returned back to the proximal stomach producing a mixing and grinding action. Feeding is associated with shortening of gastric muscle length and alteration of the distal stomach configuration. Antropyloroduodenal activity is observed manometrically, pressure measurement, as either intermittent isolated pressures or as peristaltic pressure waves that move varying distances through the antrum, across the pylorus and into the duodenum.⁴¹ Furthermore, peristaltic activity is regulated by small intestine receptors. Nutrients in the small intestine trigger a neurohumoral feedback loop leading to a decrease in antral contractility and an increase in pyloric contraction with a reduced antegrade propagating pressure wave resulting in a decrease in transpyloric movement of nutrients.

Retrograde peristaltic activity in the proximal duodenum moves chyme back into the distal antrum delaying gastric emptying. Motor activity following a meal depends on the consistency and composition of the ingested meal. Antral contractions are more intense when eating solids than those induced by a homogenized meal.⁴⁰

In response to a meal, the stomach also initiates secretory activity in response to gastric wall stretch. The stomach secretes several secretory products including hydrochloric acid, histamine, gastrin, ghrelin, pepsinogen and mucus. The volume of gastric secretion is approximately 1500 ml/day. Emotional stimuli, such as pain, increase gastric secretion during the fasting state from a physiologic few ml/hr to as much as 50 ml/hr.³³ Pepsinogen is secreted by the chief cells of the fundus and body of the stomach and is stored in apical granules until stimulation. Pepsinogen is inactive until autocatalytically activated to pepsin under acidic conditions. Pepsinogen has a N-terminal prosegment domain containing 44 amino acids. Under acidic conditions below a pH of 5, the prosegment is removed through hydrolysis. Removal of the prosegment domain leads to pepsin in its mature and active state.⁴²

Gastric emptying occurs faster with liquid intake than with a meal of digestible solids. Gastric emptying of liquids is volume dependent with approximately 50% of emptying occurring within 8-18 minutes following a liquid meal. The volume propagated to the duodenum is a constant fraction of the volume remaining in the stomach. Thus, a larger volume of liquid will empty faster than a smaller volume.⁴⁰ Nutrient containing liquids are emptied more slowly in women,⁴³ and lipid containing liquids are emptied more slowly in the elderly.⁴⁴ In addition, liquids of high caloric density empty slower than lower density liquids. However, approximately 200 kcal/hr are propelled to the duodenum regardless of primary nutrient, carbohydrate, protein or fat.⁴⁴ Inhibition of liquid emptying is highest after acid, glucose or oleic acid contact with the

proximal duodenum. Hence, carbohydrates and amino acids are the prime regulators of gastric emptying.⁴⁰

During fasting the migrating motor complex (MMC) is observed with three phases in the stomach and duodenum over approximately 84-112 minutes. MMC phase I is a period of relative motor inactivity with small pressure waves lasting approximately 50% of the cycle length. Increasing frequency of irregular contractions occurs in MMC phase II. Although comprising the shortest duration, 5-10 minutes, phase III is characterized by frequent, higher pressure contractions. The contractions primarily originate in the stomach although approximately one fifth of the contractions start in the proximal duodenum. The MMC contractile pattern allows for movement of undigested food residue and sloughed enterocytes from the stomach and proximal small intestine.⁴⁰

Duodenum

After feeding, chyme that is emptied from the stomach and subsequently mixed with bile and pancreatic juice is propelled away from the stomach through the small intestine. Stretch and mucosal stimulation provide the stimulus for peristalsis. In the proximal duodenum, bile and pancreatic secretion add approximately 2000 ml of volume to the ingested volume.³³ As mentioned previously, some phase III MMC contractions originate in the duodenum. These contractions propagate orally leading to retroperistalsis activity.⁴⁶ Duodenogastric reflux of bicarbonate and immunoglobulin A may reconstitute the antral mucosa during fasting.⁴⁷ Duodenal motor contractions can also lead to chyme backflow into the stomach and can impact gastric emptying.⁴⁸

Anti-reflux Mechanisms

GER is a normal physiologic process occurring several times a day in most people,

especially after large meals.⁴ GERD occurs when there is a failure of the normal anti-reflux mechanisms. Three mechanisms are involved in the esophageal protective anti-reflux mechanism: 1) anti-reflux barriers, 2) esophageal acid clearance and 3) tissue resistance.^{4, 49}

Anti-reflux Barriers

The anti-reflux barrier is comprised of the intrinsic LES, the diaphragm crura, the intra-abdominal location of the distal segment of the LES, the phrenoesophageal ligaments and the acute angle formed between the cardia of the stomach and the esophagus. The major component of the anti-reflux barrier is the LES. The diaphragm crura provides extrinsic contraction around the LES contributing to LES pressure during inspiration as well as augmenting pressure during periods of increased abdominal pressure. The ligaments anchor the diaphragmatic crura. Lastly, the acute angle creating a flap valve type effect and the intra-abdominal location of the distal segment of the LES both contribute to gastroesophageal junction competency. Anatomical anti-reflux barriers help prevent reflux even during increased intra-abdominal pressure events.^{4, 49-50}

Esophageal Acid Clearance

Esophageal acid clearance provides the second level of defense against reflux esophageal damage. The amount and severity of mucosal damage is dependent on the time required for esophageal acid clearance. Two processes are involved in esophageal acid clearance, volume clearance of the reflux material and acid clearance which involves restoration of normal pH in the esophagus after acid exposure. Esophageal peristalsis works to clear acid reflux material. Primary peristalsis is initiated by swallowing regardless of reflux. Swallowing occurs approximately once per minute in awake individuals. One or two primary peristaltic contractions can clear a 15 ml bolus from the esophagus.^{4, 49} Esophageal peristalsis clears reflux material in the upright and supine positions although it is inoperative during deep rapid eye movement

sleep.^{4, 51}

Secondary peristalsis which is initiated by esophageal distention during reflux is less effective in acid clearance with less significant protection than primary peristalsis. Failed peristaltic function leads to an increased severity of esophagitis. With peristaltic dysfunction some of the refluxed material is cleared from the esophagus. Gravity contributes to bolus clearance when reflux occurs in the upright position; however, during supine positioning, the mechanism is not operative unless the head of the bed is elevated.^{4, 32}

The basicity of saliva ranges from a pH of 6.4-7.8⁴ and contributes to the clearance of the acidic reflux.⁴⁹ Saliva is capable of neutralizing small amounts of acid remaining in the esophagus after the refluxed bolus has been cleared by several peristaltic contractions. However, saliva is not effective in neutralizing large volumes of acid (> 5 ml).⁴ Spontaneous swallowing results in saliva production. Average saliva volume is 1000 ml per day.³³ Acidic fluids in the esophagus increase salivation. Physiological or pathological alteration in salivation may contribute to the esophageal damage associated with GERD. For example, during sleep, decreased salivation has been demonstrated to prolong acid clearance times. The aqueous bicarbonate rich secretions of the esophageal submucosal glands contribute to the dilution and neutralization of residual acid from reflux. Acidic reflux stimulates secretion by the esophageal submucosal glands even when swallowing does not occur.⁴

Tissue Resistance

Despite anti-reflux barriers and esophageal acid clearance, individuals may experience 1-2 hrs of esophageal acid contact time and not necessarily develop GERD. The final protection that prevents the development of GERD is tissue resistance. Tissue resistance is a combination of both structural and functional components of the esophagus. Structural resistance is provided by

the relatively tight junctions of the epithelium and the lipid-rich glucoconjugates in the intercellular space of the esophageal mucosa which resist ionic movement at the intercellular as well as cellular level. The functional resistance includes buffering and removal of hydrogen ions by the esophageal epithelium. Neutralization of the acidic reflux occurs via a sodium/hydrogen ion transporter and a sodium dependent chloride/bicarbonate exchanger. These ion transporters restore intracellular pH to neutral after acid reflux occurs. Additionally, esophageal blood flow removes hydrogen ions and carbon dioxide to maintain normal tissue acid-base balance. Blood flow is increased to the esophagus during acidic reflux. Lastly, esophageal cell injury with exposure to acid reflux stimulates cell proliferation with thickening of the basal cell layer of the epithelium. Esophageal repair requires days to weeks.⁴

Injury Secondary to Gastric Reflux

Inflammatory Response

Esophageal mucosal injury secondary to GER is characterized by endoscopic findings of mucosal breaks, strictures, columnar metaplasia (Barrett esophagus) and adenocarcinoma. An inflammatory response contributes to the development of GERD complications.

Proinflammatory cytokines such as interleukin (IL)-1 β , IL-6 and IL-8 are increased. In addition platelet activating factor (PAF) is produced and released from the esophageal mucosa. PAF enhances eosinophil adherence to vascular endothelial cells and activates immune and non-immune cells. PAF is produced and released after acid exposure. One of the immune mediator types activated by PAF is the reactive oxygen species (ROS). Increased ROS levels lead to oxidative stress. ROS levels are elevated in GERD with a depletion of antioxidants. In turn, the inflammatory mediators affect the fibroblasts, muscles cells, endothelial cells and immune cells in the esophagus leading to a chronic inflammatory condition. Gram-negative strains in the

esophageal microbiome are associated with GERD and Barrett esophagus. The inflammatory state as a result of GER results in reduced esophageal muscle contraction, increased esophageal fibrosis, dysplasia and carcinogenesis.²

Pepsin Induced Injury

Pepsin plays a major role in cell damage of the esophagus and extraesophageal structures during reflux. Pepsin is most active at an acidic pH of approximately 1.5-2.0 with declining activity as pH increases. However, the inactive enzyme remains stable at the higher pH and is reactivated when pH lowers again to a pH of approximately 3.0. Pepsin adhering to the epithelium can thus become reactivated during an acidic state. Also during reflux, pepsin adherent to epithelial cells can be subsequently endocytosed and cause internal cell derangements. Intracellular derangements occur from reactivation of pepsin within the cell. Derangements include changes in the Golgi system, the mitochondria and increased expression of genes associated with cell stress. Mitochondrial damage with repeated exposure to pepsin may lead to cell death.^{3, 52}

Factors Increasing Reflux

Transient Lower Esophageal Sphincter Relaxations

Transient LES relaxations (tLESRs) occur without swallowing or esophageal peristalsis and persist for longer periods (> 10 seconds) of relaxation than swallowing. The frequency of tLESRs associated with gastric acid reflux is increased in patients with GERD compared to healthy persons.^{4, 49} tLESRs occur most frequently in the postprandial state. Gastric distention is the major stimulus for tLESRs.^{35, 49} Additional factors that increase the rate of tLESRs include stress (coughing, straining) and subthreshold swallowing stimulation of the pharynx.³⁵ Morbid obesity is also associated with an increased frequency of post-prandial tLESRs at a rate similar to

patients with GERD.⁵³

Gastric Factors

Gastric basal acid secretion rate, duodenogastric reflux and the rate of gastric emptying combine to determine gastric volume. The stomach secretes several secretory products including hydrochloric acid, histamine, gastrin, ghrelin, pepsinogen and mucus. The volume of gastric secretion is approximately 1500 ml per day. Emotional stimuli, such as pain, increase gastric secretion during the fasting state from a physiologic few ml/hr to as much as 50 ml/hr.³³ The combination of acid and pepsin in GER disrupt the mucosal barrier of the esophagus leading to changes in the ion transporters, tissue changes and gross hemorrhage.⁴ Duodenogastric reflux can result in bile acid reflux. When combined with gastric acid and pepsin, bile acids from duodenogastric reflux cause further injury to the esophagus.^{49, 54}

Gastric emptying is the rate at which ingested food and secretions are emptied from the stomach. Gastroparesis is a chronic motility disorder of the stomach manifested as delayed gastric emptying without mechanical obstruction. Delayed gastric emptying is associated with GER in approximately 30% of patients with GERD diagnosis.⁵⁵ Gastric stasis leads to proximal fundic distention which promotes tLESRs. Delayed gastric emptying is likely due to an impaired and disordered motor response throughout the stomach.⁵⁶ With delayed gastric emptying, the increased volume in the stomach can result in gastric distention and subsequent reflux.

Risk Factors for Gastroesophageal Reflux

Several diseases and circumstances predispose patients to reflux and GERD. Pregnancy increases the risk of reflux due to the relaxing effects of circulating estrogen and progesterone on the LES. Patients with scleroderma develop smooth muscle fibrosis which lowers LES pressure and weakens esophageal peristalsis. Patients with Zollinger-Ellinson syndrome have increased

gastric volume due to hypersecretion of acid.⁴ Delay in gastric emptying has been demonstrated with several diseases and surgical conditions including hiatal hernia, liver cirrhosis, chronic pancreatitis, gastric cancer, gastric resection and cardiac or lung transplantation.⁵⁶

Reflux in Critically Ill Patients

Critically ill mechanically ventilated patients with a nasally or orally inserted tube that transgresses the esophageal sphincters for decompression or feeding purposes are at increased risk for reflux. Reflux in this patient population may be infrequent or result in esophagitis. GER in the critically ill does not equate to GERD although patients with a history of GERD may demonstrate increased frequency and volume of reflux.

Mechanism of Reflux

Nind et al. studied 15 mechanically ventilated patients in the ICU. Patients underwent esophageal manometry, pH monitoring and intraluminal electrical impedance measurement. Patients were studied after a 4 hr fast and during a liquid gastric feed. An initial 100 ml nutrient bolus was administered through the central lumen of the manometric device followed by a 50 milliliter (ml)/hr infusion for 5 hrs. Forty-six acid reflux episodes were measured. A decrease in esophageal pH to < 4 were detected 42 times in 11 patients and persisted for prolonged periods. The authors proposed impairment of volume and acid clearance as the cause of the downward pH drifts. Two patterns of esophageal motor events were associated with reflux: 1) absent basal LES pressure and 2) straining associated with coughing during suctioning. tLESRs were not observed in any patients. Basal LES pressure was uniformly low with a mean basal pressure of 2.2 ± 0.4 mm Hg. Swallowing was infrequent and no swallow-induced LES relaxation was observed. Esophageal body contractions were also infrequent and the majority of pressure waves were not propagated. These findings demonstrate the mechanisms of GER during mechanical

ventilation in critically ill patients which are vastly different than the mechanisms discussed earlier.⁵⁷

In a recent pilot study, 10 of 50 (20%) gastric fed mechanically ventilated patients who were suctioned once had pepsin positive oral secretions via western blot analysis.⁵⁸ Incidence of reflux over longer times, with various positions, and medical conditions requires further research. There is some literature which provides some evidence of conditions that increase reflux in the critically ill patient. These conditions are described in detail below.

Gastric Tubes

Gastric tubes are placed for decompression post-operatively and during mechanical ventilation to prevent gastric distention, reflux and aspiration. In the early 1960's, the idea that acid may track toward the oral cavity along a nasogastric (NG) tube because the tube mechanically interferes with the LES barrier function was first proposed.⁵⁹ Subsequently, large-bore NG tubes were found to be associated with GER in mechanically ventilated patients at a significantly higher rate than patients without an NG tube.⁶⁰ Three mechanisms have been identified that contribute to reflux and subsequent aspiration in patients with NG tubes: 1) loss of anatomic integrity of the UES and LES; 2) increased frequency of tLESRs; and 3) desensitization of the pharyngoglottal reflex.⁶¹

Conflicting results regarding effect of NG tube size have been reported. In normal volunteers, 8 Fr compared to 14 Fr NG tubes resulted in no difference in amount of reflux or reflux episodes.⁶² Also, no differences in GER and microaspiration were observed in intubated patients with large bore (6.0 mm) compared to small bore (2.85 mm) NG tubes.⁶³ However, a small bore NG tube (2.66 mm diameter) in continuous gastric fed mechanically ventilated patients eliminated GER and aspiration.⁶⁴ The size of the NG tube traversing the esophageal

sphincters may be important but needs further investigating.

NG tubes for gastric drainage, sump tubes, are used to reduce gastric volume. A study conducted in cardiac surgery patients examined three groups: 1) no NG, 2) NG (14 French) to gravity, and 3) NG (14 French) to suction. Esophageal and tracheal pH probes were placed to detect reflux and aspiration. The researchers found that in patients at low risk of GER (excluded patients with known GERD, diabetes, hiatal hernia and morbid obesity) reflux was very low in patients managed without an NG. The use of low, intermittent suction also resulted in an infrequent rate of reflux. However, reflux was increased when the NG tube was drained by gravity. One patient in the NG gravity group had a tracheal pH indicative of aspiration.⁶⁵ Similar results were found with patients undergoing elective bowel surgery. Seven patients had NG tube placement intraoperatively and for 24 hrs postoperatively while 8 were randomized to no NG tube. All patients had continuous manometry, pressure measurement recording, and esophageal pH monitoring. Patients managed with an NG tube had significantly more reflux episodes (137 ± 71.1 compared to 7.8 ± 3.5) and a longer duration of reflux. Additionally, the mean LES pressures were lower in the NG group (6.4 ± 4.2 vs. 20.6 ± 12.8). However, this difference was not statistically significant.⁶⁶ Size of NG tube was not reported.

Percutaneous endoscopic gastric (PEG) tubes are frequently placed to reduce GER associated with NG tubes. LES pressures are maintained at normal levels in patients with a PEG until rapid intragastric bolus instillation which was found to reduce LES pressure and led to GER.⁶⁷ Patients with neurologic dysphagia with a PEG tube may be at higher risk for GER than patients who require a PEG tube for mechanical reasons. Additionally, at the time of PEG tube placement, observations of a more severe reflux esophagitis grade was associated with higher GER after PEG tube placement.⁶⁸ In both non-ventilated and ventilated patients, PEG tubes have

been found to reduce GER compared to NG tubes but not completely prevent it.⁶⁹⁻⁷² Therefore, while PEG tubes might reduce the frequency of GER in critically ill patients they do not completely eliminate reflux.

Gastric Motility

Gastric motility and gastric emptying are altered during critical illness. Gastric emptying is delayed in up to 50% of critically ill patients. During intragastric nutrient bolus, fewer antegrade and more retrograde waves were reported in the gastric antrum and duodenum in critically ill patients and the waves were shorter in length. With duodenal feeding infusion, critically ill patients demonstrated longer and more frequent mixed duodenal propagated waves, a reduced percentage of antegrade antroduodenal waves and an increased percentage of mixed antroduodenal waves.³⁹ The functional association between the proximal and distal gastric regions is abnormal and may further contribute to delayed gastric emptying during critical illness.⁷³ These alterations combine to slow gastric emptying during gastric or duodenal feeding. This motor pattern of antral hypomotility, reduced propagated waves and increased retrograde propagation is similar to the stress response seen in healthy volunteers.³⁹

Delayed gastric emptying has also been shown in animal models with induced acute stress while prolonged stress led to adaptation and return to normal gastric contractions and gastric emptying.⁷⁴⁻⁷⁵ Decreased gastric emptying and decreased gastrointestinal motility has been identified in various models with endotoxin administration and sepsis.⁷⁶ The effects of stress on gastric emptying in the critically ill patient remains to be elucidated. However, several factors such as physical stress, as observed with abdominal surgery or sepsis, have been shown to result in decreased ghrelin levels with potential for decreased gastric emptying.⁷⁷

Duodenogastric Reflux and Esophageal Damage

Intragastric bile concentration in 26 critically ill mechanically ventilated patients was significantly higher than healthy controls indicating duodenogastric reflux.⁷⁸ These findings were supported by a study of mechanically ventilated critically ill patients who received a radioactive traced jejunal liquid diet. Duodenogastric reflux was documented in 10 of the 11 patients with a significant increase in radioactivity of the gastric contents and an increase in bile acid concentration from 392 μmol during fasting to 1446 μmol in the fed state.⁷⁹ In critically ill mechanically ventilated patients, duodenogastroesophageal reflux led to an increased severity of esophagitis as the volume of gastric aspirate increased. Furthermore, erosive esophagitis with bile reflux was reported in 48% of a sample of 26 critically ill patients after less than one week of mechanical ventilation despite acid-suppressive therapy. Esophagitis was attributed to mechanical irritation of the nasogastric tube and chemical injury from acid and bile during duodenogastroesophageal reflux.⁸⁰ Thus, while duodenogastric reflux is physiologic, mechanically ventilated patients may have an increase in GER secondary to an increase in duodenogastric reflux which leads to erosive esophagitis.

Pulmonary Aspiration of Gastric Contents

Farrell et al. attributed the first description of GER and respiratory disease to Sir William Osler in 1892.⁸¹ Aspiration involves inhalation of material (oral or gastric) into the airway below the level of the true vocal cords. Microaspiration refers to the aspiration of a small volume of material that is generally not detected clinically. Macroaspiration involves aspiration of a large volume of material that is often detected clinically. Large-volume aspirations following vomiting are infrequently witnessed by clinicians.²⁹ However, microaspirations occur frequently and are clinically undetected.¹⁴ Aspiration could involve repeated episodes of microaspiration yet not

result in acute symptoms.⁸² Pulmonary pathology after aspiration varies widely. Variables impacting pathology include quantity and nature of aspirated material (blood, bacteria, gastric/oral secretions, liquids or food particles), chronicity of aspiration and the individual's host defense mechanisms.⁸²⁻⁸³

Aspiration pneumonia is defined as “a parenchymal inflammatory reaction to aspirated material mediated by an infectious agent, characterized by an infiltrate on chest x-ray.”¹ The infectious process of aspiration pneumonia is most frequently a result of aspiration of oropharyngeal or gastric secretions colonized by bacteria. Aspiration pneumonitis entails a non-infectious acute inflammatory response to the aspirated material that also demonstrates an infiltrate on chest x-ray. Aspiration pneumonitis is a chemical pneumonitis associated with aspiration of gastric contents. Additional conditions related to aspiration include bronchiolitis, airway obstruction, lung abscess, acute lung injury and acute respiratory distress syndrome.⁸³⁻⁸³

Risk Factors for Aspiration

Critically ill patients often have a decreased level of consciousness which impairs the gag reflex and leads to pooling of oral secretions in the posterior oropharynx. In patients with an endotracheal tube, a direct pathway is available for these secretions to enter the lungs.¹⁶ The cuff of an endotracheal tube may also result in dysfunction of the UES.⁶³ Subthreshold swallowing stimulation of the pharynx is reported to increase tLESRs.³⁵ The presence of an endotracheal tube may provide sufficient stimulation of the pharynx to increase tLESRs although no tLESRs were observed by Nind et al. in patients with endotracheal tubes.⁵⁷ Alterations in both UES and LES function secondary to endotracheal tubes may increase reflux and lead to aspiration.

Aspiration of gastric contents is a complication associated with general anesthesia, occurring in one of every 2000-3000 general anesthetic procedures.⁸²⁻⁸³ The risk of anesthesia

associated aspiration is lowest in healthy patients with no known risk factors for aspiration.⁸³

Aspiration occurs more frequently in patients requiring emergent intubation of the airway which most commonly occurs in the field or in the emergency department after trauma. Aspiration also occurs frequently in acutely decompensating patients in the emergency department and inpatient settings during emergent intubation.⁸²

Other risk factors include decreased level of consciousness secondary to sedation, alcohol intoxication or neurologic disease process and neuromuscular diseases. Risk factors for GER discussed previously increase the possibility for aspiration. Although risk factors for aspiration have been identified, Raghavendran et al. stated that “the true incidence of aspiration –induced lung injury is difficult to establish considering that most aspiration events are silent or unwitnessed.”⁸²

Airway and Lung Injury Associated with Aspiration

Gastric content has been shown to cause hyperpermeability of airway epithelium as a result of acid, pepsin activity and low osmolarity.⁸⁴ Pepsin is associated with mucosal inflammation of the esophagus and extraesophageal structures.⁸⁵ A study conducted to determine the effects of pepsin at a higher pH on epithelial cells of the pharynx demonstrated microscopically that the mitochondria and Golgi system were damaged. Conversely, the authors found no damage in the control cells, cells with no pepsin exposure. Additionally, pepsin altered the expression of multiple genes connected to stress and toxicity.⁸⁶

Gastric acid and pepsin also damage lung cells and stimulate inflammatory factors through ROS,⁸⁷ increased susceptibility to bacterial load,⁸⁸ and alveolar macrophage inflammatory response.⁸⁹ Several local and systemic inflammatory mediators are reported to increase secondary to aspiration of gastric contents including tumor necrosis factor- α and IL-8.⁸²

In a rat model, intratracheal instillation of dilute hydrochloric acid resulted in an acute neutrophilic inflammatory response at 4-6 hrs after instillation leading to a loss of pulmonary microvascular integrity and extravasation of fluid and protein into the airways and alveoli.⁸² Unique inflammatory mediator profiles found in mice and rat bronchoalveolar lavage specimens in response to various types of aspiration (normal saline, hydrochloric acid, small non-acidified gastric particles or acid and gastric particles) were used in a statistical model to predict the various aspiration forms and demonstrated the inflammatory insult seen in aspiration.⁹⁰⁻⁹¹ Similar to acid instillation, neutrophilic inflammation occurs at 4-6 hrs but no edema was observed with food particle induced lung injury.⁸² In a rabbit model, human gastric secretions were highly proinflammatory and caused dysfunction of the alveolar capillary barrier leading to lung edema.⁹² These changes were not pH dependent. Therefore, medications to alkalinize the gastric secretions would not eliminate damage to the lungs.

Further evidence of lung damage secondary to gastric aspiration was found in neonates. The neonates who had tracheal aspirates with higher concentrations of pepsin had a higher incidence of bronchopulmonary dysplasia.⁹³ Evidence of gastric aspiration in patients with lung allografts who reported GER demonstrated positive pepsin levels in bronchoalveolar lavage secretions and the detection of pepsin was associated with mild to moderate organ rejection.⁹⁴ Pepsin was not detected in control volunteer patients. These findings were subsequently validated in a study of lung transplant patients compared to control subjects. The authors concluded that gastric aspiration may play a role in the development of lung allograft rejection.⁹⁵

Additional Risk Factors for Reflux and Aspiration in ICU Patients

Several risk factors have been identified that lead to GER, aspiration pneumonia and pneumonitis. Previously discussed factors include gastric distention, obesity, stress related to

coughing or sneezing and tubes traversing the UES and LES. The elevation of the HOB to less than 30°, vomiting, gastric feeding and decreased level of consciousness have been identified as significant risk factors for aspiration and pneumonia.¹⁴ Presence of a tracheostomy, nasogastric feeding, histamine (H2) blockers and decreased level of consciousness were significant risk factors in a study by Carrilho et al.¹¹ Metheny et al., found that maintaining HOB elevation greater than 30° and use of a distal small bowel feeding tube significantly reduced aspiration and aspiration pneumonia.⁹⁶ Another study demonstrated that emergent intubation in the pre-hospital setting compared to more controlled intubation in the emergency room was associated with a higher incidence of aspiration measured by a qualitative pepsin plate assay based on fibrinogen digestion.⁹

Lastly, several medications commonly administered to ICU patients increase reflux and aspiration risk. Opioid analgesics, nitrates, calcium channel blockers and theophylline relax smooth muscle and are reported to decrease LES pressure which can lead to reflux.³⁵ Opioid analgesics also delay gastric emptying. In addition, anticholinergic agents such as prochlorperazine, promethazine and scopolamine, delay gastric emptying due to inhibition of acetylcholine receptors of cholinergic neurons that supply the stomach via the vagus nerve.⁴⁰ Other medications administered to ICU patients with reported delay in gastric emptying include proton pump inhibitors, H2 receptor antagonists, sucralfate, and diphenhydramine.⁵⁶

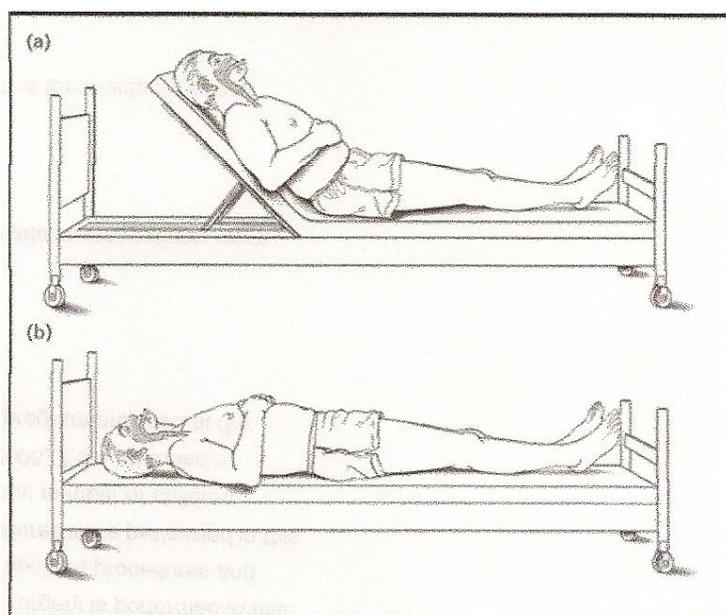
Interventions to Reduce Reflux and Aspiration

Head of Bed Positioning

Positioning of patients is identified as one of the most important nursing interventions to decrease GER, aspiration and VAP. In the supine flat position, the esophagus is positioned horizontally while in the semi-recumbent position the esophagus is oriented above horizontal.

Therefore, during semi-recumbent positioning, reflux of gastric contents is counterbalanced by gravity.³² Figure 4 is an illustration which demonstrates esophageal alignment in the semi-recumbent position compared to the supine position. The top panel (a) demonstrates esophageal alignment above the horizontal position in the semi-recumbent position. The bottom panel (b) illustrates esophageal alignment below horizontal in the flat, supine position. In the semi-recumbent position, esophageal alignment above horizontal hinders the reflux of gastric contents.

Figure 4
Esophageal Orientation in the Semi-recumbent Compared to Supine Position³²



Permission to use figure was granted by Lippincott Williams & Wilkins. Promotional and commercial use of the material in print, digital or mobile- device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins.

To reduce the risk of aspiration, guidelines from many organizations recommend that the HOB of ventilated patients be maintained at 30-45°. These organizations include the CDC,²¹ AACN,²² ASPEN,¹ Canadian Critical Care Trials Group,²³ and SCCM.²⁴ HOB positioning recommendations found in the above cited guidelines are based on several studies. In a randomized trial of 19 ventilated patients using radioactive labeling of gastric contents, mean

radioactive counts of endobronchial secretions were higher in patients in the supine position compared to patients positioned at 45° and aspiration pattern was time dependent.⁹⁷ Supine positioning in the first 24 hrs of mechanical ventilation was associated with an increased risk of VAP in a cohort study of 277 ventilated patients.⁹⁸ In a subsequent randomized trial in 86 ventilated patients, patients in the semi-recumbent group (45°) had a lower rate of clinically suspected nosocomial pneumonia than patients in the supine position. Healthcare providers were instructed not to change the position except for medical requirements. However, correctness of position was only checked daily and method for measuring HOB elevation was not reported.⁹⁹

A randomized feasibility study of semi-recumbent (45°) positioned patients compared to supine positioned patients demonstrated that the target position of 45° was not achieved for 85% of the 6-7 day study period with no significant difference in VAP rates. HOB elevation was measured every 60 seconds with a transducer and stored in a computer. Patient preferences for positioning for comfort were respected.¹⁰⁰ A randomized control trial comparing HOB elevations of 45° versus 25° on VAP rates in 30 patients was underpowered to detect a difference in VAP rates. Protractors were used to measure HOB elevation but no discussion on frequency of measurements or compliance with assigned group was provided.¹⁰¹ Finally, a meta-analysis of randomized controlled trials on HOB positioning on incidence of VAP concluded that HOB elevation of 15-30° was not sufficient to prevent VAP and that patients positioned to 45° had a lower incidence of VAP compared to supine patients.¹⁰²

Despite guideline recommendations for HOB elevation, several studies have demonstrated that patients are often maintained at less than 30° HOB elevation.^{18, 20, 100, 103-104} Hemodynamic instability and procedures are cited as reasons for HOB positioning less than 30°. Rose et al. identified the need for research to confirm the superiority of 45° semi-recumbent

positioning for VAP reduction before more quality initiatives to improve compliance with 45° HOB elevation are developed since maintenance at this HOB elevation may not be clinically feasible.¹⁰⁴

Similar findings were reported with the implementation of a comprehensive 45° HOB elevation program that included education of nurses and physicians and standardized orders. Although HOB angle increased with implementation, less than one-third of patients were observed at 45° elevation. Helman et al. also surveyed nurses regarding barriers to 45° HOB elevation positioning. Fifty-seven nurses were surveyed and cited the following concerns with the 45° positioning: 1) increased probability of patient sliding down in bed (100%), 2) increased difficulty with turning on a rotation bed (77%), 3) patient's discomfort and sleep disruption (35%), 4) concern over increased skin breakdown (22%), and 5) affect on hemodynamic monitoring (13%).¹⁰⁵ Other reasons for lowering the HOB can be found on the practice alert document by AACN related to the prevention of VAP. Reasons cited include cardiovascular and neurological alterations, and processes of care.²²

On occasion, patients' beds are placed in a head down position resulting in the head being lower than the feet. This position is termed trendelenburg. A bariatric repositioning algorithm describes the use of trendelenburg position when pulling the patient up in bed to facilitate movement.¹⁰⁶ Also, bedside procedures such as central venous cannulation and central venous catheter removal are performed in the trendelenburg position to enhance jugular vein cannulation and reduce the risk of air embolism. No studies have examined the impact of trendelenburg position for procedures or repositioning on GER or aspiration.

With the implementation of an aspiration risk-reduction protocol, Metheny et al. were able to achieve mean HOB elevations of 30° in 90% of patients. Investigators were present 16

hrs/day, 7 days/week which likely influenced the high compliance.⁹⁶ Interruptions in HOB elevation and trendelenburg impact on reflux and aspiration need further study.

Gastric Residual Volume Monitoring

Delayed gastric emptying is an important factor associated with GER and subsequent aspiration of gastric contents especially in gastric fed supine patients. Gastric residual volumes (GRV) are measured by critical care nurses every 4 to 6 hrs to assess for gastric emptying and feeding tolerance. Syringe aspiration of the gastric tube is the primary method used by nurses to measure GRV. Patient position, tube material, location and number of aspiration ports, tube location in the stomach and syringe gauge will all impact the ability to obtain an accurate GRV.¹⁰⁷⁻¹⁰⁹ Patients with higher GRV during gastric feeding display delayed gastric emptying.¹¹⁰ GRV is higher in the first few days of tube feeding.¹¹¹⁻¹¹² The use of GRV to detect feeding intolerance and its association with aspiration or VAP has been debated.¹¹³⁻¹¹⁷ The differences observed in feeding intolerance and pneumonia rates may be related to different detection techniques used to identify aspiration of gastric contents and diagnose pneumonia. Furthermore, different GRVs were examined in various studies. Although no consistent relationship between GRV and aspiration pneumonia was found, a gastric residual volume greater than 250 ml was associated with a higher rate of aspiration pneumonia in mechanically ventilated gastric fed patients.¹¹⁵ GRV trends of increasing volumes can be a marker of intolerance and provide a reasonable indicator for impaired gastric emptying. Gastric residual volumes between 250-500 ml should alert the nurse to the patient's increased risk for reflux and consideration of interventions such as prokinetic agents or placement of the feeding tube beyond the second portion of the duodenum.⁹⁶

Other methods used to measure gastric emptying include refractometry,¹⁰⁹ acetaminophen absorption,^{111, 118} scintigraphy,¹¹⁹⁻¹²⁰ electric impedance tomography,¹¹⁹ breath tests¹²⁰⁻¹²² and ultrasound.¹²³ However, these methods are generally not available to most bedside critical care clinicians. Recent studies have examined the clinical utility of ultrasonographic measurement of the antral cross section area in the preoperative setting as a measure of gastric volume.¹²⁴⁻¹²⁵ Ultrasonography holds potential as a clinical measure of gastric volume and gastric emptying. The future role of ICU bedside ultrasonography and the other previously mentioned methods is uncertain. However, new methods may provide better evaluation of gastric emptying in patients at high risk for reflux than GRV syringe aspiration measurements.

Gastric or Small Bowel Tube Location

A meta-analysis of the prophylactic use of an NG tube for gastric decompression in surgical patients examined 37 studies. Patients in these studies were placed into two groups. Group one included all patients who did not have a NG tube placed in the peri-operative period, NG tube was removed in the operating room or post-anesthesia care unit or within the first 24 hrs post-operatively. Patients in group two had a NG tube maintained until return of bowel function, generally indicated by spontaneous passage of flatus. Several outcomes were examined including postoperative pulmonary complications. Twenty-seven of the studies examined pulmonary complication of pneumonia or atelectasis. Non-routine use of NG decompression provided some benefit although it was not statistically significant ($p = .09$, $OR = 1.45$, $CI = 1.10-1.92$).¹²⁶

The incidence of VAP was studied in patients receiving duodenal or jejunal feeding with a smaller bore tube. The use of small bowel compared to gastric feedings did not result in reduced VAP rates.¹²⁷⁻¹²⁹ Feeding tube placement was reported in the second portion of the duodenum or beyond in one study¹²⁷ and post-pyloric in one study.¹²⁸ In the third study, a dual

lumen nasojejunal tube was used with four different placement techniques, including blind technique. Exact location was not described.¹²⁹ In a study of 33 patients randomized to either gastric or post-pyloric feeding tube, GER and microaspiration were both reduced in patients fed post-pyloric. These authors also found that 92% of post-pyloric fed patients had episodes of duodenogastric reflux. Post-pyloric feeding tube location was within the first portion of duodenum in 8 patients, the second portion in 3 patients and the fourth portion in 1 patient.¹³⁰

Jejunal feeding compared to gastric feeding was compared in 38 critically ill patients. No pneumonia was observed in the 19 jejunal fed patients while 2 of the 19 gastric fed patients were diagnosed with pneumonia.¹³¹ Additionally, pneumonia occurred less often when feeding tubes were placed in the second portion of the duodenum or beyond in mechanically ventilated tube fed patients¹³²⁻¹³³ with pneumonia rates lowest when tubes were placed in the fourth portion of the duodenum or beyond.¹³³ Therefore, small intestine location in the distal duodenum or jejunum may be the significant factor in reducing reflux.

For long term feeding, the use of distal duodenal or jejunal feeding in addition to gastric decompression may reduce reflux and aspiration.¹³⁴ Feeding into the small bowel while maintaining gastric decompression with a gastric tube may provide a feasible method to reduce GER and aspiration in the critically ill mechanically ventilated patients.¹³⁵ However, this requires further research since 2 tubes, a feeding and a decompression tube, would be traversing the LES.

Feeding Method

Patients who do not tolerate bolus gastric feeds may benefit from continuous feeds.⁷ However, one study of 106 mechanically ventilated patients demonstrated that intermittent feeding compared to continuous feeding resulted in lower risk of aspiration pneumonia.¹³⁶ Other studies have found no difference in feeding method in critically ill or healthy volunteers on

pneumonia or GER respectively.¹³⁷⁻¹³⁸ More research is needed comparing intermittent bolus and continuous feeding.

Recently, several studies have reported the impact of thickening agents added to liquid meals.¹³⁹⁻¹⁴² In healthy volunteers, addition of pectin to enteral solution resulted in accelerated gastric emptying.¹³⁹ Liquid nutrients prepared with agarose, a gel, and administered via a PEG tube in a geriatric population resulted in decreased reflux without tube clogging in patients with established PEG tubes.¹⁴⁰ A similar study found that the addition of agar to the enteral solution and administered via a PEG tube in patients with a known history of aspiration reduced GER but did not eliminate it in all patients.¹⁴¹ However, another study using half-solidification of liquid nutrients showed no reduction in GER with PEG tube administration.¹⁴² Research is needed to examine the impact of thickening gastric tube feeding in a mechanically ventilated population on reflux and aspiration.

Prokinetics

Prokinetics are agents that increase gastrointestinal motility. Prokinetics are widely used to promote tolerance to gastric enteral nutrition in the setting of delayed gastric emptying.¹⁴³ Several studies have examined metoclopramide and erythromycin on gastric emptying and GRV in the critical care population. Metoclopramide acts primarily as a dopamine (D2 receptor) antagonist, 5-hydroxytryptamine (5-HT)₃ antagonist and 5-HT₄ agonist with efferent myenteric cholinergic neurons releasing acetylcholine.¹⁴⁴ Activation of these receptors triggers an intense burst of gastric contractions and accelerates gastric contractions.⁴⁸ Erythromycin is a macrolide antibiotic which also acts as a motilin receptor agonist.¹⁴⁴ Motilin is synthesized from endocrine cells of the duodenojejunal mucosa.¹⁴⁵ Motilin receptors are primarily found in smooth muscle cells of the gastric antrum, duodenum and colon but their density is highest in the gastroduodenal

region.¹⁴⁶ Erythromycin stimulates high-amplitude antral contractions which are rapidly transmitted across the pylorus to the duodenum.¹⁴⁴ Erythromycin improves coordination of antroduodenal motility in a dose dependent fashion. The dosage required to accelerate gastric emptying is less than the dose required for antibacterial activity.⁴⁸ Moderate doses of 200 mg are frequently given; however, lower doses of 70 mg may be equally effective.¹⁴⁷

Studies of erythromycin have demonstrated an improvement in gastric emptying with the greatest impact on patients with delayed gastric emptying¹⁴⁷ and in the first few days of therapy.¹⁴⁸ In two studies, both erythromycin and metoclopramide were found to reduce GRV in critically ill patients receiving gastric feedings. However, erythromycin led to lower GRV^{118, 148} and improved the proportion of patients who achieved successful feeding.¹⁴⁸ Combination therapy with both erythromycin and metoclopramide was found to be even more effective than erythromycin alone.¹⁴⁹ Of concern with erythromycin is the possibility of antibiotic resistance with frequent use and diminished effectiveness after several days.⁴⁸

Ghrelin receptors are the most recent focus of prokinetic agents. Ghrelin is structurally similar to motilin and both motilin and ghrelin are now classified as members of a new motilin-ghrelin peptide family.^{145, 150} Secreted by the enteroendocrine cells of the oxyntic mucosa of the gastric fundus, ghrelin is the endogenous ligand for the growth-hormone secretagogue receptor and is known to have many endocrine activities. Ghrelin receptors are expressed throughout the gastrointestinal tract, but similar to motilin receptors, their density is highest in the stomach and duodenum with minimal colonic activity in humans.¹⁵¹ Most often identified with appetite stimulation, ghrelin also has prokinetic activity.¹⁵⁰ In healthy volunteers, ghrelin induced phase II like contractions of the stomach.^{143, 150} Ghrelin is reported to stimulate the MMC, increase gastric motility and promote gastric emptying.¹⁵¹ Long term use of ghrelin for gastric motility may not

be warranted because of its various actions. However, ghrelin may be useful in acute episodes of decreased gastric emptying.¹⁵² Synthetic non-peptide ghrelin receptor agonists have been developed to stimulate gastric emptying without the full complement of ghrelin receptor activity and are currently being studied in healthy volunteers, diabetics and post-operative patients.¹⁵¹ Ghrelin blood concentrations are reduced in critical illness, with observed levels of acyl ghrelin lowest in patients intolerant to gastric feeds. However, no research of ghrelin agonists and gastric emptying in ICU patients exists.^{48, 152}

Subglottic Secretion Drainage

The use of subglottic secretion drainage (SSD) in intubated patients has been studied since 1992. Theoretically, removal of subglottic secretions will reduce microaspiration and the risk of VAP. SSD requires an endotracheal tube with a separate dorsal lumen directly above the endotracheal tube cuff allowing for removal of secretions. Dezfulian et al. conducted a meta-analysis of the use of SSD to prevent VAP. The authors concluded that SSD is effective in preventing early-onset VAP in patients expected to require intubation and mechanical ventilation for > 72 hrs.¹⁵³ A more recent meta-analysis was published by Leasure and colleagues. In an analysis of ten studies, the authors found a 52% reduction in VAP with SSD (risk ratio 0.52, 95% CI = 0.43-0.64).¹⁵⁴ Authors of the second meta-analysis arrived at similar conclusions as Dezfulian et al. regarding the benefit of SSD to prevent VAP.

Measures to Detect Reflux and Aspiration

Esophageal pH Monitoring for Reflux

Ambulatory intraesophageal pH monitoring is the standard for establishing pathological reflux. A pH probe is passed nasally and positioned 5 cm above the LES as determined under esophageal manometry studies. The probe is connected to a data device capable of collecting pH

values every 4-6 seconds. The patient can record events such as symptoms, meals and position changes over the 18-24 hr data collection period.⁴ Placement of pH probes in the esophagus of surgical and critically ill patients have also been used to study reflux in critical care patients.^{65, 80, 155} The probes are not placed by manometric identification of the LES but rather, confirmation of esophageal location is based on obtainment of acidic pH to determine gastric location. The probe is then withdrawn into the lower esophagus until a pH change is noted. To detect aspiration, pH probes can also be placed in the trachea. Russell et al. placed pH probes in the esophagus and trachea to detect reflux and aspiration in cardiac surgery patients.⁶⁵

Methods to Detect Aspiration

Detection of aspiration has been studied by different measurement techniques and diagnostic tests over the past twenty years. Diagnostic tests include chest radiograph and high resolution chest computed tomography. Both tests lack sensitivity to lung aspiration as the cause of lung injury.⁶ Meal labeling with radioactive markers is considered sensitive and specific for measurement of gastric emptying although it lacks utility for bedside use due to costs and resources¹⁵⁶ and has variable sensitivity for aspiration.⁶

The addition of blue dye to tube feedings and assessment of suctioned secretions for blue discoloration was routinely performed in the 1980's but has since been deemed unreliable and even unsafe for patients.^{157, 158} Glucose oxidase testing has also been disproved as a reliable measure of lung aspiration¹⁵⁸ because glucose presence in tracheal secretions is impacted by blood glucose levels.¹⁵⁹ Lipid-laden alveolar macrophages in bronchial alveolar lavage samples has yielded conflicting results with excellent sensitivity but low specificity for aspiration.^{6,81}

Pepsin Assay

Pepsinogen is synthesized in the exocrine chief cells of the stomach. Pepsinogen

secretion occurs in response to food ingestion. Pepsinogens are inactive proenzymes that are converted in an acid environment to the active form pepsin. Pepsin initiates protein digestion. Pepsin is an ideal marker for reflux and aspiration for several reasons: 1) pepsin is not normally found in the pharynx, tracheobronchial tree or lungs, 2) pepsin remains biologically active and detectable after reflux and aspiration, and 3) pepsin can be retrieved with minimally invasive procedures.⁸¹ Pepsin was first utilized in a study by Badellino and colleagues using a hemoglobin digestion method. In a study of rabbits with instilled gastric juice, the authors described 100% sensitivity but specificity was not reported.¹⁶⁰ However, a major limitation is that the hemoglobin digestion method can not be used to detect pepsin that has been degraded in the alkaline environment of the lung.⁸¹

Ufberg et al. examined a pepsin-specific qualitative enzyme plate assay using the digestion of fibrinogen in an acidified agarose gel. Gastric aspirates from NG tubes and tracheal aspirates from an endotracheal tube were obtained upon tube placements in 20 patients undergoing elective surgery. All tracheal aspirates were negative and all gastric aspirates tested positive.¹⁶¹

Immunoassays detect or quantitatively measure a specific protein in blood or body fluids. Immunoassay techniques utilize an antibody-antigen relationship to identify a specific protein such as pepsin. The most common immunoassay methods used are western blotting and enzyme-linked immunosorbent assay (ELISA). Western blotting uses protein immunoblotting to identify a protein based on its isoelectric point, electrical charge, molecular weight, molecular structure or a combination of these factors. With the ELISA technique, the antigen is fixed to a platform and the antibody linked to an enzyme, specific to the protein of interest, is washed over the plate which allows for binding.¹⁶² Metheny et al. developed a western blot immunoassay of rooster

polyclonal antibodies to pepsin which has subsequently been used to study aspiration in pediatric and adult patients. The technique detects pepsin concentration as low as 1 microgram/mL¹⁶³ with a sensitivity of 93% and a specificity of 100%.¹⁶⁴ Using the western blot immunoassay to detect pepsin in tracheal secretions of adult patients receiving enteral nutrition, the researchers found that patients with frequent aspiration were 4 times more likely to develop pneumonia than were infrequent aspirators.¹⁴

Another pepsin assay involves the use of a proteolytic enzyme assay with fluorescein isothiocyanate-labeled casein. This technique was reported to detect pepsin at a level of 12.5 ng/50 μ L. The fluorescein technique was used in a pediatric patient population undergoing general anesthesia. The researchers compared children with clinically significant GER to children with no known history of reflux. Pepsin was detected in 26% of children with known reflux, 88% of children with reflux and chronic respiratory symptoms and 84% of children with known reflux and chronic respiratory symptoms. None of the 26 children without a history of GER had tracheal pepsin. Specificity was not reported with this technique.¹⁶⁵

Using an enzymatic assay with a fluorescent substrate, tracheal aspirates from premature mechanically ventilated neonates were analyzed for pepsin. Tracheal aspirates were obtained 3 hrs after a feeding on 7 different days over a 28 day period from 59 neonates. Pepsin was detected in 222 of 239 tracheal aspirates.⁹³ In a similar study, an active enzyme assay was used to identify pepsin in tracheal aspirates from 27 mechanically ventilated children. Seventy percent of the children had pepsin positive tracheal aspirates. Pepsin positive secretions were found more often in children with uncuffed tracheal tubes, as opposed to those with cuffed tubes.¹¹ Other investigators have reported that pepsin positive bronchoalveolar lavage fluid in lung allograft patients was evidence of aspiration.⁹⁴ In another study, the presence of pepsin and pepsinogen

was measured in the saliva of healthy volunteers by a new technique using immunoaffinity-mass spectrometric assays. The final assay results were reported to have <15% error.¹⁶⁶

Immunoaffinity-mass spectrometric assays have not been tested in patients with known reflux or in critically ill patients.

Investigators have used these various measures to measure pepsin as a marker for GER and aspiration. To examine the use of a pepsin assay to detect reflux, Potluri et al. studied a group of 16 patients with GERD symptoms. The patients underwent simultaneous 24 hr esophageal pH monitoring and collection of saliva and sputum samples for pepsin measurement using a fibrinogen digestion pepsin assay. Of the secretions collected, 161 were negative for pepsin and 19 were positive. Esophageal reflux was not detected via pH monitoring in patients who had negative pepsin assays. In contrast, esophageal reflux was documented in 3 of 4 patients with a positive assay. The investigators concluded that detection of pepsin in saliva and/or sputum may provide a noninvasive method to test for reflux of gastric contents.¹⁶⁸ In another study in which patients with GERD symptoms were evaluated, sputum/saliva specimens collected before bedtime were analyzed by an immunoassay. The test for pepsin was positive in 20 of the 40 patients. When the investigators compared the pepsin results to 24 hr pH-metry in 9 of the patients, the sensitivity and negative predictive value of the pepsin test were excellent. However, its specificity and positive predictive value were relatively low.¹⁶⁶ Knight et al. examined pepsin in 63 sputum samples cleared from the back of the throat in 23 subjects with known GER and compared results with pH monitoring from a pH esophageal manometry catheter. The majority of throat samples (78%) contained no pepsin and was associated with no decrease in pH at the esophageal or pharyngeal probe. Fourteen (22%) of the throat samples had detectable pepsin. Subjects with samples positive for pepsin had significantly decreased

esophageal and pharyngeal pH ($p = .01$). The researchers reported pepsin immunoassay results that were 100% sensitive and 89% specific for EER at the pharyngeal probe.¹⁶⁹

In a pilot study, 10 of 50 gastric fed mechanically ventilated patients who were suctioned once had pepsin positive oral secretions via western blot analysis.⁵⁸ Mean oral secretion volume in orally intubated patients was recently reported to be 7.5 ml with a 2 hr oral suctioning frequency.¹⁷⁰ Oral secretions are easy to obtain and less invasive than esophageal pH monitoring and may provide a good biomarker for GER in the critically ill patient and predictor of aspiration.

In summary, studies have indicated that pepsin is a reliable marker for both reflux and pulmonary aspiration. Different techniques for measuring pepsin report different sensitivity and specificity. Of the various methods to measure pepsin to detect reflux and aspiration, the western blot assay appears to be the optimal method to measure pepsin.

Conclusion

Mechanically ventilated gastric fed patients in the ICU are at risk for reflux and aspiration. The primary recommendation to reduce reflux and aspiration is HOB elevation to 45°.

However, studies have demonstrated the challenges to maintaining elevation at 45°. ¹⁰²⁻¹⁰³ No comparative studies of the incidence of reflux and aspiration with analysis of pepsin presence according to HOB elevation (30° versus 45°) were identified in the literature. A study was needed to examine the association of reflux and aspiration at the two HOB elevations. This study was the first to examine the association between reflux and aspiration in critically ill mechanically ventilated gastric fed patients according to a 45° HOB elevation versus a 30° HOB elevation.

Results from the study will provide clinicians with some evidence to support positioning practices to reduce risk for reflux and subsequent aspiration in critically ill, mechanically ventilated patients who are receiving gastric feedings. Pepsin in oral secretions has been shown

to be a reliable marker of reflux. A simple measure of pH of oral secretions at the bedside may provide a marker for reflux thus, this study examined pepsin presence in oral secretions and association with pH measurements.

CHAPTER III
METHODOLOGY

The primary aims of this study were: 1) to describe the frequency and duration that patients' HOB angles are temporarily lowered for treatment purposes below 30° or below 45°; 2) to describe the occurrence of reflux (pepsin-positive oral secretions) and aspiration (pepsin-positive tracheal secretions) with HOB elevation at 30° and 45°; 3) to determine the association between reflux and aspiration with the 2 different HOB elevations in adult ICU mechanically ventilated gastric fed patients; 4) to determine the association between a temporarily lowered HOB position for treatment purposes and reflux of gastric contents; 5) to determine the association between 7 patient characteristics (gender, age, BMI, GRV, sedation level, disease severity, and use of prokinetic agents) and reflux; 6) to determine the association between the pH (range 0-14) of oral secretions and pepsin presence in oral secretions (the gold standard measure of reflux).

Currently there is minimal research that directly compares HOB elevation of 30° to 45° on the outcomes of reflux and aspiration in the population of interest. In Chapter III the research methodology is presented that was used to address the study aims and research questions.

Research Design

The design of the study was a randomized 2-day crossover trial. Subjects were ICU mechanically ventilated gastric fed patients that were randomly assigned to 1 of the 2 HOB elevation sequences. During the first sequence, the subject's HOB was elevated at 30° for 12 hrs on day 1 and 45° for 12 hrs on day 2. In the second sequence, the HOB started at 45° for 12 hrs on day 1 and 30° for 12 hrs on day 2. A 12-hr washout period was provided to allow for elimination of the effects of the first day's HOB elevation between day 1 and day 2 with the bedside nurse positioning the patient per nurse and patient preference. Thirty degree HOB elevation was considered usual care in the study setting. Therefore, the experimental condition

was implementation of 45° HOB elevation. Table 1 demonstrates the design with sample size and interventions. The independent variable for this study was HOB elevation and the dependent variables were reflux and aspiration.

Table 1
Randomized Crossover Design

RANDOMIZED CROSSOVER TRIAL (n = 15)	
Usual Care Condition	Experimental Condition
<p>8 am</p> <p>HOB 30°</p> <p>8 pm</p>	<p>8 am</p> <p>HOB 45°</p> <p>8 pm</p>

Setting

The study site was an acute care facility that delivers care to adults only. The study was conducted in 2 ICUs at Barnes-Jewish Hospital in St. Louis, MO. After Human Institutional Review Board (IRB) approval at Washington University and Barnes-Jewish Hospital, an umbrella agreement was made with the University of Kansas IRB. Verbal and written approval to conduct this study was provided to the Principal Investigator (PI) by the nurse managers and medical directors of both ICUs. One unit was a 36 bed surgical/burn/trauma ICU and the second unit was a 19 bed medical ICU. Staffing was generally 1 nurse to 2 patients with an occasional one-on-one assignment. Internal process improvement data on mechanically ventilated patients demonstrated that 30° HOB elevation was observed in more than 90% of the audits in both ICUs.

Sample

Patients were screened Monday-Friday to determine if they met inclusion and exclusion

criteria. A screening filter to identify all patients with tube feeding orders was developed for both ICUs in the electronic medical record (EMR). A list of all patients with tube feeding orders was generated each screening day. The list was reviewed 2 times per day to ensure no new orders were missed. In addition, discussions with the clinical dietitian in each unit were held to seek information about any other possible orders to be placed. The list of patients generated from the tube feeding order filter and during dietitian discussions were screened for the following inclusion and exclusion criteria.

The inclusion criteria for subjects to enter the study included:

1. X-ray confirmed gastric location of feeding tube or surgically/endoscopically placed gastric feeding tube prior to study enrollment
2. Mechanically ventilated per endotracheal tube
3. ≥ 18 years of age
4. Approval from attending physician to randomize patient to a 30° and 45° HOB elevation
5. Surrogate available to provide written consent
6. Anticipated mechanical ventilation and tube feeding duration for at least 48 hrs

The exclusion criteria of patients included:

1. Oral trauma that would prevent oral suctioning
2. Inability to tolerate having the HOB at 45° for 12 hrs
3. Elevated intracranial pressure or other reason which precluded suctioning or lowering of the patient's HOB
4. Stage I or higher pressure ulcer to the sacrum/coccyx, buttock or either trochanter region
5. Pregnancy

6. Documented history of GERD or hiatal hernia
7. Active pulmonary tuberculosis or any airborne infectious disease

A subject screening form was used to verify all inclusion criteria were met and no exclusion criteria were present (Appendix A). A total of 215 patients were screened. Surrogates of patients meeting inclusion criteria were approached for informed consent. Study details including risks were explained to the surrogate by the PI. Opportunity for the surrogate to ask questions was provided during the consent discussion. The surrogate's understanding of the study and the role of the patient in the study was verified with questions by the researcher. The surrogate was informed that participation was voluntary, that the patient could be withdrawn from the study at any time upon request and that usual care would continue for the patient whether the surrogate consented to have the patient participate or not.

Randomization

Informed consent was obtained the day before randomization. If the patient remained on mechanical ventilation per an endotracheal tube the following morning, the patient was randomized to either 30° or 45° HOB elevation on day 1 and crossed over to the other HOB elevation on day 2. Subjects were maintained in the designated HOB elevation from 0800-2000. The washout period was 2000-0800 between day 1 and day 2. Nurses positioned the patient at any HOB level during this time period. Randomization of the subjects occurred using a computer generated randomization schedule. Cards were labeled with HOB assignment and placed in a sealed security envelope. Envelopes were sequentially numbered on the outside. The morning after informed consent, mechanical ventilation and continued tube feeding orders were verified for each subject. Once verified, the envelopes were sequentially opened the first morning of data collection.

Data Collection and Procedures

Prior to study recruitment, nurses in both ICUs received education on study purpose, design, methods and HOB gauge operation by the PI. Education required approximately 15 minutes and was conducted in the conference room in each ICU division. Approximately 140 nurses worked in the 2 ICUs. For any nurse not reached in the education, real time education occurred at time of study start by the PI. Additionally, the nurse caring for a newly enrolled patient was provided verbal information on randomization assignment and an opportunity to ask any questions of the PI. At time of enrollment, the patient demographic form was completed (Appendix B).

One research nurse was employed to assist the PI with provision of the HOB elevation intervention and data collection. The research nurse was an ICU nurse from 1 of the study units. The research nurse received one-on-one education in detail regarding data collection and documentation from the PI. The PI was with the research nurse with the first 2 subjects to ensure that the procedure for data collection was completed correctly. During all data collection, the PI was available to assist and verify accuracy. The research nurse collected data on 4 data collection days. The PI collected the data on all other days.

An electronic HOB gauge, (Nextronics Patient Position Monitoring System, Toledo, OH), was placed on the under surface of the bed frame at the HOB by the PI before 0800 on the first day of data collection for each subject. A second device with a digital display component was placed by the PI on the top side rail of the bed with the measuring apparatus on the under surface of the frame near the recording device to ensure the same measurement placement. Battery function was verified in the devices with each new subject enrollment. The gauge provided information on degree of HOB elevation at 30-second intervals. With a button push, the nurse

could clearly visualize the exact HOB elevation in degrees at the subject's top side rail. Nurses were instructed by the research nurse to use the gauge for exact HOB elevation with any subject repositioning. The research nurse also assisted with repositioning of the subject on most occasions. During these times and after procedures, the research nurse assisted with return of the subject to the assigned HOB elevation. At the end of the 36-hr enrollment period, HOB information was downloaded by the PI from the device and entered into a secured computer with subject enrollment number.

A brightly colored sign with HOB study and assignment for the day was suspended above the subject's bed each morning. A different colored sign was used for the different HOB assignments. The signs were removed each evening at the end of the 12-hr data collection period. These signs provided visual cues to maintain the HOB at assigned level.

Specimen traps for oral and tracheal secretion collection were labeled with study number. Specimen traps and labels were delivered to the subject's room by the research nurse the morning of the first day of data collection and throughout the study period. Study day was completed by the research nurse on a row of labels for the day. The nurse collecting the specimen circled oral or tracheal and recorded the time of collection. The vast majority of specimens were obtained by the research nurse.

A small, hard sided ice cooler (Playmate® Mini-Cooler, Igloo Products Corporation, Katy, TX) filled with crushed ice was delivered to the subject's room at 0800 and fresh ice added at 1400 to store and transport oral and tracheal secretions. Ice was obtained from the ice machine within the ICUs. Oral secretion volume with a 4-hr oral suctioning interval was reported to range from 1 to 25 ml.¹⁷⁰ Subjects in the current study with larger secretion volumes required suctioning at least every hr while patients with smaller secretion volumes required suctioning

less than every hr. It was anticipated that suctioning of oral secretions would be required every 1 to 2 hrs. Increased or decreased frequency of suctioning interval of oral secretions depended on the patient's volume of secretions. The research nurse or bedside nurse connected an Argyle Rigid Yankauer (Kendall™ Covidien, Mansfield, MA) oral suction device to 1 opening of the specimen trap and suction tubing to the other opening of the specimen trap. The other end of the suction tubing was connected to wall suction set to 100 mm Hg. The Yankauer was placed in the oral cavity and moved throughout the oral cavity until no further oral secretions were obtained. Subjects with a RASS score of 0 who previously suctioned their own oral secretions were allowed to continue self-suctioning.

Tracheal secretions were obtained via the endotracheal tube by the research nurse or subject's bedside nurse as subject condition warranted, typically every 2-3 hrs. Several tracheal secretions were missed when tracheal specimens for culture were obtained or during bronchoscopy. For tracheal suctioning, the nurse connected the in-line suction catheter, which prevented loss of positive end expiratory pressure during suctioning, (Ballard Medical, Draper UT) to 1 opening of the specimen trap and suction tubing to the other opening of the specimen trap. The nurse followed the hospital procedure for suctioning. The time and date of specimen collection and the location of the specimen, oral or tracheal, was written on the label by the nurse suctioning the subject. Labeled secretions were placed in a bag and the bag was wedged in the ice in a biohazard labeled cooler at the subject's bedside. A laboratory technician or the PI made hourly rounds to obtain collected specimens and ensured subject's study number and collection date and time were clearly legible. Specimens were initially processed in a research laboratory on site at Barnes-Jewish Hospital by a laboratory technician under the supervision of the PI for

the first 5 subjects and by the PI for the ten subsequent subjects. Specimen processing details are described below under pepsin analysis.

Study Variables and Measurements

Variables, method of measurement and frequency of measurement for each variable are summarized in Table 2. A detailed description of each variable is provided below.

Table 2
Summary of Measurements

Study Variables		
Type of Variable	Method of Measurement	Frequency
<u>Independent Variable</u> Head-of-bed elevation	Nextronics Patient Position Monitoring System	Every 30 seconds
<u>Dependent Variables</u> Reflux Aspiration	Pepsin in Oral Secretions Pepsin in Tracheal Secretions	Every 1-2 hrs (8 am-8 pm) Every 2-3 hrs (8 am-8 pm)
<u>Predictor Variables</u> Age Gender Body mass index Gastric residual volume Level of sedation APACHE II score Prokinetics	Medical record Medical Record Medical Record Syringe aspiration Medical record Medical record Medical Record	Time of admission Time of admission Time of admission Every 4 hrs (8-12-4-8) Every 4 hrs (8-12-4-8) ICU admission and 24 hrs before enrollment 24 hrs pre and during 48 hrs of data collection

HOB Elevation

A device specially designed for this study, the Nextronics Patient Position Monitoring System (Nextronics, Toledo, Ohio), was used to measure and record the subjects' HOB angles throughout data collection. The device was pilot tested on a variety of beds at the study institution and found to be reliable on all the beds used in the ICUs prior to data collection. The system consisted of 2 components (a battery powered display and processing module, and a battery powered with plug in capability small sensor module with a micro storage device disk). The storage device obtained a HOB elevation reading every 30 seconds as plus or minus, through

a range of minus 20° to plus 90°. The device attached to the base of the hospital bed with magnets. The device disc was downloaded to a Microsoft Excel file (Microsoft Corporation, Redmond, WA) upon data collection completion for each subject. Readings were recorded every 30 seconds so that the investigator knew in detail if the HOB deviated from the assigned level (45° for the experimental condition and 30° for the usual care condition). If the bed position was altered, the research nurse determined the reason, either by direct observation or by interviewing the bedside nurse. If the patient underwent a procedure or diagnostic test that required HOB positioning other than the prescribed elevation for the day, the reason was recorded. A digital readout of the HOB elevation was accessible to the bedside and research nurse.

Pepsin Analysis for Reflux and Aspiration

The western blot immunologic analysis was used in this study to detect the presence or absence of pepsin in oral and tracheal secretions. The western blot immunoassay technique detects a pepsin concentration as low as 1 microgram/mL,¹⁶³ with a sensitivity of 93% and a specificity of 100%.¹⁶⁴ In physiologic measures, reliability is a measure of stability of the technique over time.¹⁷¹ The western blot immunoassay technique detected pepsin in all secretions at the 2-hr and 4-hr mark and 91% at the 6-hr mark demonstrating reliability of the technique over time.¹⁶⁴

Once the secretions were obtained, the bedside nurse or research nurse placed a label with the study number and day of study on the specimen trap. In addition, the nurse recorded the site, oral or tracheal, and time on the label. The specimen trap was placed in a sealed plastic bag, and placed in ice in a cooler marked as biohazards waste. Every hr a laboratory technician or the PI retrieved the specimens from the enrolled subjects and carried all the bagged specimens in a cooler of ice to the on-site research laboratory. The laboratory was housed in a connecting

building that required approximately 5 minutes to walk. In the laboratory, a trained technician or PI measured the pH and performed the initial specimen processing. A microvial was labeled with the study number, X for oral or T for tracheal, and study day and time with a black sharpie pen. Fifteen μL of each secretion was pipetted into a 1 mL microvial mixed with an equal pipetted volume of Laemmli Sample Buffer (Bio-Rad Laboratories, Hercules, CA) containing 2-mercaptoethanol. The samples were then boiled at 100°C in a water bath with continuous bubbling of water for 5 minutes. After boiling, the samples were frozen to negative 90°C in a freezer in the laboratory.

A strip of pH paper (pHydrion, MicroEssential Laboratory, Brooklyn, NY) was used to measure pH of oral secretions. Secretions from the specimen trap were pipetted onto the pH paper. The pH measurement was recorded on a data collection sheet with time, date and study number by the laboratory technician or PI (Appendix C). Specimens were placed in an ice cooler and delivered to the laboratory for western blot analysis. Records of pH were not blinded to HOB assignment or obvious reflux episodes.

The frozen samples were thawed at room temperature and centrifuged at 13.4 K rotations per minute for 10 minutes. Supernatant was removed, 5% beta-mercaptoethanol was added and the sample was boiled for 10 minutes. Proteins were resolved with Western Blotting techniques using 4-20% TGX gels (Bio-Rad Labs Hercules, CA) and transferred onto a nitrocellulose membrane paper (Bio-Rad Labs) using a wet tank apparatus (Bio-Rad Labs). The membrane was then blocked for 60 minutes in 2.5% milk/PBST, and probed with chicken anti-human pepsin antibody diluted 100 fold in 1% milk/PBST overnight. The sample was then rinsed 3 times in PBST and labeled with rabbit anti-chicken antibody conjugated to horseradish peroxidase (Sigma Chemical, St. Louis, MO) diluted 1:200 in 1% milk/PBST for 90 minutes. After the

membrane was rinsed 3 times in PBST, pepsin was visualized using Pierce Ultra TMB Blotting solution (Thermo Scientific, Rockford IL) as per manufacturer's instructions. The blots were then washed in water, air dried and the results scanned with a flatbed scanner. Positive controls of 15 ng and 30 ng pepsin from human gastric juice were utilized to analyze the human samples. Fifteen ng control pepsin is equivalent to 1.5 µg/ml pepsin solution in the samples.¹⁶³ The chicken antibody was produced in the laboratory of Dr. Yie-Hwa Chang at St. Louis University (St. Louis, MO) who supervised the laboratory technicians conducting the western blot analysis.

Results of the assays were interpreted by a biochemist blinded to condition assignment or any clinical events. The assay was interpreted as positive if pepsin was detected in the oral secretions or tracheal secretions in a concentration ≥ 1.5 µg/ml. Ten percent of the samples were randomly selected for test-retest to determine reproducibility of results. The extent of reflux was computed as the percentage of oral secretions that were pepsin-positive. Similarly, the extent of aspiration was computed as the percentage of tracheal secretions that were pepsin-positive.

Universal precautions were followed during the collection and handling of the oral and tracheal secretions. As part of these precautions, the data collectors wore gloves when obtaining specimens. Laboratory technicians wore gloves, oral masks and eye protection when the secretions were transferred from the sputum traps to vials for processing and analysis. The specimen traps and all contaminated personal protective equipment were disposed of in an appropriate container marked for biohazardous waste. The coolers were cleaned with a Hype-Wipe® Disinfecting Bleach Towelette (Daigger & Company, Inc., Vernon Hills, IL) and allowed to air dry overnight between subject uses.

Age and Gender

Age (in years) and gender were entered in the EMR by the admitting department. The PI

confirmed age with the subject or surrogate and gender by direct visualization. The PI recorded both age and gender in the research record.

Gastric Residual Volume

Every 4 hrs, the research nurse instilled 30 ml of air into the irrigation port of the gastric feeding tube with a 60 ml catheter tipped syringe. Negative pressure was then applied to the syringe to allow for withdrawal of gastric contents. The subject's gastric contents were removed and emptied into a calibrated container until no further aspirate could be obtained. Any sample greater than 250 ml was discarded and the feeding tube was flushed with 30 ml of water. GRVs less than 250 ml were returned to the subject. The feeding tube was flushed with 30 ml of water and tube feedings resumed if continuous. In subjects ordered for bolus tube feedings, the subject's bedside nurse was informed of the GRV prior to the next bolus feed. In addition, the GRV was documented in the subject's EMR and the research record (Appendix D). It is standard of practice at the study hospital for nurses to measure GRV every 4 hrs per the above procedure.

Richmond Agitation-Sedation Scale (RASS)

The Richmond Agitation-Sedation Scale (RASS) is a 10 item clinician scored assessment of the patient's sedation and agitation level (see Table 3 below).¹⁷² In the study ICUs, the RASS was documented every 4 hrs by the bedside nurse in the patient's EMR. The ICUs have used this scale for over four years. The RASS score documented by the bedside nurse was entered into the research record every 4 hrs from 0800-2000 on both days. The RASS has reported interrater reliability (interclass correlation 0.956-0.964, weighted κ 0.73 to 0.91); criterion validity (RASS compared to neuropsychiatric assessment over time, significant changes identified with both methods over time); construct validity ($r = 0.78$ with Sedation Agitation Scale, -0.78 with Ramsay Sedation Scale, 0.78 to 0.91 with Glasgow Coma Scale, 0.93 with visual analog scale)

when utilized in both mechanically ventilated and non-ventilated patients for a variety of ICU populations. In these studies a high degree of correlation has been demonstrated among multiple types of ICU practitioners including nurses, physicians, pharmacist, and neuropsychiatric experts.¹⁷²⁻¹⁷³ All RASS scores were recorded on the data collection sheet (Appendix D).

Table 3
Richmond Agitation-Sedation Scale¹⁷²

Score	Richmond Agitation-Sedation Scale	
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and Calm	
-1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to voice (>10 seconds)
-2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Acute Physiology and Chronic Health Evaluation (APACHE II)

Acute Physiology and Chronic Health Evaluation (APACHE II) is a severity of disease classification system that is a point score based on 12 standard physiologic measurements, age and previous health condition. The total score ranges from 0-71 with a higher score representing higher severity of illness.¹⁷⁴ Since introduction, the APACHE II has several international studies validating its use in ICU patients.¹⁷⁵⁻¹⁷⁷ Validation was performed with 1,573 admissions in a Hong Kong ICU from 1988-1990. Survivors had lower APACHE II scores. Logistic regression analysis of mortality and APACHE II demonstrated a close correlation ($r^2 = 0.81$).¹⁷⁵ In a study by Del Bufalo et al., predicted mortality with APACHE II was compared to predicted mortality with the Simplified Acute Physiology Score (SAPS II) in 306 ICU patients with respiratory

disease. The ratio between the actual and predicted hospital mortality was 86% for APACHE II and 83% for SAPS II. The receiver operating characteristic curve analysis demonstrated a better predictive ability of the APACHE II (80.88%) compared to the SAPS II (73.52%) with a significantly larger area under the curve ($p < .01$).¹⁷⁶ Lastly, a study of 1,144 patients in a medical-surgical ICU compared the APACHE II and APACHE III. Risk assessments showed a strong positive correlation between both scores (non-survivors $r^2 = 0.756$, $p < .001$; survivors $r^2 = 0.787$, $p < .001$). However, risk predictions did not fit uniformly across various disease categories with APACHE II predictions better for patients with gastrointestinal disease and surgical admissions but similar predictions for medical patients.¹⁷⁷

Parameters used to calculate the APACHE II score include temperature; mean arterial pressure; heart rate; respiratory rate; oxygenation; serum levels of sodium, potassium, and creatinine; hemoglobin; white blood cell count; Glasgow Coma Score, chronic health points and age. The APACHE II score was calculated from variables using data from the first 24 hrs of ICU admission and 24 hours prior to the first day of data collection.

Body Mass Index (BMI)

Obese patients may experience an increase in tLESRs and therefore may be at increased risk of reflux and aspiration. BMI was calculated at the time of admission to the ICU when the admitting nurse entered the patient's height and weight. The EMR used a BMI calculator to determine the patient's BMI based on the entered height and weight information. The BMI calculated by the EMR was entered in the research record.

Prokinetics

The medication administration record in the EMR was checked every 4 hrs for administration of any prokinetic agents. The dose and number of doses received for 24 hrs before

study inclusion and for the 48 hrs during data collection were documented on the data collection sheet (Appendix D). The two major prokinetic agents used at the study hospital were metoclopramide and erythromycin.

Sample Size and Data Analysis

No studies were identified from which to calculate effect sizes for each of the proposed aims and research questions. With the cross over design of 15 subjects, the number of specimens collected for each individual and in total was relatively large. Thus, it was assumed that this initial study would allow the researchers to detect an effect size for future studies.

All data entered onto the written research record was entered by the PI into SPSS 18 (IBM Corporation, Armonk, NY) within 1 week of collection. Upon completion of all data collection, all entered results were reviewed for accuracy. Results of western blots were reported by subject number, day, time and specimen type by the biochemist. The results were then entered into SPSS by the PI and verified twice on subsequent dates.

For the HOB angles, a Microsoft Excel file was created by the manufacturer that converted the radians to degrees of HOB elevation. Data was downloaded from the micro secure digital disc from the device within 1 week of data collection. All data from each subject was saved in an individual excel file. HOB information from every 30 seconds was retrieved. The data was then separated on the Excel file in hourly sheets for both days. All data for the 12-hr night washout period were placed on one sheet. The hourly sheets were filtered to obtain angle entries less than the assigned level for that day. Minutes less than prescribed was determined. Mean values when less than prescribed, overall hourly mean and HOB mean for nights were calculated with the Excel average formula. The results were confirmed on two separate dates. All results were then entered manually into SPSS 18 and verified again on two later dates by the PI.

Non-parametric statistical tests were used to analyze the data due to the small sample size. Mean and standard deviation results were determined. For research question 1, the analysis included 12 hourly data points for three variables, each measured under the usual care and experimental conditions: 1) the number of minutes that the bed was lowered below 30° (usual care) or 45° (experimental), 2) the average HOB angle when the bed was lowered, and 3) overall mean HOB angle for each day. Median differences between total minutes lowered for each HOB assignment, mean when lowered less than assigned and overall mean at each assignment were examined with related samples Wilcoxon Signed Rank Tests. Also, a 2 X 12 (condition X hr) repeated measures Friedman test was used to analyze mean changes over time on the number of minutes per hr that the bed was temporarily lowered and the average HOB angle while lowered for each HOB assignment.

For research question 2, descriptive statistics were used to summarize the percentage of secretions in which pepsin-positive oral secretions and pepsin-positive tracheal secretions were observed across the 12 hrs in the 30° usual care condition and the 45° experimental condition. A related samples Wilcoxon Signed Rank test was used to compare the usual care and experimental conditions on the summary scores for % pepsin-positive oral secretions and % pepsin-positive tracheal secretions at each HOB assignment.

For research question 3, using summary scores from the 15 patients, two Kendall's tau correlation coefficients were computed between % pepsin-positive oral secretions and % pepsin-positive tracheal secretions. One correlation was computed for the usual care condition and a second correlation for the experimental condition. Scatterplots were examined for outliers, nonlinearity, and homoscedasticity. Percent of matched samples, oral and tracheal secretions simultaneously collected with same results, was also calculated

For research question 4, Kendall's tau was computed using summary scores measuring total minutes the HOB was lowered, the average angle during lowered periods, overall mean angle and % pepsin-positive oral secretions for the usual care and experimental conditions. In addition, scatterplots were examined for the various bivariate relationships.

To examine the association between patient characteristics and reflux in research question 5, Kendall's tau correlations were computed between each of the patient characteristics (gender, age, BMI, GRV, RASS, APACHE II, and use of prokinetic agents) with the summary score of % pepsin-positive oral secretions. Scatterplots were also examined.

For research question 6 to examine the association between pH (range 0-14) of oral secretions and pepsin in saliva, Kendall's tau correlation was computed between the average pH of oral secretions (over the 12 hrs) and the summary score of % pepsin-positive oral secretions. Scatterplots were also used. In addition, pH measures of 4 and 5 were descriptively compared with pepsin results.

Ethical Considerations

Human Research Protection Office approval was obtained at Barnes-Jewish Hospital at Washington University. A reliance agreement was then obtained between Washington University and the University of Kansas prior to study initiation.

Subject preferences for positioning for comfort were considered. The research nurse documented when the HOB was less than the allocated level because of subject request. After 30 minutes at the lowered position if the subject appeared awake, an attempt was made to elevate the subject's HOB to the randomized level and maintained per subject tolerance. If at any time the subject or surrogate wanted to withdraw from the study, the subject would have been

immediately removed from any further data collection and the subject positioned for comfort and per the nurse's discretion.

The subject's HOB was lowered at any time by the bedside nurses and physicians as the clinical situation warranted or during procedures and diagnostic tests. If the subject's condition changed and required lowering of the HOB, for clinical or safety concerns, the bedside nurses and physicians could withdraw the patient at any time. Management of the ventilator and weaning from the ventilator was performed by the multi-disciplinary ICU team. Removal of the endotracheal tube, extubation, was determined by the medical team. Upon extubation, data collection stopped.

The subject may have been at increased risk for pressure ulcers with the HOB elevation to 45°. To minimize the risk, research nurses assisted the bedside nurse with turning the subject every 2 hrs. During the repositioning, the subject's skin was assessed at the sacral, buttock and greater trochanter regions. Patients on mechanical ventilation in both ICUs are maintained on pressure relieving mattresses which lowers the risk of pressure ulcers and was standard of care. All study subjects were on a low air loss pressure relieving mattress prior to data collection. However, if the subject had demonstrated an alteration in skin integrity, Stage I pressure ulcer (redness without blanching upon skin touch), which could be related to the HOB elevation, the subject would have been removed from the study. Any reason for subject withdrawal or removal from the study was documented on the demographic sheet (Appendix B).

The other primary risk of this study was a breach of confidentiality. Confidentiality of subjects was maintained throughout the study data collection, analysis and reporting. Each subject was assigned a code number that was used on all data forms and laboratory specimens. The data sheets were kept in a closed binder in the possession of the research nurse at all

times. During nights and non-data collection days, the binder was kept in the PI's locked desk in a locked office. Only the PI and the research nurse had access to the subjects' names and code numbers. The master list was kept in the PI's office in a locked file cabinet. All identifiers were destroyed at the completion of the study. As data were entered into an electronic file, a password protected computer which was in the locked office of the PI was used. Only the PI had access to the electronic files.

CHAPTER IV

RESULTS

Sample

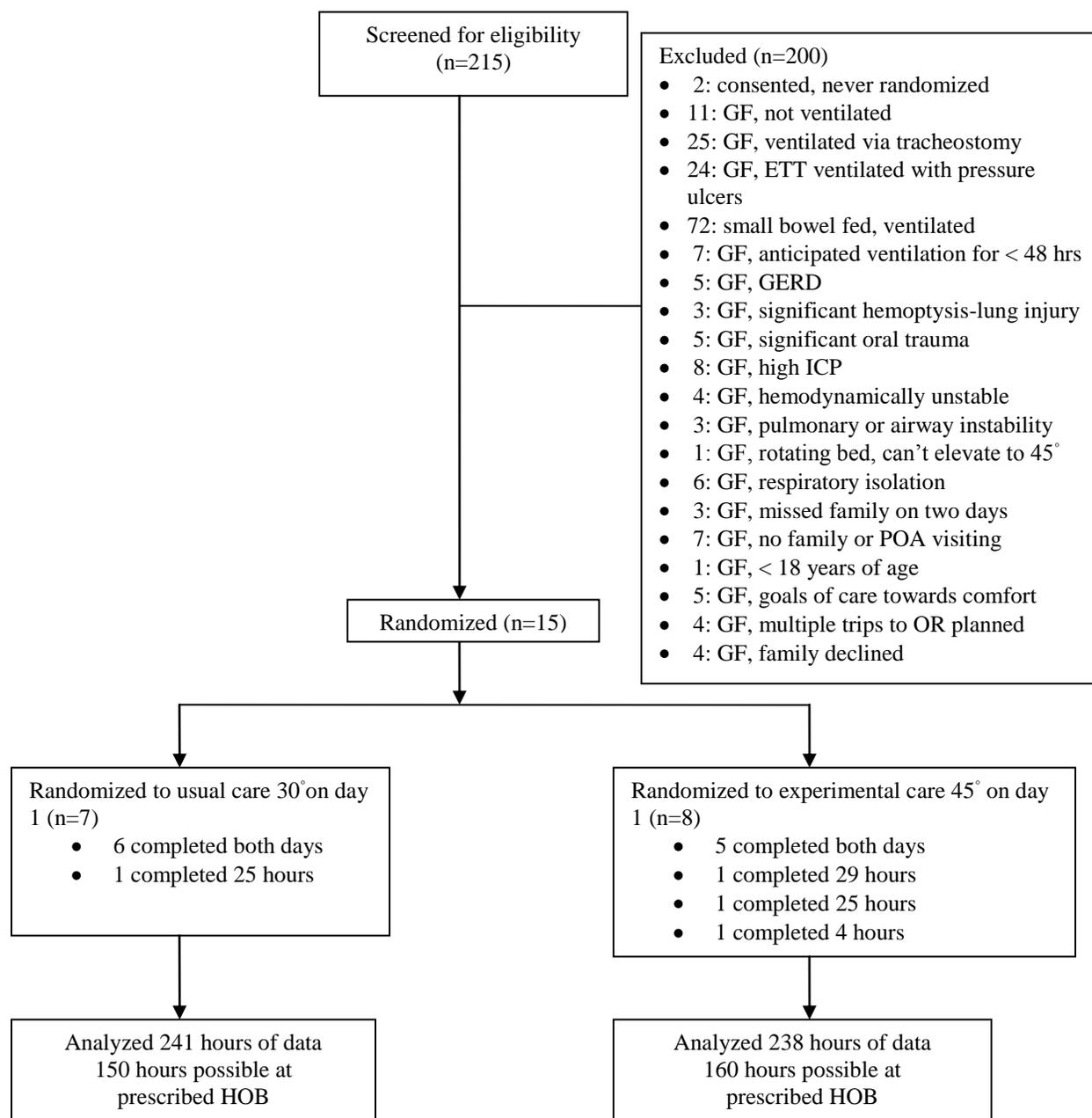
Screening and Enrollment

After approval from both Washington University and the University of Kansas, the study was conducted from August 2012 through January 2013. The EMR was screened for tube feeding orders in both participating ICUs to identify potential subjects. Patients were screened 4-6 days per week based on the inclusion and exclusion criteria. Screening for subjects was not completed on certain days because of events occurring in the ICU, such as outside agency surveys or unavailability of the PI to review the records for subject screening.

A total of 215 patients were screened for a final convenience sample of 17 subjects. Patient screening and randomization is outlined in Figure 5. The primary reasons for gastric fed patients to be excluded were ventilation via a tracheostomy ($n = 25$) or pre-existing pressure ulcers to the sacral/coccyx or buttock areas ($n = 24$). No patients were excluded for pressure ulcers to the greater trochanter regions. A variety of other conditions led to exclusion. For example, 8 patients had a high intracranial pressure measured with a subarachnoid bolt which prevented suctioning frequency and required HOB elevation maintenance near 45° . Therefore, these patients also could not be lowered to the 30° position. Conversely, 4 patients were gastric fed but were receiving continuous veno-venous hemodialysis requiring vasoactive medication to maintain blood pressure and could not be elevated to 45° . Several patients were excluded because of contraindications to regular oral or tracheal suctioning: hemoptysis from large airway or lung tumors ($n = 3$); pulmonary or airway instability ($n = 3$); significant oral trauma ($n = 5$). Five patients were excluded for previous diagnosis of GERD. With the EMR screening filter set for any tube feeding order, 72 patients had orders for small bowel feeding and thus were excluded from the study.

The PI obtained a total of 17 consents from patients' surrogates to participate in the study. One subject who was consented to be in the study was never randomized due to delay in validation of an outside hospital placed gastrostomy tube location. The subject was extubated 2 days after consent and was never randomized into a study group. A second subject was extubated the morning after consent and thus was never randomized into a study group. Thus, only 15 subjects were randomized to a study group. Validation of feeding tube placement was completed via radiograph for nasal or oral placed tubes. Other types of placement (endoscopic or surgical gastrostomy tube) were confirmed during the procedure. Information on screening, randomization and completion of data collection is outlined in Figure 5.

Figure 5
Patient enrollment, randomization and disposition



Note: *GF*, gastric fed; *ETT*, endotracheal tube; *GERD*, gastroesophageal reflux disease; *ICP*, intracranial pressure; *POA*, power of attorney; *OR*, operating room, *HOB*, head of bed

Eleven patients completed the entire 36-hr data collection period. For all those who completed less than 36 hrs, the reason was due to extubation by the healthcare team. Both ICUs

conducted a protocol driven daily wake up and spontaneous breathing trial of all intubated patients. Although each subject enrolled was expected to remain ventilated for the necessary 2-day data collection period, there were 2 subjects prior to randomization and 4 subjects randomized that were extubated early. All subjects were identified at risk for pressure ulcer development with a mean Braden score of 11.9 ± 1.8 and a range of 9-14. Risk for pressure ulcer is identified as a score < 18 .¹⁷⁸ No subjects developed a pressure ulcer despite a low Braden score. Subjects served as their own controls with the cross over design, hence all data collected was included in the analysis.

Baseline Characteristics

Subject characteristics and a description of equipment used to provide care to the subjects are shown in Table 4. The mean age of the subjects was 59.6 ± 15.3 years; mean BMI was 33.8 ± 10.4 ; mean ICU admission and study admission APACHE were 21.5 ± 9.3 and 18.3 ± 7.9 respectively. There were no significant differences in the study by gender (8 males, 7 females). The majority of subjects were Caucasian (80%); the remaining subjects were African American. Almost three-fourths (73%) of the subjects were fed via large-bore Salem Sump (gastric decompression tubes). Two subjects had gastrostomy tubes and 2 had pliable small-bore nasally inserted feeding tubes. All subjects received stress ulcer prophylaxis with the majority receiving esomeprazole intravenously (47%). No subjects received any prokinetic agents 24 hrs prior to or during data collection. Two subjects received continuous infusion of tube feedings; the remainder received bolus feeds every 4 hours. As shown in Table 4, all subjects were on low air loss pressure relieving mattresses manufactured by Hill-Rom Corporation (Batesville, IN); slightly over half (53%) were cared for on the Envision mattress. Use of pressure relieving mattresses and turning every 2 hrs is the standard of care for both units. From the recorded

hourly observations of subject position, subjects were turned 154 times out of the 310 possible turn opportunities demonstrating every 2-hr repositioning. Each day resulted in an opportunity for 12 repositions. The total of 310 overall possible opportunities was derived from the number of subjects with data collected at the start of each hr. Subjects were positioned on their right side for 123 (36%) observations, left side for 96 (28%) observations and back for 120 (36%) observations. Thus, for a majority of the time (65%) subjects were observed in a side lying position.

Table 4
Subject and Baseline Characteristics

Characteristic	Mean \pm SD	Frequency (%)
Age (years)	59.6 \pm 15.3	
Gender:		
Male		8 (53%)
Female		7 (47%)
Race:		
Caucasian		12 (80%)
African American		3 (20%)
Intensive Care Unit		
Surgical		10 (67%)
Medical		5 (33%)
Reason for Admission		
Trauma		4 (27%)
Surgery		4 (27%)
Sepsis		3 (20%)
Respiratory Failure		3 (20%)
Liver Failure		1 (6%)
Body Mass Index (BMI)	33.8 \pm 10.4	
APACHE II:		
Time of Unit Admission	21.5 \pm 9.3	
Time of Study Admission	18.3 \pm 7.9	
Braden Score	11.9 \pm 1.8	
Type of Bed Surface		
Envision		8 (53%)
Sport		3 (20%)
Total Care Bariatric		3 (20%)
Synergy		1 (7%)
Feeding Tube Type		
Large Bore Salem Sump		11 (73.3%)
Small Bore Feeding Tube		2 (13.3%)
Gastrostomy Tube		2 (13.3%)
Feeding Tube Size		
10 Fr		1 (6.7%)
12 F		1 (6.7%)
14 Fr		3 (20%)
16 Fr		8 (53.3%)
18 Fr		1 (6.7%)
22 Fr		1 (6.7%)
Stress Ulcer Prophylaxis		
Esomeprazole IV		7 (47%)
Esomeprazole PT		3 (20%)
Famotidine PT		5 (33%)

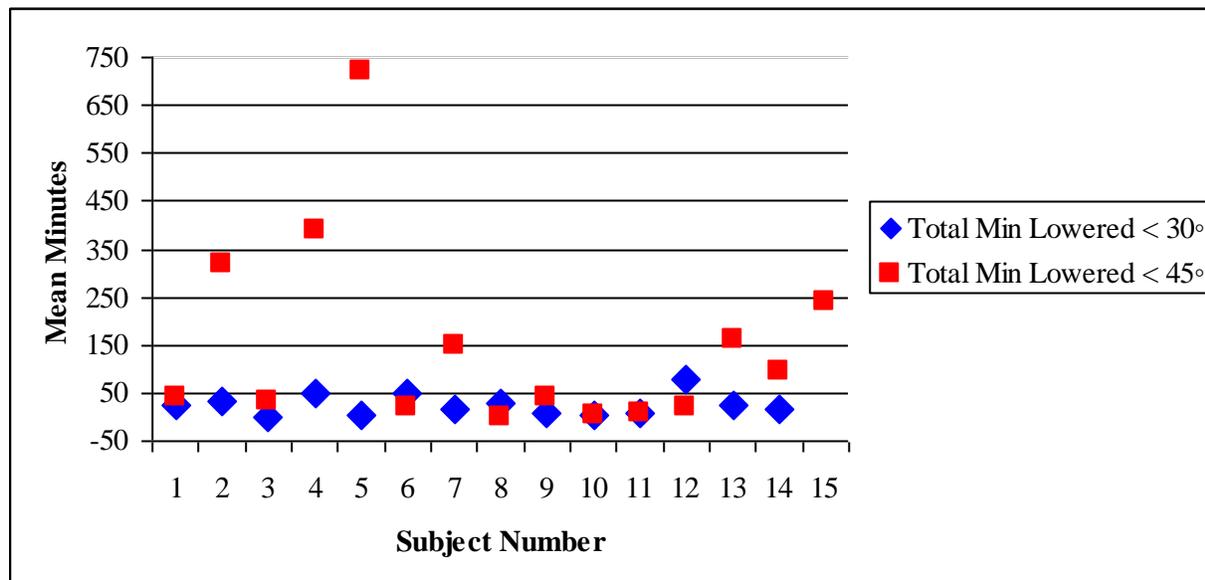
Note: *IV*, intravenous; *PT*, per (feeding) tube

A total of 188 oral secretions were obtained. Missing oral secretions were due to absence of oral secretions sufficient to clear the Yankauer suction device. For oral specimens, 106 (56%) were pepsin-negative and 82 (44%) were pepsin-positive. A total of 174 tracheal secretions were obtained. Missing tracheal specimens were due to bronchoscopy or orders for tracheal culture. Sixty-six (38%) tracheal specimens were pepsin-negative and 108 (62%) were pepsin-positive.

Description of HOB Maintenance at Usual and Experimental Level

For the first aim, a description of the frequency and duration to which subjects' HOB angles were temporarily lowered for treatment purposes below 30° or below 45° and overall hourly mean for each day is provided below. The total time that the HOB was lowered at usual care of 30° was 340.5 minutes with an average of 24 minutes/subject and median of 20.5 minutes/subject. The total time that the HOB was lowered at the experimental condition of 45° was 2236.5 minutes with an average of 149.1 minutes/subject, median 40 minutes/subject. There was a significant difference in median minutes lowered between the 2 HOB assignments ($p = .035$). However, the minutes lowered were highly variable for subjects in the 45° assignment day (Figure 6). A calculation of the percent of time subjects' HOB levels were maintained at the assigned HOB condition was calculated using the total number of minutes the HOB was at prescribed level and the total possible minutes for each assignment. Subjects maintained usual care 30° HOB elevation for 96% of the possible minutes and 77% of the minutes at the experimental condition of 45°.

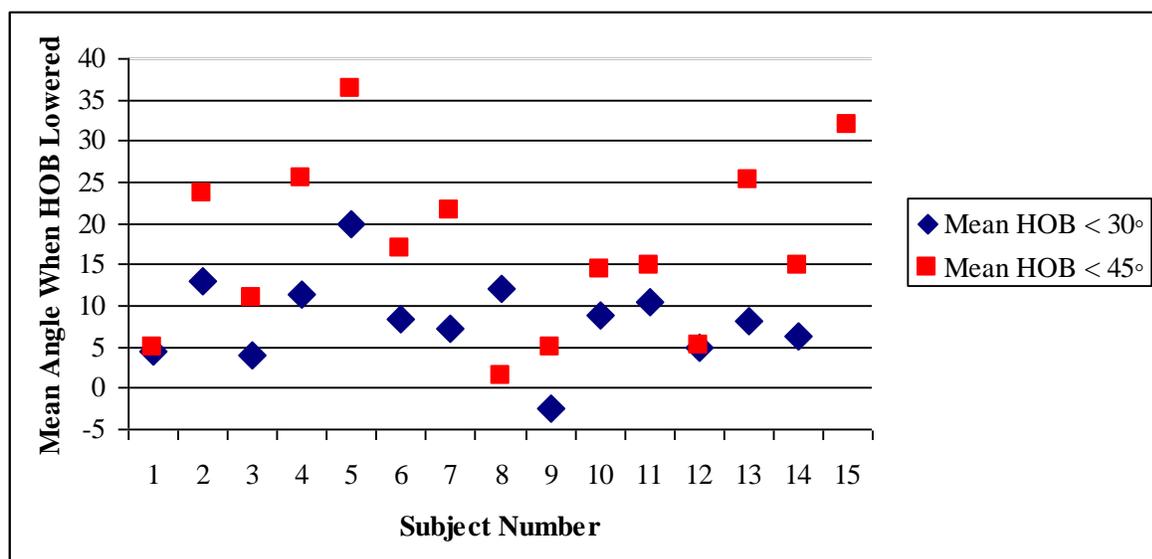
Figure 6
Total Minutes the HOB was Lowered for Each HOB Assignment



Note: One subject with no data at 30° assignment

The mean HOB elevation when lowered was 8.2°, median 8.3°, in the 30° condition and 19.4°, median 14.9°, in the 45° condition ($p = .008$). Figure 7 displays mean HOB when lowered for each HOB assignment.

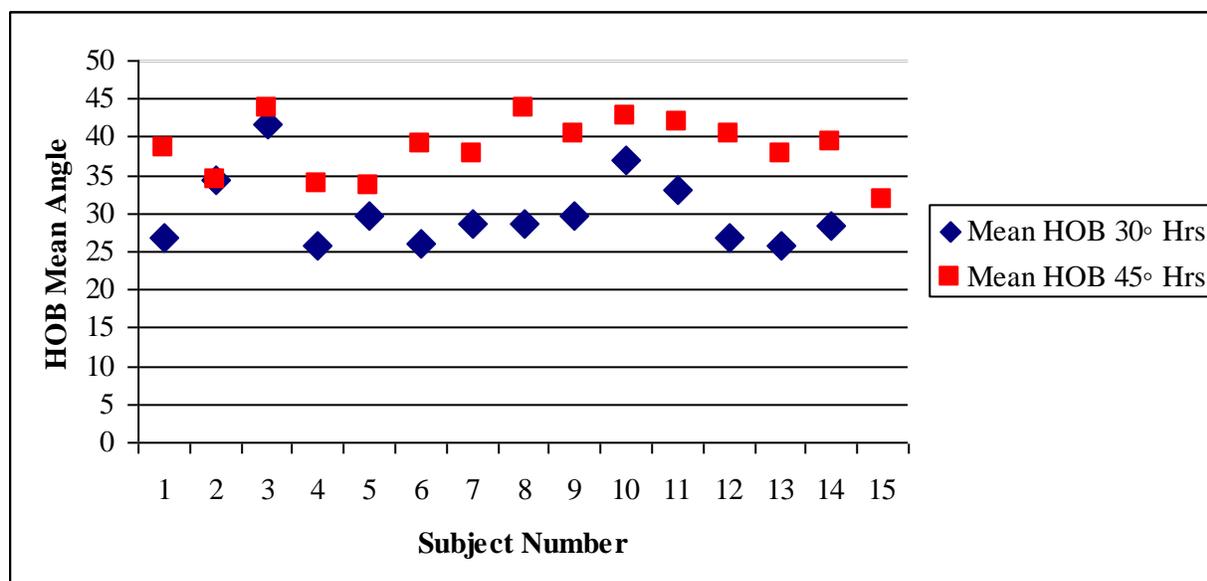
Figure 7
Mean Angle When HOB Lowered Less Than Assigned



Note: One subject with no data at 30° assignment

The overall mean HOB angle includes the full 720 minutes of data collection available for each day (or time in study) and includes the mean angle when lowered. The overall mean angle was $30.2^\circ \pm 4.8^\circ$, median 28.7° , with a range of 25.7° to 41.7° for the usual care hrs. For the experimental hrs, the overall mean angle of elevation was $38.6^\circ \pm 3.6^\circ$, median 39.2° , with a range of 31.9° to 43.8° . There was a significant difference in overall mean angle elevation between the 2 HOB assignments ($p = .001$). Figure 8 demonstrates mean HOB per subject over the data collection period for each HOB assignment.

Figure 8
Overall Mean of the HOB



Note: One subject with no data at 30° assignment

Friedman tests were conducted to assess for differences among the mean ranks of the hourly minutes that the HOB was temporarily lowered and mean HOB angle when lowered for each HOB assignment. Results indicated that minutes lowered and mean HOB levels when lowered were not significantly different over time for either usual care or experimental HOB assignment. Values for minutes lowered for usual care were $\chi^2 (11, n = 12) = 10.7, p = .469$.

Results for mean HOB angle when lowered less than 30° were χ^2 (11, n = 12) = 9.7, p = .554.

Results for minutes HOB lowered for experimental HOB level were χ^2 (11, n = 13) = 5.2,

p = .919. Lastly, values for mean HOB angle when lowered less than 45° over 12 hours were χ^2 (11, n = 13) = 4.75, p = .943.

The subjects' HOB levels were lowered 66 times (mean = 4.7/subject) in the usual care group and 76 times (mean = 5/subject) in the experimental condition. Thus, subjects did not appear to slide more frequently at the experimental 45° elevation than at usual 30° elevation. Subjects were placed in trendelenburg position on 13 occasions, 11 times for repositioning, once for central venous catheter placement and once for central venous catheter removal. A flat HOB was used for 1 central venous catheter placement on a patient with a cervical spine fracture. As noted in Figure 7, subject 9 had a mean less than 0 when lowered on the usual care day due to central venous catheter removal and use of trendelenburg for repositioning. Trendelenburg time for repositioning required an average of 1.75 minutes. Central line removal trendelenburg required 5 minutes. The central line placement trendelenburg use required 36 minutes. The low number of trendelenburg positioning events was not amenable to statistical analysis. Rather, the data were reviewed to determine the pepsin results of oral and tracheal secretions following use of trendelenburg. On four occasions, participants had no secretions available the hour after trendelenburg positioning. For the other 9 times of trendelenburg use, all subjects had either a pepsin-positive oral (5) or tracheal secretion (7). When both specimens were available, 3 (50%) were both pepsin-positive (reflux and aspiration); 1 (17%) occasion resulted in a pepsin-positive oral secretion and a pepsin-negative tracheal secretion (reflux, no aspiration); 2 (33%) instances resulted in pepsin-negative oral secretions and pepsin-positive tracheal secretions (aspiration without detected reflux).

The specimen pepsin results were examined for conversion from negative to positive after use of trendelenburg position. Specimens were not available at the start of the hour for 5 trendelenburg uses. On 5 occasions, the subject converted from a negative specimen at the start of the hr of trendelenburg use to a positive specimen on the next specimen after trendelenburg use. On 3 occasions, the specimen was positive at the start of the hr of trendelenburg use and remained positive.

Mean HOB during the night hrs was 33.4° for the 14 subjects who completed 25 hrs or more of the study. Only 1 subject had a mean $< 30^{\circ}$ (20.5°) for the 12-hr night period.

Lowering the HOB for subject repositioning (moving towards HOB and turning) most frequently took 0.5-2 minutes however, some repositioning required up to 5 minutes. Reasons for lowering other than repositioning included personal care (i.e. incontinence cleaning, baths, dressing change), travel to radiology and during CT scan, bedside procedures (i.e. bronchoscopy, central venous catheter placement) clinician decision (i.e. atrial fibrillation, bedside dialysis) and subject request or sliding. Frequency of reasons for lowering at each HOB assignment, other than subject repositioning, as well as hrs lower than assigned due to subject intolerance are outlined in Tables 5 and 6. The frequency of HOB lowering events for patient care, procedures, radiology and clinical decision was higher in the 45° assigned hours ($n = 24$) compared to the 30° assigned hours ($n = 18$ events).

Table 5
Reasons and Frequencies the HOB was Lowered for Other than Repositioning

REASON HOB LOWERED	30° Assignment n	45° Assignment n
Personal Care		
Bath with full linen change	7	8
Cleaning after stool incontinence	3	6
Cleaning and fecal containment device placement	0	2
Dressing change	1	1
Straight catheterization	1	0
Bedside Procedures		
Bronchoscopy	0	3
Ultrasound	0	1
Radiograph	1	0
Central Venous Catheter Placement	1	1
Central Venous Catheter Removal	0	1
Clinician Decision		
Atrial fibrillation bedside cardioversion	1	0
Bedside dialysis	0	1
Travel to Radiology for CT scan	3	0
Total Frequency	18	24

Table 6
Hours HOB was Lowered for Patient Intolerance

REASON HOB LOWERED	30° Assignment n/hrs	45° Assignment n/hrs
Patient Intolerance		
Patient requested lower than assigned	0/0	3/20.5
Patient sliding	0/0	1/4
Total Hours	0	24.5

No subjects required invasive cardiac hemodynamic monitoring with a pulmonary artery catheter or esophageal doppler monitor. Two subjects experienced hypotension (mean arterial pressure < 60 mm Hg) and required initiation of vasopressor medications. The first subject developed rapid atrial fibrillation and experienced a decrease in mean arterial pressure to approximately 55 mm Hg on the usual care 30° assignment day. With sedation for cardioversion, the mean arterial pressure remained in the low 50's. A phenylephrine infusion was started at 100

micrograms (mcg)/minute. The HOB was lowered for cardioversion and then placed in trendelenburg for central line placement, noted as 2 events on Table 5. After placement of the central line, the subject remained on phenylephrine infusion of 90-60 mcg/minute throughout the remainder of data collection that day. However, the subject was returned to 30° HOB elevation after central line placement and maintained at that angle with slow titration of the phenylephrine for the last 4 hrs of data collection. The night mean HOB angle was 33°. The phenylephrine was discontinued at 0600 on day 2 and the subject never required vasopressor medication support at HOB elevation of 45°. The subject had an overall mean of 42° for the 12 hrs of day 2 without experiencing hypotension.

The second subject with a sepsis diagnosis was off vasopressor medications for 20 hrs prior to the first day of data collection. At 0900 the subject had an increase in temperature to 40.1° Celsius, was agitated at a RASS score of +3 and was desaturating to pulse oximetry readings of 85%. The subject's sedation medications of fentanyl and dexmedetomidine were increased. Subsequently, the mean arterial pressure dropped to 54 mm Hg and a norepinephrine infusion was started at 2 mcg/minute. The infusion continued at that dose for 1.5 hours. The HOB was maintained at the assigned 30° throughout this period except for 1 period of repositioning. The subject's temperature decreased to 38.2° within 90 minutes of temperature peak and returned to 39° later in the day. The subject's temperature never rose again above 40° and the subject did not require any vasopressor medication for the remainder of data collection.

No subject requested the HOB to be lowered while at usual care 30° while 2 subjects requested higher HOB on usual care day for more comfortable breathing. Three subjects requested the HOB lowered at 45° assignment. Two of these subjects were primarily at a RASS score of 0, alert and oriented, while the third subject was a RASS score of -1. One subject was

uncomfortable in the side lying position in the last half of the 12-hr day. The subject was maintained at 25-39° based on her comfort for a mean of 29° during the lowered minutes. For 2 of the hrs, the subject slept at a HOB elevation of 23° and was not disturbed to raise the HOB during the 2 hrs.

One subject was maintained < 45° due to discomfort for the entire 12 hrs. This subject's BMI was 38 with central obesity, the majority of excess accumulation of fat in the abdominal area. The subject was not on a bariatric bed frame that allowed lowering of the feet which may have contributed to the discomfort. The subject's mean HOB was 36.4° for the 12 hrs with 1 hr means ranging from 35.5° to 38.4°. It is possible that a bariatric bed at 45° with the ability to lower the foot of the bed would have been more comfortable for the subject. Three other bariatric patients with central obesity were able to tolerate 45° using a bariatric bed that allowed for lowering of the feet as the HOB was elevated. Two subjects with obesity were comfortable at 45° with the standard bed frame.

The third subject who requested HOB < 45° had multiple traumatic injuries and required acclimation to 45° in the first 2 hrs of data collection. The mean HOB elevation for the first 2 hrs was 35°. The subject was comfortable at 45° for the remaining 10 hrs.

Lastly 1 subject with a BMI of 21.7 slid down in bed when the HOB was raised to 45°. Therefore, to prevent sliding and friction, the subject was kept at a mean of 35° which was the level observed to stop the sliding. The mean hourly HOB angle ranged from 36.6° to 34.2° when not lowered for provision of patient care. The highest HOB elevation achieved with this subject was 39° for 45 minutes.

Description of Reflux and Aspiration Occurrence

The second aim was to describe the occurrence of reflux (pepsin-positive oral secretions)

and aspiration (pepsin-positive tracheal secretions) with HOB elevation at 30° and 45°. Initially obtaining secretions from the oropharynx was planned to measure the occurrence of reflux. However, due to the subjects' alertness with minimal sedation per the RASS scores and concern for elicitation of the gag reflex with induction of reflux, secretions only from the oral cavity were suctioned instead. Overall 44% of oral secretions were positive and 62% of tracheal secretions were positive. Related samples Wilcoxon Signed rank tests were used to compare summary scores of percent pepsin-positive oral and tracheal secretions for each HOB elevation. The mean percent of pepsin-positive oral secretions was higher at 30° HOB elevation (48.4 ± 31.3), median 54, compared to 45° HOB elevation (32.3 ± 33.2), median 20; however, it was not statistically significant ($p = .108$). The mean percent of pepsin-positive tracheal secretions was also higher at 30° HOB elevation (69.4 ± 33.8), median 71, than 45° HOB elevation (62.5 ± 34.5), median 67, and was not statistically significant ($p = .366$). Figures 9 and 10 present the percent (median and range) pepsin-positive oral and percent pepsin-positive tracheal secretions per HOB assignment.

Figure 9
Boxplots of Percent of Pepsin-Positive Oral Secretions at Both HOB Elevations

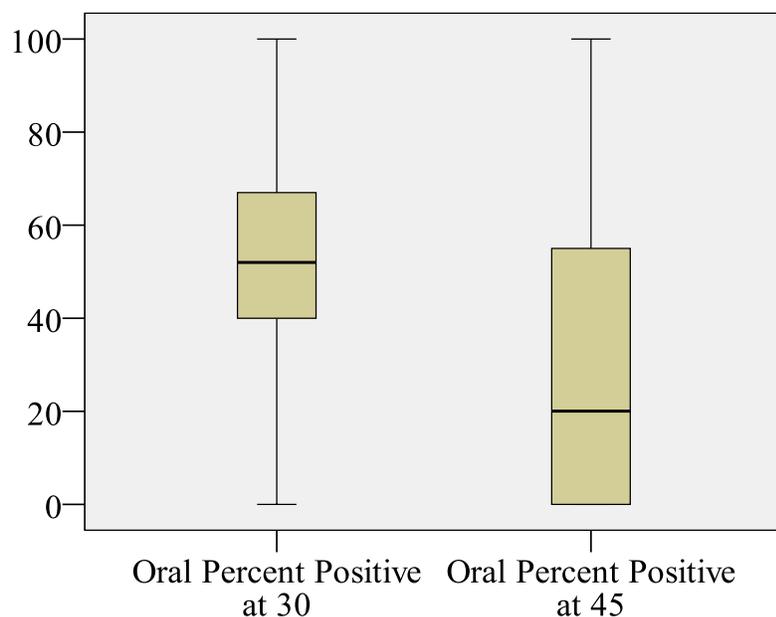
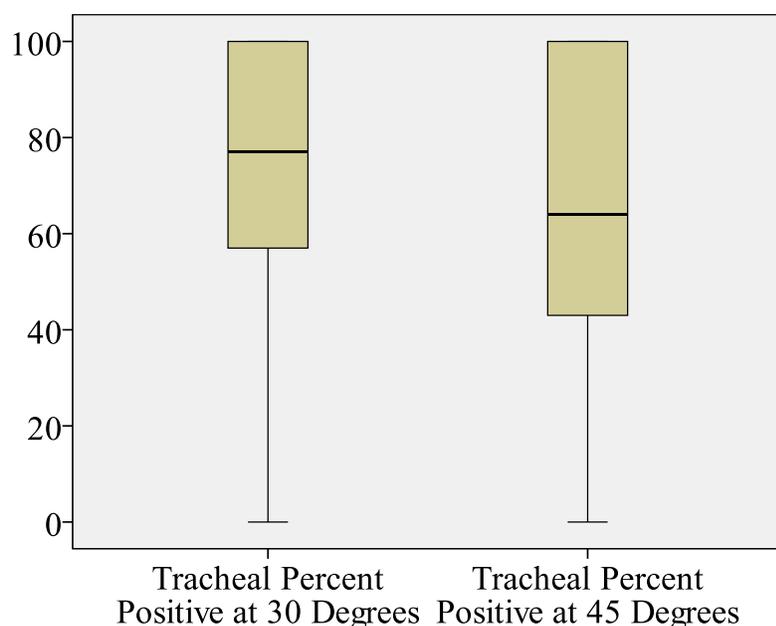


Figure 10
Boxplots of Percent-Positive Tracheal Secretions at Both HOB Elevations



A pattern in lower frequency of oral secretions during the experimental 45° HOB elevation day was identified. Therefore, an additional related samples Wilcoxon Signed Rank Test of frequency of oral secretions comparing 30° and 45° elevation was conducted. The median frequency of oral secretion, (mean, SD, median) 8.5 ± 3.6 , 9.5 at 30° and 5.7 ± 3.2 , 5, at 45°, was significantly lower at 45° ($p = .035$).

Association between Reflux and Aspiration

The third aim was to examine the association between reflux and aspiration with the 2 different HOB elevations in adult ICU mechanically ventilated gastric fed patients. There were 142 paired samples of an oral secretion obtained at the same time as a tracheal secretion. A slight majority (60%) had the same results while 40% of the samples had different results. Table 7 summarizes the descriptive relationship of the paired samples.

Table 7
Results of Paired Oral and Tracheal Samples

Pepsin + oral Pepsin + tracheal Reflux and aspiration n (%)	Pepsin – oral Pepsin – tracheal No reflux or aspiration n (%)	Pepsin + oral Pepsin – tracheal Reflux without aspiration n (%)	Pepsin – oral Pepsin + tracheal Aspiration without reflux n (%)
45 (32%)	39 (27%)	15 (11%)	43 (30%)
Matched 84 (60%)		Unmatched 58 (40%)	

The scatterplot of percent pepsin-positive tracheal secretions in relationship to percent pepsin-positive oral secretions at 30° demonstrated a non-linear relationship. Kendall's tau ($\tau = -.362$, $p = .089$) correlation was not significant at usual condition. The scatterplot of the experimental condition was random and the correlation results were not significant as well, ($\tau = -.037$, $p = .864$).

Tracheal pepsin-positive secretions were also examined in relationship to positive oral secretions 1 hr and 2 hrs prior to the positive tracheal specimen. When available 1 hr before a positive tracheal secretion, the oral secretion was positive 14 times and negative 14 times. When an oral specimen was available 2 hrs before a pepsin-positive tracheal specimen, the oral secretions were negative 38 times and positive 30 times. Thus, no relationship was observed with the delayed results as well.

Two subjects had observed reflux based on tube feeding appearance of oral secretions. Subject 4 had 12 ml of oral secretions with tube feeding appearance obtained with the Yankauer suction device at 1000 and 5 ml obtained at 1100 on the usual care day, 30°. The 1000 time was shortly after return from CT scan and a prolonged period of lying flat, being moved from bed to table to bed and then repositioning for linen change. The subject's oral and tracheal secretions were both positive for the next 6 hrs. After the 6 hrs, the subject had 1 more pepsin-positive oral

secretion 9 hours after observed reflux and a final negative oral and tracheal specimen. An example of the pattern of specimens associated with the reflux event is presented in Table 8. The previous day at experimental condition, the patient had all negative oral secretions and two positive tracheal secretions.

Table 8
Specimen Results Log for One Subject with Observed Reflux

Hour	Pepsin Results Oral Secretions	Pepsin Results Tracheal Secretions
0800	- (negative)	+
0900	+ (positive)	+
1000: reflux noted	+	+
1100: reflux noted	+	no specimen
1200	+	+
1300	no specimen	no specimen
1400	+	+
1500	no specimen	no specimen
1600	no specimen	no specimen
1700	no specimen	no specimen
1800	+	-
1900	no specimen	no specimen
2000	-	-

Subject 12 had tube feedings infusing on usual care day at 0900. At that time 5 ml of secretions with tube feeding appearance were suctioned from the oral cavity and obvious emesis was cleaned from the subject's face, gown and cervical collar. Prior to the observed reflux and emesis, at 0800 the subject's oral secretions were negative and tracheal secretions were positive. At 0900 both oral and tracheal secretions were positive and remained positive for the next several hours. Oral secretions remained positive for 4 hrs, tracheal secretions remained positive for 9 hrs. Subject 12 also required trendelenburg for central line placement at 1545 on the same day. The final oral and tracheal secretions at 2000 were negative. Table 9 demonstrates the pattern of specimens associated with reflux for this subject.

Table 9
Specimen Results Log for Second Subject with Observed Reflux

Hour	Pepsin Results Oral Secretions	Pepsin Results Tracheal Secretions
0800	- (negative)	+
0900: reflux noted	+ (positive)	+
1000	+	+
1100	+	no specimen
1200	+	+
1300	+	no specimen
1400	-	+
1500: trendelenburg	no specimen	no specimen
1600	-	+
1700	no specimen	no specimen
1800	-	+
1900	no specimen	no specimen
2000	-	-

Lowered HOB and Reflux

The fourth aim was to determine the association between a temporarily lowered HOB position for treatment purposes and reflux of gastric contents. Minutes HOB was lowered, mean when HOB lowered and overall mean were correlated with percent pepsin-positive oral secretions for each HOB assignment. Scatterplots demonstrated a non-linear pattern for mean minutes HOB lowered at 30° and a linear pattern at 45° however with several outliers. However, both Kendall's tau correlations were not significant. Scatterplots demonstrated a non-linear pattern for mean HOB angle when less than assigned HOB for each condition. Both Kendall's tau correlations were not significant. Mean HOB angle and percent pepsin-positive oral secretions at both HOB assignments were linear with a few outliers and did not demonstrate homoscedasticity. Both Kendall's tau correlations demonstrated a significant moderate to large negative correlation (Table 10).

Table 10
Correlations of Minutes and Mean Less than HOB Assignments and Overall Mean at each HOB Elevation and Percent of Pepsin-Positive Oral Secretions

Relationship	Kendall's tau τ value	Significance 2-tailed p value
Minutes < 30° and % pepsin-positive oral secretions	.158	.461
Minutes < 45° and % pepsin-positive oral secretions	.092	.668
Mean when lowered < 30° and % pepsin-positive oral secretions	-.092	.668
Mean when lowered < 45° and % pepsin-positive oral secretions	-.010	.959
Overall mean HOB Day 30° and % pepsin-positive oral secretions	-.536	.008*
Overall mean HOB Day 45° and % pepsin-positive oral secretions	-.433	.026*

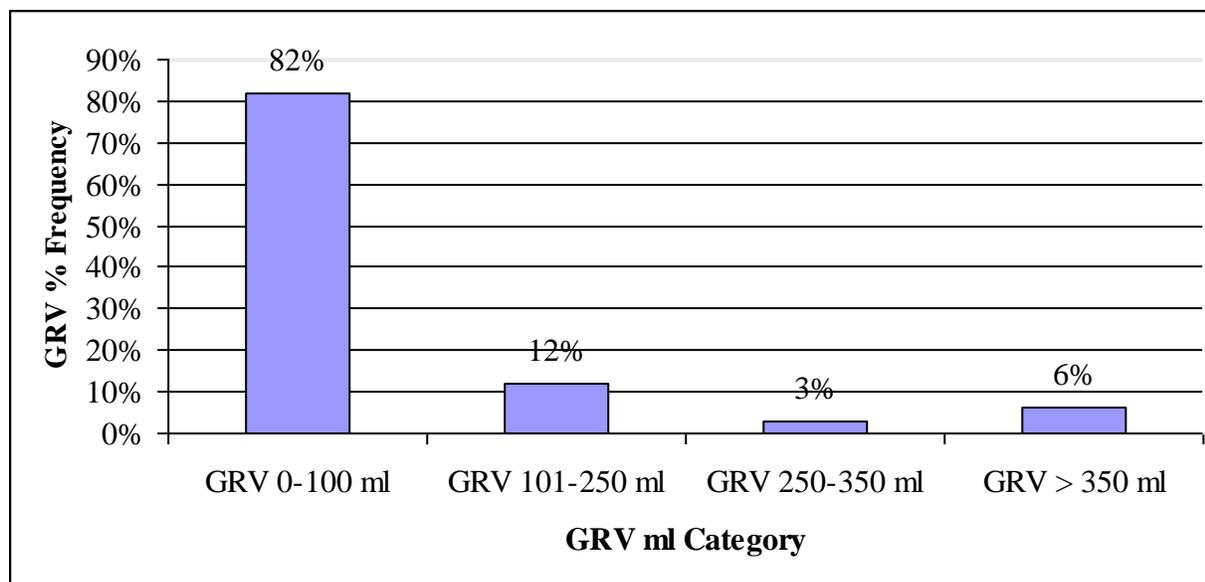
* $p < .05$

Association of Subject Characteristics and Reflux

The fifth aim was to determine the association between 7 patient characteristics (gender, age, BMI, GRV, sedation level, disease severity, and use of prokinetic agents) and reflux. As previously noted, 8 men and 7 women participated in the study. The mean age of the participants was 59.6 ± 15.3 years. The mean BMI was 33.8 ± 10.4 . Three subjects were of normal weight (BMI 18-25), 3 subjects were overweight (BMI 25-29.9), 7 subjects were obese (BMI 30-39.9) and 2 subjects were obese class III (BMI >40) often described as morbid obesity.¹⁷⁹

A total of 103 GRV measurements were obtained. The average GRV was 59.4 ± 68.1 with a range of 0-440 ml. GRV was measured as less than 100 ml for 82 (82%) measurements. Eight GRVs were ≥ 250 , 4 obtained in 1 subject, 2 in another subject and 1 each in 2 subjects. GRVs were separated into 4 categories based on volume. Figure 11 illustrates the frequency of each GRV category as percentage of total GRV measurements.

Figure 11
Frequency of Gastric Residual Volume (GRV) in Categories



RASS scores ranged from +3 to -5 with a mean of -1.2 ± 1.2 . Mean ICU admission and study admission APACHE were 21.5 ± 9.3 and 18.3 ± 7.9 respectively. No subjects received prokinetic agents; therefore, no analysis could be performed.

Kendall's tau correlations were conducted for each of the 6 subject characteristics with data. There were no significant relationships of gender, age, BMI, GRV and APACHE II with percent of pepsin-positive oral secretions. A significant negative correlation was observed with RASS sedation scores. Scatterplots demonstrated a linear pattern without homoscedasticity. As sedation deepened (higher negative RASS score), the percent of pepsin-positive oral secretions increased. Table 11 displays all correlation results for subject characteristics and percent pepsin-positive oral secretions.

Table 11
Correlations of Subject's Characteristics and Percent Pepsin-Positive Oral Secretions

Relationship	Kendall's tau: τ value	Significance 2-tailed p value
Gender and % pepsin-positive oral secretions	.290	.202
Age and % pepsin-positive oral secretions	-.155	.427
BMI and % pepsin-positive oral secretions	-.337	.083
GRV and % pepsin-positive oral secretions	.329	.091
RASS and % pepsin-positive oral secretions	-.429	.028*
APACHE II and % pepsin-positive oral secretions	.020	.920

* $p < .05$

Oral Secretion pH and Pepsin Measurements to Detect Reflux

The final aim was to determine the association between the pH (range 0-14) of oral secretions and pepsin presence in oral secretions (the gold standard measure of reflux). The range of pH measurements was 4-8 with a mean of $6.3 \pm .05$. All subjects received oral care at approximately 0900 with 0.7% sodium monofluorophosphate toothpaste and tooth brushing followed by .12% chlorhexidine gluconate oral rinse.¹⁸⁰ Chlorhexidine gluconate oral rinse has a pH range of 5-7.¹⁸¹ All subjects were receiving acid-suppressant medication, thus, only results for pH measurements of 4 and 5 were hand matched with the pepsin result. Eight subjects had no pH measurements less than 6. Seven subjects had at least 1 pH measurements equal to 4-5 for a total of 49 measures. Oral secretion pH measurements in 4 subjects were at pH 4-5 for the majority of the oral secretions, ranging from 65%-100% of their secretions, and accounting for 44 (90%) of the specimens with a pH of 4-5. Oral secretion pH was 5 at 0900 and 1000, near the time of oral care, in only 1 subject which was also the time of observed reflux in this subject.

Nineteen (39%) of measurements were associated with pepsin-positive oral secretions. Table 12 displays the pH measurements and matched oral secretion pepsin results. With the 3 observed reflux events, pH was 5 for 1 specimen and 4 for the 2 specimens in the same subject.

Table 12
pH Measurements and Associated Oral Secretions Pepsin Results

Immunoassay for Pepsin in Oral Secretions total number of specimens with pH < 6 = 49	pH 4 n	pH 5 n
Pepsin-positive	12	7
Pepsin-negative	24	6

The scatterplot demonstrated a non-linear relationship of average pH and overall percent pepsin-positive oral secretions. The Kendall's tau correlation ($\tau = -.135$, $p = .487$) was not significant.

CHAPTER V
DISCUSSION, IMPLICATIONS, CONCLUSION

The primary aims of this study were: 1) to describe the frequency and duration that patients' HOB angles are temporarily lowered for treatment purposes below 30° or below 45° 2) to describe the occurrence of reflux (pepsin-positive oral secretions) and aspiration (pepsin-positive tracheal secretions) with HOB elevation at 30° and 45°; 3) to determine the association between reflux and aspiration with the 2 different HOB elevations in adult ICU mechanically ventilated gastric fed patients; 4) to determine the association between a temporarily lowered HOB position for treatment purposes and reflux of gastric contents; 5) to determine the association between 7 patient characteristics (gender, age, BMI, GRV, sedation level, disease severity, and use of prokinetic agents) and reflux, 6) to determine the association between the pH (range 0-14) of oral secretions and pepsin presence in oral secretions (the gold standard measure of reflux). Data from 15 patients, 11 who completed both days of a randomized cross over design, were analyzed to address each aim. This chapter includes a discussion of the results of the study, implications for nursing practice, recommendations for future research and limitations of the study.

HOB Elevation

Previous research demonstrated difficulties with obtaining 45° HOB elevation^{18, 20, 100, 103-105} and at times 30° HOB elevation in ICU patients.¹⁸²⁻¹⁸³ In the current study, HOB elevation at 30° was maintained for 96% of all possible minutes and HOB elevation at 45° was maintained for 77% of all possible minutes. While HOB elevation at 30° was maintained for significantly more minutes than 45° elevation, this study demonstrated that many patients can maintain greater than 30° elevation and near 45° elevation without any significant change in the frequency of lowering of the bed to reposition the patient due to sliding. The Friedman test results for minutes lowered than assigned HOB elevation and mean angle when

lowered were not significantly different over the 12 hour period for each HOB assignment.

Therefore, patients generally tolerated (comfortable and not sliding) both conditions over the entire day at each HOB elevation. At the experimental condition, 2 subjects did not tolerate 45° HOB elevation over the full period of data collection (uncomfortable or sliding) and 2 subjects requested a lower HOB elevation for some hrs and tolerated 45° for other hrs. One subject was comfortable initially however, requested the HOB lowered in the last 4 hrs. Another subject requested the HOB lower than 45° for the first 2 hrs and then was comfortable the remaining 10 hrs near 45°.

The mean HOB when lowered was significantly higher for the 45° experimental hrs compared to the 30° usual condition hrs. This may be explained by the elevations for patient comfort or sliding prevention near 30°. In addition, during the 4 hrs of dialysis for 1 subject, the HOB elevation was at 30° rather than 45° for the entire dialysis treatment.

Maintenance at assigned HOB elevation was achieved with the assistance of several interventions. Bright signs with HOB assignment for the day were suspended at the bottom of the subjects' monitors and provided a continuous visual reminder. In addition, the nurse researcher was at the bedside during data collection and was able to assist with repositioning and provided a verbal reminder of the HOB assignment. Lastly, a one button click digital readout of the HOB elevation allowed for accurate measurements and assisted with returning patients to the assigned HOB elevation after repositioning, patient care and procedures.

Night time HOB elevation was a mean of 33.3°. Only 1 subject was maintained at less than a mean of 30° for the 12-hr washout period during the night. All night nurses were aware of the subjects' participation in the study however no signs or reminders to maintain HOB elevation at 30° or higher were provided during the 12-hr washout period. The gauge with HOB digital

display remained on the bed for the nurses to use which may have helped with maintenance of 30° elevation during the night.

Beds with incorporated accurate digital measurement readings could provide an easy method to assist nurses with HOB positioning to maintain elevation at $\geq 30^\circ$ and up to 45°. Rose et al. found that the use of a bed measurement device initially improved HOB elevation to 45°. However, the device did not improve HOB elevation to 45° over a sustained 6 month period. Nevertheless, maintenance of the HOB to 30° was sustained throughout the 6 month period.¹⁰² The results of the current study confirmed that the VAP prevention standard of care for HOB elevation was 30° at the study site. Previous research identified difficulty with maintaining 30°. ¹⁸²⁻¹⁸³ However, implementation of VAP prevention guidelines in both units for more than 5 years may explain the high compliance with HOB elevation maintenance at 30° observed in the current study during data collection and during the night time washout period.

Reasons for HOB lowering were similar to findings from previous researchers; however not all of the concerns expressed in previous surveys were identified in the current study.^{22,105,183} Delivery of personal care was the most frequent reason found for HOB lowering. The American Association of Critical-Care Nurse's VAP prevention practice alert recommended elevating HOB after these procedures as soon as feasible.²² In a survey by Helman et al., ICU nurses identified probability of the patient sliding down in the bed as the primary concern with HOB positioning to 45°. ¹⁰⁵ In the current study, only 1 subject had problems with sliding at 45° elevation. Mean frequency of lowering HOB per subject was similar in both HOB assignment groups; therefore, sliding at the higher 45° angle does not appear to be an issue. Another reason cited by Helman and colleagues was patient discomfort at 45°. Three subjects requested HOB to be decreased less than 45° for comfort but each subject tolerated elevation higher than 30°. The

other 2 reasons cited in the survey included concerns over increased skin breakdown and hemodynamic monitoring.¹⁰⁵

No patients in this study developed an alteration in skin integrity. Turning patients regularly to relieve pressure and prevent pressure ulcers has been a standard practice recommendation for over 150 years.¹⁸⁴ However, in the side lying position at 30°, interface pressures ≥ 32 mm Hg may occur in healthy adults. Interface pressures above 32 mm Hg is the point at which tissue hypoperfusion is believed to occur.¹⁸⁵ Therefore, regular repositioning of ICU patients is necessary. In a review of the practice of every 2-hr turning, Hagisawa and Ferguson-Pell reviewed the evidence which supports this practice. The authors identified that studies initially conducted with animals demonstrated microscopic changes with 70-100 mm Hg of applied pressure for 2 hrs. The authors also discussed a study of tissue tolerance of tissue over bony prominences in humans that suggested acceptable tolerance was maintained for up to 2 hrs. In addition, the authors reviewed a study of pressure-induced ischemia on tissue metabolism that identified recovery of glucose and ATP within 30 minutes of pressure relief after 2 hrs of sustained pressure but not after 4 hrs. Hagisawa and Ferguson-Pell concluded that no strong scientific evidence was found to explain the 2-hr turning interval in humans.¹⁸⁴ However, turning every 2 hrs remains the standard of care in ICUs and was associated with reduction of pressure ulcers compared to non-routine every 2-hr turning.¹⁸⁶⁻¹⁸⁷ Research has also shown the benefit of pressure relieving mattresses to prevent pressure ulcers in ICU patients.¹⁸⁸⁻¹⁸⁹ In the current study, the use of pressure relieving mattresses and turning patients every 2 hrs per institution protocol were important interventions in preventing pressure ulcer development at the sacral, ischial and trochanter regions. Thus, despite the concern for pressure ulcer risk with HOB elevation $> 30^\circ$, the current study demonstrated the safety of HOB elevation near 45° for 12 hrs in

this sample population with pressure ulcer prevention measures in use. Further study is needed with a larger sample size and for longer time periods of HOB elevation at 45° to validate this finding. The potential to reduce reflux and aspiration with a HOB elevation > 30° without increased pressure ulcer rates is an important intervention that should be examined with various populations and settings.

In a descriptive study of HOB angle in cardiothoracic ICU patients, Ballew et al. found that the strongest factor associated with a lower backrest elevation was administration of a vasopressor medication ($p = .001$). Subjects receiving vasopressor medication support had a mean backrest elevation of 19° compared to 26° for subjects not receiving any support. They also found that a mean blood pressure of 64 mm Hg or less without vasopressor medication support was associated with a significantly lower mean HOB angle of 17° compared to 24° ($p = .01$) for patients with a mean blood pressure > 65 mm Hg. HOB angle was measured with a protractor, line-of-site angle indicator, plumb line, and plumb bob.¹⁸³

In the current study, no subjects had invasive cardiac hemodynamic monitoring and 2 subjects experienced hypotension with a mean blood pressure < 60 mm Hg. Other than the cardioversion and central line placement in 1 subject, both subjects were maintained at 30° elevation during vasopressor medication infusion and ultimate discontinuation. Also both of these subjects tolerated 45° elevation on the second day without requirement of vasopressor medication support. Data from these 2 subjects provide initial evidence that HOB elevation at 30° can be maintained despite vasopressor medication support requirement. Further investigation is needed on HOB elevation and vasopressor medication administration. Use of a continuous electronic device as used in the current study would provide more comprehensive data to analyze

the impact of HOB angle elevation with patients experiencing hypotension or requiring vasopressor medication support.

A bariatric repositioning algorithm described trendelenburg positioning to facilitate moving the bariatric patient up in bed.¹⁰⁶ The primary reason for trendelenburg positioning in the current study was for repositioning of bariatric subjects. Trendelenburg positioning for longer time periods were needed for central venous catheter placement and removal. The impact of trendelenburg position in all subjects with a specimen available the hour following a negative HOB trendelenburg angle resulted in a pepsin-positive oral or tracheal secretion or both. On 5 of the 10 occasions when specimens were available, the previous specimen was negative. On 3 occasions the previous specimen was also positive and on 5 occasions no specimen was available. Thus, use of trendelenburg positioning appears to have a positive relationship with reflux and aspiration in gastric fed patients. More data are needed for any statistical analysis but these pilot results warrant the need for further investigation of use of trendelenburg in gastric fed patients. Additionally, exploration of interventions to reduce reflux and aspiration when trendelenburg positioning is required, central line placement and removal, could reduce the risk of reflux and aspiration. For example, prior to extended period of trendelenburg for procedures, the impact of emptying the patient's stomach via suction and deep oral suctioning could be examined. The use of distal small bowel feeding in relationship with trendelenburg could also be examined.

The majority of the subjects were overweight or obese in this study. However, use of trendelenburg for repositioning was highly variable by nurse and subject position in relationship to the distance the subject's head was away from the top of the bed. The use of ceiling lifts to facilitate repositioning of all patients, including obese patients, using a flat HOB to prevent the use of trendelenburg could be explored. Previous research has examined the impact of ceiling

lifts for turning, repositioning and mobilization to a chair or stretcher for patients in an ICU and extended care facilities.¹⁹⁰⁻¹⁹² Silverwood and Haddock implemented ceiling lifts in an ICU and found a decrease in nurses' self-reported fatigue, pain and frustration levels. In addition, the authors also found a decrease in doctors' visits, medication use and time off due to injury from patient care and transfer tasks. Workers compensation claims also decreased by 70%.¹⁹⁰ In extended care facilities, a significant decrease in worker compensation claims secondary to musculoskeletal injury from patient care and transferring was found.¹⁹¹⁻¹⁹² Future studies could examine the impact of ceiling lifts without trendelenburg use for ICU patient repositioning to decrease reflux and aspiration events without increasing the risk of injury to bedside clinicians.

Description of Reflux and Aspiration Occurrence

Both reflux and aspiration occurred frequently with the majority of oral and tracheal secretions being pepsin-positive. For oral specimens, 82 (44%) were pepsin-positive and 108 (62%) tracheal secretions were pepsin-positive. While the mean scores of percent of pepsin-positive oral and tracheal secretions were higher at usual care (30°) than experimental care (45°), neither Wilcoxon Signed Rank Tests were significant. As this was an initial study, a larger sample size in the future may detect a significant difference. The lower percent of pepsin-positive oral and tracheal secretions at the experimental condition is consistent with previous findings that found semi-recumbent positioning (45°) compared to supine positioning led to lower aspiration and pneumonia rates compared to supine.^{97-99, 102} Furthermore, Metheny et al. found that elevations to a mean HOB angle of 38° led to a reduction in aspiration compared to a mean elevation of 24°. ⁹⁶ The only other study to compare 45° and near 30° (25°) found a 25% reduction in VAP rate with the higher HOB angle. The findings were not significant due to the small sample size.¹⁰

In earlier tests of pepsin presence in tracheal secretions in an animal model, pepsin was detected for up to 6 hrs after a forced aspiration.¹⁶⁴ Known time of aspiration is difficult in patients unless obvious reflux or vomiting is detected. Furthermore, length of time pepsin can be detected in oral secretions is unknown. Pepsin results of oral and tracheal secretions from the 2 subjects with observed reflux episodes provide some insight that oral and tracheal secretions in humans may remain positive for several hours after a reflux and aspiration event. Therefore, it is difficult to exactly describe the frequency of a new reflux and aspiration event occurrence unless there is a negative result followed by a return to positive.

The percent of pepsin-positive tracheal secretions at 62% was considerably higher than previous studies of adult ICU patients.^{14,96} Using the same western blot technique to detect pepsin used in the current study, 31% of 6000 tracheal specimens were pepsin-positive. Forty percent of patients were fed via the small bowel and the mean HOB angle was 24°. Specimens were obtained at the discretion of the bedside nurse.¹⁴ A later study by the same researchers with HOB elevation > 30° (mean 38°), with 72% use of small bowel feedings and a GRV management algorithm resulted in only 12% pepsin-positive tracheal secretions.⁹⁶ Suctioning was again at the discretion of the bedside nurse. Previous studies of small bowel feedings, mid-distal duodenum or jejunal, were shown to decrease reflux, microaspiration and VAP.¹³⁰⁻¹³³ All patients in the current study were gastric fed which may partially explain the higher percent of pepsin-positive tracheal secretions obtained compared to studies using some or the majority of small bowel feedings. It is also feasible as discussed earlier that multiple sequential pepsin-positive tracheal secretions represented 1 aspiration event and resulted in the high percent of pepsin-positive tracheal secretions. The lower percent (44%) of pepsin-positive oral secretions may represent a faster clearance of pepsin from oral secretions or failure of reflux to reach the oral cavity.

Oral secretions were pepsin-positive in 44% of the samples. Other researchers have found different reflux rates with several different techniques to detect reflux in mechanically ventilated patients including pepsin,^{58,193} esophageal pH measurement⁵⁷ and radio-isotope levels.¹³⁰ Pepsin was found in oral secretions of 7 subjects and 55% of specimens (11/20) in a descriptive pilot study of 10 patients.¹⁹³ A difference in the sensitivity level of the pepsin analysis technique may lead to variation in results reported as positive.

In another descriptive pilot study of 50 gastric fed mechanically ventilated patients suctioned once for both oral and tracheal secretions, 10 subjects (20%) demonstrated pepsin-positive oral secretions.⁵⁸ Nind and colleagues used an esophageal pH electrode placed 5 cm above the LES to detect reflux in mechanically ventilated ICU patients rather than pepsin; pH was measured before and for 5 hrs with a nasogastric feeding. Forty-six acid reflux episodes were recorded with a range of 0 to 8 per patient.⁵⁷ Heyland et al. used measurements of radio-isotopes in oropharynx secretions to detect reflux. Mechanically ventilated ICU patients were administered a radio-isotope labeled enteral feed, gastric or post-pyloric. Hourly samples were obtained from the oropharynx and trachea for 6 hrs. GER was defined as an increase in radioactivity > 100 counts per minute/g. Gastric fed patients had 39.8% of oral specimens positive for regurgitation.¹³⁰ This rate of reflux is comparable to the rate of 44% found in the current sample population.

Two studies of outpatients with or without known GERD measured pepsin in oral secretions. In 14 patients with known GERD, 108 saliva and sputum (patient coughed into specimen cup) specimens were collected over 24 hrs during esophageal pH monitoring at home. Specimens were collected every 2 hrs when awake and when they had coughing or reflux symptoms. Samples were not collected in the first hr after a meal. Only 10% of sputum and

saliva specimens were pepsin-positive, exact breakdown of each was not reported.¹⁶⁷ The second study examined 40 patients with suspected GERD and 8 healthy volunteers without GERD symptoms, no erosive esophagitis on esophagogastroduodenoscopy and no pathologic reflux on 24-hour esophageal pH monitoring. Sputum and saliva was collected by the patient at bedtime and upon awakening in all patients. Patients with suspected GERD were instructed to collect sputum and saliva specimens with symptoms as well. In the patients with suspected GERD, 22% of saliva and sputum specimens were pepsin-positive, percent of each specimen type was again not specified. None of the healthy volunteers had pepsin-positive specimens.¹⁶⁸

Several reasons and risk factors may explain the higher percent of pepsin-positive oral secretions found in this study compared to the 2 studies of alert patients at home with GERD symptoms and the descriptive studies by Schallom et al. and Sole et al.^{58,193} In this investigation, multiple oral secretions over each 12-hr period were obtained for each subject. It is unknown how long pepsin can be detected in oral secretions after a reflux episode. The 44% pepsin-positive oral secretion rate is similar to findings in the study by Heyland et al. where oral secretions were obtained hourly for 6 hrs that found reflux in 39% of oral secretions.¹³⁰ Also, no control of secretion obtainment and tube feeding administration was performed. Oral secretions were obtained hourly when there was sufficient volume. Two subjects received tube feedings administered by continuous infusion. For bolus fed subjects, oral specimens may have been obtained during, just after or up to 4 hours after a bolus infusion. Other factors are known to increase the risk of reflux in the ICU gastric fed population compared to GERD patients at home. Straining with coughing induced by suctioning of the endotracheal tube or spontaneous coughing is associated with reflux in ventilated patients and would not be seen in home patients.⁵⁷ Also, the presence of a tube traversing the esophageal sphincters has been associated with reflux which

were not present in the study of GERD patients at home.⁵⁹⁻⁶¹ Delay in gastric emptying and altered duodenal motility which results in duodenal gastric reflux has also been demonstrated in critically ill patients compared to healthy individuals.^{41, 78-80} Additionally, the risk factor of BMI and sedation levels of ICU patients will be discussed later. The multiple risk factors observed in the study sample and the high frequency of oral specimen sampling may account for the high percent of pepsin-positive oral secretions.

Association between Reflux and Aspiration

No relationship was observed between percent of pepsin-positive oral and tracheal secretions. Obtainment of oral secretions changed in the study protocol during data collection. Initially, obtainment of secretions from the oropharynx was proposed. EER includes gastric content reflux to the pharynx, larynx and oral cavity. Sole and colleagues suctioned the oropharynx of orally intubated patients with a deep suction catheter and retrieved greater than 5 ml of secretions. Sedation level was not reported in the sample. No report of gagging was reported. A deep suction catheter was used.¹⁷⁰ A pilot study using the same suctioning technique to measure pepsin and amylase of oral secretions was conducted on 10 patients by the same researchers and again no gagging was observed.¹⁹³ However, instrumentation of the oral cavity and pharynx can stimulate the gag reflex. In healthy adults, Hughes and Wiles initiated the gag reflex by depression of the tongue with a stick, touching of the soft palate or touching of the pharyngeal wall. Retching was the second most frequent symptom secondary to gag reflex stimulation.¹⁹⁴ Retching can lead to gastroesophageal reflux and vomiting. Gagging is a protective reflex to prevent unwanted entry into the mouth and pharynx. During dental procedures, stimulation of the gag reflex occurs from stimulation of the oral cavity or pharyngeal area. The higher the classification of gagging problem index, the more often IV sedation or

general anesthesia was required.¹⁹⁵ In critically ill neurologic patients, absence of a cough or gag reflex was an independent risk factor for acute lung injury/acute respiratory failure most likely related to the impaired neurologic activity.¹⁹⁶ Therefore, less sedation with maintenance of the gag reflex is important to prevention of aspiration but stimulation of the gag reflex can lead to more reflux.

The first subject in the current study was sedated at a RASS score range of -4 to -1 with a mean score of -2.5. Suctioning of the oropharynx was conducted. However, subjects 2 and 3 were predominantly alert throughout the data collection period. Subject 2 had a mean RASS score of 0.375 while subject 3 had a RASS score of 0 at every assessment. Subject 2 demonstrated the gag reflex during oral suctioning. To prevent gagging and inducing reflux of these subjects, only the oral cavity was suctioned. After this observation, only the oral cavity was suctioned in the remaining 12 subjects to be consistent and prevent induction of reflux. It is highly likely that EER was missed by suctioning only the oral cavity. Therefore, the association between reflux and aspiration may be inaccurate with the revised method of oral secretion obtainment from the oral cavity only. Although a large number of oral and tracheal secretions were pepsin-positive, frequently tracheal secretions were pepsin-positive while oral secretions were pepsin-negative. It is feasible that if secretions were obtained from the oropharynx, a significant relationship may have been found. A Yankauer suction device was used in this study which might have stimulated the gag reflex compared to a smaller, softer suction catheter. In future studies, the use of a small, soft suction catheter may allow improved access to the oropharynx without stimulation of the gag reflex and more accurate identification of refluxed secretions in the critically ill patient.

In the pilot study by Sole and colleagues, specimens were obtained at baseline and then 1-4 hrs later on 10 subjects for a total of 20 specimens. Seven patients were being gastric fed and 3 post-pyloric. The researchers found that 35% of matched oral and tracheal specimens were both negative, 35% were both positive; 20% were positive for reflux and negative for aspiration and 10% were negative for reflux and positive for aspiration.¹⁹³ The higher rate of reflux without aspiration found by Sole et al. compared to results from this investigation may be attributed to their use of a small oropharynx suction catheter to obtain secretions from the oropharynx. In the current study secretions were obtained with the Yankauer suction device with suctioning of the oral cavity only. However, similar patterns of reflux and aspiration were observed in both studies. Reflux and aspiration were detected simultaneously the majority of the time. However, at other times, reflux was not detected and aspiration was present or reflux was present and aspiration was not detected.

Additionally, the frequency with which secretions were obtained may partially explain the lack of relationship between tracheal and oral secretions. In a pilot study, subjects were suctioned at only 1 time point. The 2 pepsin-positive tracheal secretions were both associated with pepsin-positive oral secretions.⁵⁸ The potential difference in length of time pepsin is detected in oral compared to tracheal secretions may have impacted the relationship. In an animal model, pepsin was detected for 6 hrs after forced aspiration.¹⁶⁴ It is feasible that oral secretions were measured as negative with no further reflux yet the tracheal secretions remained positive for 6 hrs.

Effect of Lowered HOB on Reflux and Aspiration

Correlations of the mean minutes the HOB was lowered and the mean HOB angle when lowered at each HOB assignment with percent pepsin-positive oral secretions were not

significant. However, the overall mean HOB angle for each assignment was significant. A lower mean HOB angle was associated with a higher percent of pepsin-positive oral secretions and an increased yield of oral secretion obtainment. No studies previously examined the impact of intermittently lowering the head of bed on gastric reflux, defined in this study as minutes lower than assigned elevation. Rather most studies have examined intermittent observations of HOB elevation and the association of aspiration and pneumonia.

The significant association of mean lower HOB and increased reflux is consistent with findings that a lower HOB was associated with increased aspiration and VAP rates.⁹⁶⁻¹⁰² The findings from the current study provide the foundation for demonstrating the association of reflux and HOB elevation. However, more research is needed with a larger sample size.

Association of Subject Characteristics and Reflux

Of the 6 patient characteristics examined, only sedation level was significant with the non-parametric Kendall's tau. A deeper sedation level was associated with an increased percent of pepsin-positive oral secretions. A more sedate patient and a lower level of consciousness as risk factors for aspiration and VAP have been reported in several studies.^{14,82-83} As sedation levels deepen, the cough reflex is diminished thus clearing of refluxed material may be delayed or absent. In this study, the sample was too small for analysis of interactions between variables. However, when considering the results of the lower frequency that oral secretions were obtained at the experimental HOB condition, it is possible that gravity facilitated clearing of refluxed material independent of sedation level. Gravity is known to assist with clearance of reflux in upright positions.^{4,32}

The Kendall's tau correlation was not significant for BMI. Previous research indicated that tLESRs were observed in patients with morbid obesity at a rate similar to patients with

known GERD.⁵³ Thus, patients are expected to have a higher percent of pepsin-positive oral secretions with increased BMI. The mean BMI fell in the range of obesity. Therefore, the small sample size of predominantly overweight and obese patients may have strongly impacted the findings. Additionally, the predominance of overweight and obese patients could partially explain the high percent of pepsin-positive oral secretions. Also, sedation levels and HOB levels may explain the 2 outliers observed in the scatterplot of BMI and percent pepsin-positive oral secretions. The 2 subjects with the highest BMI were alert throughout most of the data collection and maintained their HOB elevation assignment or higher throughout data collection. Both subjects were in the experimental group where the 45° HOB was assigned on Day 1. Mean HOB was 44° and 43° on day 1, 44° and 37° overnight and 42° and 37° on usual care day. Both subjects were comfortable with the higher HOB elevation and preferred to be higher than 30° because of easier breathing. Both of these subjects had no positive oral secretions despite frequent pepsin-positive tracheal secretions. It is likely that these subjects were refluxing to the level of the pharynx and larynx with aspiration without refluxing into the oral cavity. Another possibility is they were clearing secretions from their oropharynx by swallowing or with the aid of gravity and refluxed secretions did not reach the oral cavity.

No significant correlations were found with age, gender and APACHE II scores. One study found liquids emptied more slowly in women compared to men. All women were pre-menopausal.⁴³ In the current study, only 1 female was pre-menopausal. Aging was associated with delayed gastric emptying associated with high lipid laden soup compared to non-lipid soup.⁴⁴ No studies on aging and delayed gastric emptying with tube fed patients were found. Also both the gender and aging studies examined the outcome of gastric emptying and not

reflux.⁴³⁻⁴⁴ The characteristics of age and gender were not associated with increased reflux in the current study.

Previous research of GRV and aspiration found variable results because of different methods to detect aspiration and diagnose pneumonia.¹¹³⁻¹¹⁷ Studies have demonstrated that GRV is higher in the first few days of tube feeding.¹¹¹⁻¹¹² In this investigation, most subjects were consented the first or second day of tube feeding orders yet the GRV was < 100 ml for the majority of the measurements. GRV measurement with the syringe method is highly variable depending on patient position, tube material, tube type and location in stomach.¹⁰⁷⁻¹⁰⁹ Subjects in this study had a variety of gastric tube sizes and types. Also position for GRV measurement was not controlled. Thus, the accuracy of GRV measurements may have varied.

In the current study, the average GRV was 59.4 ± 68.1 with a range of 0-440 ml. GRV was measured as less than 100 ml for 82 (80%) measurements. In a study by Metheny and colleagues, GRVs greater than 250 ml were associated with a higher rate of aspiration pneumonia.¹¹⁵ However, a recent study by Reignier et al. examined absence of GRV monitoring in mechanically ventilated gastric fed patients on VAP rates. Intolerance to enteral nutrition was defined as observed regurgitation and vomiting without GRV measurement in the intervention group. Intolerance to enteral nutrition was defined as GRV measures greater than 250 ml, observed regurgitation and vomiting in the control group. Regurgitation events during procedures associated with the vomiting reflex, such as oral care, were not counted. The study excluded a large number of patients due to a past history of abdominal surgery in the past month and feeding via a gastrostomy tube. Patients were maintained at 30° to 45°. However, there was no information on how HOB was measured and recorded. Intolerance was higher in the control group while the proportion of patients who vomited was significantly higher in the intervention

group. Also there were more reported vomiting episodes in the intervention group. There was no significant difference in the primary outcome of VAP rate between groups. VAP rates were high in both groups, 16.7% in the intervention and 15.8% in the control group.¹⁹⁷ The higher number of vomiting episodes when GRV was not monitored in the study by Reignier et al. would suggest that a potentially higher GRV may be associated with more reflux. However, the researchers concluded non inferiority of absence of GRV monitoring due to no difference in VAP rates.¹⁹⁷

In this study, a total of 8 GRVs were ≥ 250 ml. One subject had 4 GRVs ≥ 250 ml. This subject had 78% pepsin-positive tracheal secretions and 62% pepsin-positive oral specimens. The small sample of subjects and small number of GRVs ≥ 250 ml may have resulted in the no significant findings. However, due to the controversy over the use of GRV, more accurate measures of GRV are needed. Studies related to ultrasound measurement of gastric volume in the preoperative setting have shown clinical utility¹²⁴⁻¹²⁵ and warrant investigation in the critically ill tube fed patient population.

Oral Secretion pH and Pepsin Measurements to Detect Reflux

In the 1970's a clinical syndrome of gastric bleeding termed "stress ulceration" was described in ICU patients. Several medications are administered to prevent this syndrome including proton pump inhibitors (PPI), histamine 2 receptor antagonists (H2RA) and sucralfate. These medications aim to maintain pH above 3.5-5 to prevent gastric mucosal injury and bleeding.¹⁹⁸ All subjects in this study received either a PPI or H2RA medication throughout the data collection period. In addition all subjects received .12 % chlorhexidine gluconate oral rinse, pH 5-7, at approximately 0900. The pH of saliva ranges from a pH of 6.4-7.8 Therefore, pH measures of oral secretions < 6 were considered indicative of reflux. The lowest pH observed was 4. No association was found in the correlation of pH and pepsin measure.

Measurement of ambulatory esophageal pH is the gold standard for detection of pathologic reflux.⁴ Studies of esophageal pH monitoring in ICU patients were all conducted with probes just proximal to the LES.^{65, 80, 155} Traditional distal esophageal pH monitoring may miss pharyngeal reflux.¹⁹⁹ Yuskel and Vaezi stated that ambulatory pH monitoring lacks the sensitivity and specificity to detect laryngopharyngeal reflux and that hypopharyngeal and proximal esophageal pH monitoring have sensitivity and specificity of only 40% and 55% respectively.²⁰⁰

In this study, the oral cavity was suctioned for secretions and subsequent measurement of pH and presence of pepsin. Some chronic conditions can lower salivary pH such as hypertension and hypothyroidism yet the pH does not lower below 6.5.²⁰¹⁻²⁰² Therefore, the reason some subjects with a pH of 4-5 demonstrated no pepsin while others with a pH of 4-5 had pepsin-positive oral specimens is not entirely clear. The majority of pH measurements of 4-5 (90%) were obtained in 4 subjects. It is possible that these subjects were refluxing to the oropharynx which lowered the pH of oral cavity secretions. Pepsin presence not detected in secretions from the oral cavity may have been detected in secretions from the oropharynx. Other possible reasons for low pH in the absence of pepsin include faster clearance of pepsin from oral secretions than acid clearance and medications that were not recorded. Based on these findings, pH measurements of oral secretions from the oral cavity are not indicated as a marker for gastric reflux in oral secretions in mechanically ventilated gastric fed patients. Research on oropharyngeal secretions may result in a more accurate measure of pH as an indicator of EER.

Limitations of the Study

The major limitation of the study was the small sample size. Although percent pepsin-positive oral and tracheal secretions were lower at experimental 45° condition, the sample was

likely underpowered to detect a significant difference. A power analysis was conducted on the results from the 10 subjects with at least a 9° difference in HOB elevation from day 1 to day 2. A sample of 56 subjects per HOB assignment would be needed at $p = .05$ level and power of .80 to detect a difference in reflux occurrence. A sample of 249 subjects per HOB assignment would be needed at $p = .05$ level and power of .80 to detect a difference in aspiration occurrence.

The sample also included a high number of obese patients which may have prevented detection of differences in subject characteristics. Only 11 patients completed all 36 hrs of data collection which may have impacted the results as well. Additionally, some subjects had little variance of mean HOB angles on both days.

The second important limitation was the use of oral secretions from the oral cavity rather than the oropharynx. This may have impacted the results of the association between reflux and aspiration and pH and pepsin-positive oral secretions. RASS scores near 0 and the risk of inducing the gag reflex and producing reflux limited the ability to obtain oropharyngeal secretions. A study with a different suction catheter for the oropharynx is needed.

Implications for Practice and Future Research Directions

Despite the small sample size, several findings have implications for caring for the mechanically ventilated gastric fed patient. First, patients can be maintained at higher HOB angles without sliding and without pressure ulcer development when turned regularly and maintained on low air loss mattresses. It is feasible to maintain patients near 45° for extended periods although further research is needed with a larger sample and for a longer period of time at the elevated HOB angle. Several patients were excluded from the study because they could not have the HOB lowered, for example patients with elevated intracranial pressure measurements. A descriptive study with the continuous HOB angle measuring device in that patient population

could provide evidence on the impact of maintenance of HOB elevation above 30° for prolonged periods on pressure ulcers. Another group of patients was excluded due to concerns for hemodynamic instability when elevating HOB above 30°. In this study, 2 subjects were on vasopressor medications with the HOB at 30° and were able to remain in the study. Although more research is needed, the automatic response of critical care clinicians to lower the HOB with use of vasopressor medications needs to be further investigated.

Most patients are comfortable with the higher HOB elevations or may require some acclimation, as 1 subject in the current study required, to a higher HOB angle when previously maintained < 45°. Bariatric patients, especially with central obesity, may be most comfortable at higher HOB elevations with a bariatric bed that allows for lowering of the foot of the bed into more of a chair position.

Minutes lowered < 30° or 45° and mean angle when lowered may not be significant but replication of the study in a larger population is needed. However, the association between higher mean HOB angles and lower reflux with both usual care and experimental condition implies that gastric fed patients should be maintained at as high a HOB elevation as the patient is comfortable. Also the use of trendelenburg positioning appears to be a risk for reflux. This is the first study to report trendelenburg positioning, reflux and aspiration events. For repositioning of bariatric patients, a study of overhead lifts to assist with turning and repositioning in the bed to eliminate trendelenburg use is needed.

Regarding patient characteristics, GRV was not significant although most GRVs in this study were low. Findings discussed from previous studies demonstrated an increase in reflux, aspiration and pneumonia with higher GRVs. Findings in the literature are inconsistent due to the inaccuracy of GRV measurements by the syringe method. However, if a patient has a GRV \geq

250 ml, it is optimal to elevate the HOB greater than 30° to reduce reflux as much as possible until GRV measurements are lower. Also research of a more accurate method to measure GRV at the bedside is needed. Lastly, the current study found that deeper sedation levels were associated with increased percent of pepsin-positive oral secretions. Thus, patients who are moderately to deeply sedated would probably benefit from higher HOB elevations to decrease reflux.

Recent studies offer 3 new areas of research in this field.²⁰³⁻²⁰⁵ Yuksel and colleagues reported on the use of a noninvasive rapid salivary pepsin lateral flow device using 2 monoclonal antibodies specific to human pepsin. The device is capable of detecting pepsin in saliva secretions within 15 minutes. Expecterated saliva was obtained from 58 subjects with known GERD and 51 control patients. The specimens were not read immediately but rather citric acid in the collection tube was used to delay degradation of pepsin and the samples were stored on ice and refrigerated. The samples were vortexed and centrifuged to obtain supernatants and then processed for analysis with the lateral flow device. Pepsin was detected in saliva in 19 (17%) samples overall, 13/58 (22%) with known GERD and 6/51 (12%) in the controls.²⁰³ Additional research is needed on the rapid salivary pepsin lateral flow device. Further development of a rapid test to detect pepsin in oral secretions could be beneficial to detecting reflux promptly in gastric fed patients. Hence interventions, such as placement of a distal small bowel feeding tube, could be instituted in patients who cannot maintain HOB elevation and are frequently having gastric reflux.

Two meta-analysis studies have shown that the use of subglottic secretion drainage reduces VAP¹⁵³⁻¹⁵⁴ However, use of special endotracheal tubes has not been fully accepted primarily due to the expense and unpredictability of knowing which patients will require mechanical ventilation for > 72 hours. A new device that continuously clears oral secretions by a

saliva ejector was examined in a pilot study by Chow and associates. The device was originally used in dental surgery. It has a spiral head with five holes for suction on the inner rim with a distal saliva ejector connected to suction. The device was placed between the patient's cheek and teeth and connected to 100 mg Hg suction. Thirteen patients used the continuous oral suction device, 3 developed VAP; 12 patients received standard care, 10 developed VAP.²⁰⁴ Overall, the reported VAP rate was high despite patients reported to be maintained at 30° HOB elevation and implementation of other VAP prevention interventions. The reduction in VAP in the continuous oral suction device group warrants further study in a larger population. The device reduces aspiration of contaminated oral secretions yet its ability to remove gastric reflux is uncertain based on its position in the oral cavity.

A third study examined the detection of amylase in bronchoalveolar lavage (BAL) specimens. Amylase is secreted in saliva and by the pancreas thus amylase in tracheal secretions could identify aspiration of oral secretions and duodenogastric secretions. BAL amylase levels significantly increased as the number of pre-intubation risk factors increased such as vomiting, swallowing dysfunction and altered level of consciousness. From these findings, the authors suggested that BAL amylase levels could be used as a screening tool of patients suspected of aspiration.²⁰⁵ Further study of amylase in oral and tracheal secretions in gastric fed patients is needed.

Conclusions

In conclusion, this study provides initial evidence that HOB elevation > 30° is feasible in many patients and was associated with decreased percent pepsin-positive oral and tracheal secretions and significantly decreased frequency of oral secretions without development of pressure ulcers. Lower mean HOB angles as well as deeper sedation levels were associated with

a significantly higher frequency of reflux. Additionally, reflux was observed after trendelenburg positioning. The associations of reflux and aspiration with elevation to 45° compared to 30° and trendelenburg positioning require additional research with a larger sample.

Appendix A Subject Screening Form

Inclusion Criteria:

	Yes	No
X-ray confirmed gastric location of feeding tube or surgically/endoscopically placed gastric feeding tube		
Mechanically ventilated per endotracheal tube		
≥ 18 years of age		
Approval from attending physician to elevate HOB to 45°		
Surrogate available to provide consent		
Anticipated mechanical ventilation and tube feeding duration of at least 48 hrs		

If all of the above items are answered yes, screen for the below exclusion criteria

Exclusion Criteria:

	Yes	No
Oral trauma that would prevent oral suctioning		
Inability to tolerate 45° HOB elevation		
Elevated ICP or condition that would prevent tracheal suctioning q 2 hours		
Stage I or higher pressure ulcer to sacrum/coccyx, buttocks or greater trochanter regions		
Planned procedures outside of the ICU in the next 48 hours		
Pregnancy		
History of GERD or hiatal hernia		
Active pulmonary tuberculosis or any airborne infectious disease		

If all of the above items are answered no, approach surrogate for consent.

Appendix B Subject Demographic Form

Subject Number: _____

Admitting Diagnosis: _____

	Date
Hospital Admission	
ICU Admission	
Data Collection Start	
Data Collection Complete	

Check or Enter Information

Unit	Medical ICU <input type="checkbox"/>	Surgical ICU <input type="checkbox"/>
Gender	Male <input type="checkbox"/>	Female <input type="checkbox"/>
Age in years at time of enrollment		
Apache II score from the 24 hrs prior to data collection		
BMI at time of admission		
Type of Gastric Feeding Tube	Salem Sump <input type="checkbox"/>	Soft Small Bore <input type="checkbox"/>
	PEG Tube <input type="checkbox"/>	Other: Describe
Size of Gastric Feeding Tube	_____ French	

Patient Completed both days of data collection	Yes <input type="checkbox"/>	No <input type="checkbox"/>	
If no what was the reason?	Patient/Family withdrew from study <input type="checkbox"/>	Researchers withdrew patient due to change in skin integrity <input type="checkbox"/>	Caregiver withdrew patient due to change in patient condition <input type="checkbox"/>

Appendix D Data Collection Sheet

Subject Number _____

Date Started _____

Day 1									
Hour	Oral Secretions Hourly (check hour obtained)	Tracheal Secretions q 2 hrs PRN: (check hour obtained)	GRV 08-12-16-20	RAS S 08-12-16-20	Prokinetic Agent given: Enter dose, route	TF Flow Rate ml/hr	Skin Check 08-20 and each turn	Position B-R-L	Comment
0800									
0900									
1000									
1100									
1200									
1300									
1400									
1500									
1600									
1700									
1800									
1900									
2000									
Day 2									
0800									
0900									
1000									
1100									
1200									
1300									
1400									
1500									
1600									
1700									
1800									
1900									
2000									

Check box when completed.

Record prokinetics administered for 24 hours prior to data collection.

References

1. McClave SA, DeMeo MT, DeLegge MH, DiSario JA, Heyland DK, Maloney JP, et al. North American summit on aspiration in the critically ill patient: Consensus statement. *Journal of Parenteral and Enteral Nutrition*. 2002; 26: S80-5.
2. Rieder F, Biancani P, Harnett K, Yerian L, Falk GW. Inflammatory mediators in gastroesophageal reflux disease: Impact on esophageal motility, fibrosis, and carcinogenesis. *American Journal of Physiology Gastrointestinal Liver Physiology*. 2010; 298: G571-G581.
3. Bardhan KD, Strugala V, Dettmar PW. Reflux revisited: Advancing the role of pepsin. *International Journal of Otolaryngology*. 2012; 2012: 1-13.
4. Richter JE. Gastroesophageal reflux disease. In: Yamada T, Alpers DH, Kalloo AN, Kaplowitz N, Owyang C, Powell DW eds. *Gastroenterology* 5th Edition. West Sussex, UK: Wiley-Blackwell; 2009: 772-801.
5. Starosta V, Kitz R, Hartl D, et al. Bronchoalveolar pepsin, bile acids, oxidation, and inflammation in children with gastroesophageal reflux disease. *Chest*. 2007; 132: 1557-1564.
6. de Benedictis FM, Carnielli VP, de Benedictis D. Aspiration lung disease. *Pediatric Clinics of North America*. 2009; 56: 173-190.
7. Mims JW. The impact of extra-esophageal reflux upon diseases of the upper respiratory tract. *Current Opinion in Otolaryngology Head & Neck Surgery*. 2008; 16: 242-246.
8. Shigemitsu H, Afshar K. Aspiration pneumonias: Under-diagnosed and under-treated. *Current Opinion in Pulmonary Medicine*. 2007; 13: 192-198.
9. Ufberg JW, Bushra JS, Karras DJ, Satz WA, Kueppers F. Aspiration of gastric contents: Association with prehospital intubation. *American Journal of Emergency Medicine*. 2005; 23: 379-382.
10. DeLegge MH. Aspiration pneumonia: Incidence, mortality, and at-risk populations. *Journal of Parenteral and Enteral Nutrition*. 2002; 26: S19-S24.
11. Gopalareddy V, He Z, Soundar S, et al. Assessment of the prevalence of microaspiration by gastric pepsin in the airway of ventilated children. *Acta Paediatrica*. 2008; 97: 55-60.
12. Meert KL, Daphtary KM, Metheny NA. Gastric vs small-bowel feeding in critically ill children receiving mechanical ventilation: A randomized controlled trial. *Chest*. 2004; 126: 872-878.

13. de Maio Carrilho CMD, Grion CMC, Bonametti AM, Medeiros EAS, Matsuo T. Multivariate analysis of the factors associated with the risk of pneumonia in intensive care units. *The Brazilian Journal of Infectious Disease*. 2007; 11: 339-344.
14. Metheny NA, Clouse RE, Chang Y-H, Stewart BJ, Oliver DA, Kollef MH. Tracheobronchial aspiration of gastric contents in critically ill tube-fed patients: Frequency, outcomes, and risk factors. *Critical Care Medicine*. 2006; 34: 1007-1015.
15. Turan A, Wo J, Kasuya Y, et al. Effects of dexmedetomidine and propofol on lower esophageal sphincter and gastroesophageal pressure gradient in healthy volunteers. *Anesthesiology*. 2010; 112: 19-24.
16. Cason CL, Tyner T, Saunders S, Broome L. Nurses' implementation of guidelines for ventilator-associated pneumonia from the centers for disease control and prevention. *American Journal of Critical Care*. 2007; 16: 28-36.
17. Krein SL, Kowalski CP, Damschroder L, Forman J, Kaufman SR, Saint S. Preventing ventilator-associated pneumonia in the United States: A multicenter mixed-methods study. *Infection Control and Hospital Epidemiology*. 2008; 29: 933-940.
18. Williams Z, Chan R, Kelly E. A simple device to increase rates of compliance in maintaining 30-degree head of bed elevation in ventilated patients. *Critical Care Medicine*. 2008; 36: 1155-1157.
19. Johnson KL, Meyenburg T. Physiological rationale and current evidence for therapeutic positioning of critically ill patients. *AACN Advanced Critical Care*. 2008; 20: 228-240.
20. Luttenberger K. Battling VAP from a new angle. *Nursing 2010*, 2010; 40: 52-55.
21. Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R. Guidelines for preventing health-care associated pneumonia, 2003. *Morbidity and Mortality Weekly Report*. 2004; 53: 1-36.
22. American Association of Critical Care Nurses. Ventilator associated pneumonia, clinical practice alert. Available at <http://www.aacn.org/wd/practice/content/practicealerts.pcms?menu=practice>. Accessibility verified May 2013.
23. Muscadere J, Dodek P, Keenan S, for the VAP Guidelines Committee and the Canadian Critical Care Trials Group. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: Prevention. *Journal of Critical Care*. 2008; 28: 126-137.
24. Martindale RG, McClave SA, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition. *Critical Care Medicine*. 2009; 37: 1-30.

25. Peterson M, Schwab W, McCutcheon K, van Oostrom JH, Gravenstein N, Caruso L. Effects of elevating the head of bed on interface pressure in volunteers. *Critical Care Medicine*. 2008; 36: 3038-3042.
26. Peterson MJ, Schwab W, van Oostrom JH, Gravenstein N, Caruso LJ. Effects of turning on skin-bed interface pressures in health adults. *Journal of Advanced Nursing*. 2010; 66:1556-1564.
27. Lyder CH, Ayello EA. Patient Safety and Quality: An Evidence-Based Handbook for Nurses. Hughes RG, editor. Chapter 12 pressure ulcers a patient safety issue. Available at <http://www.ncbi.nlm.nih.gov/books/NBK2650/>. Accessibility verified May 2013.
28. National Pressure Ulcer Advisory Panel. Pressure ulcer prevention: quick reference guide pdf. Available at http://www.npuap.org/wp-content/uploads/2012/02/Final_Quick_Prevention_for_web_2010.pdf. Accessibility verified May 2013.
29. Elpern EH, Stutz L, Peterson S, Gurka DP, Skipper A. Outcomes associated with enteral tube feedings in a medical intensive care unit. *American Journal of Critical Care*. 2004; 13: 221-7.
30. Institute of Medicine. IOM 100 Initial Priority Topics for Comparative Effectiveness Research. Available at <http://www.iom.edu/~media/Files/Report%20Files/2009/ComparativeEffectivenessResearchPriorities/Stand%20Alone%20List%20of%20100%20CER%20Priorities%20%20for%20web.pdf>. Accessibility verified May 2013.
31. The Joint Commission. The Joint Commission 2012 Hospital National Patient Safety Goals. Available at http://www.jointcommission.org/assets/1/6/2013_HAP_NPSG_final_10-23.pdf. Accessibility verified May 2013.
32. Li Bassi G, Torres A. Ventilator-associated pneumonia: Role of positioning. *Current Opinion in Critical Care*. 2011; 17: 57-63.
33. Hall JE. Secretory functions of the alimentary tract. In: Hall JE eds. *Guyton and Hall Textbook of Medical Physiology* 12th Edition. Philadelphia, PA: Saunders Elsevier; 2011:773-788.
34. Pandol SJ, Raybould HE, Yee Jr HF. Integrative responses of the gastrointestinal tract and liver to a meal. In: Yamada T, Alpers DH, Kalloo AN, Kaplowitz N, Owyang C, Powell DW eds. *Gastroenterology* 5th Edition. West Sussex, UK: Wiley-Blackwell; 2009: 3-14.

35. Kahrilas PJ, Pandolfino JE. Esophageal motor function. In: Yamada T, Alpers DH, Kalloo AN, Kaplowitz N, Owyang C, Powell DW eds. *Gastroenterology* 5th Edition. West Sussex, UK: Wiley-Blackwell; 2009: 187-206.
36. Kahrilas PJ, Dodds WJ, Dent J, Wyman JB, Hogan WJ, Arndorfer RC. Upper esophageal sphincter function during belching. *Gastroenterology*. 1986; 91: 133-140.
37. Shaker R, Ren J, Kern M, Dodds WJ, Hogan WJ, Li Q. Mechanisms of airway protection and upper esophageal sphincter opening during belching. *American Journal of Physiology*. 1992; 262: G621-G628.
38. What-When-How in depth tutorials and information. Paramedic Care. Available at <http://what-when-how.com/paramedic-care/airway-anatomy-and-physiology-clinical-essentials-paramedic-care-part-1/>. Accessibility verified May 2013.
39. Your Surgery. Anesthesia. Available at <http://www.yoursurgery.com/procedures/anesthesia/anesthesia.cfm>. Accessibility verified May 2013.
40. Hasler WL. The physiology of gastric motility and gastric emptying. In: Yamada T, Alpers DH, Kalloo AN, Kaplowitz N, Owyang C, Powell DW eds, *Gastroenterology* 5th Edition. West Sussex, UK: Wiley-Blackwell; 2009: 207-30.
41. Chapman MJ, Fraser RJ, Bryant LK, Vozzo R, Nguyen NQ, Tam W, et al. Gastric emptying and the organization of antro-duodenal pressures in the critically ill. *Neurogastroenterology Motility*. 2008; 20: 27-35.
42. Dee DR., Yada RY. The prosegment catalyzes pepsin folding to a kinetically trapped native state. *Biochemistry*, 2010; 49: 365-371.
43. Caballero-Plasencia AM, Valenzuela-Barranco M, Martin-Ruiz JL, Herrerias-Gutierrez JM, Esteban-Carretero JM. Are there changes in gastric emptying during the menstrual cycle? *Scandinavian Journal of Gastroenterology*. 1999; 34: 772-776.
44. Nakae Y, Onouchi H, Kagaya M, Kindo T. Effects of aging and gastric lipolysis on gastric emptying of lipid in liquid meal. *Gastroenterology*. 1999; 34: 445-449.
45. Calbet JAL, MacLean DA. Role of caloric content on gastric emptying in humans. *Journal of Physiology*. 1997; 498: 553-559.
46. Castedal M, Abrahamsson H. High-resolution analysis of the duodenal interdigestive phase III in humans. *Neurogastroenterology Motility*. 2001; 13: 473-481.
47. Hasler WL. Motility of the small intestine and colon. In: Yamada T, Alpers DH, Kalloo AN, Kaplowitz N, Owyang C, Powell DW eds, *Gastroenterology* 5th Edition. West Sussex, UK: Wiley-Blackwell; 2009: 231-63.

48. Deane AM, Fraser RJ, Chapman MJ. Prokinetic drugs for feed intolerance in critical illness: Current and potential therapies. *Critical Care and Resuscitation*. 2009; 11: 132-43.
49. Patrick L. Gastroesophageal reflux disease (GERD): A review of conventional and alternative treatments. *Alternative Medicine Review*. 2011; 16: 116-113.
50. Miller LS, Vegesna AK, Brasseur JG, Braverman AS, Ruggieri MR. The esophagogastric junction. *Annals of the New York Academy of Sciences*. 2011; 1323: 323-330.
51. Orr WC, Robinson MG, Johnson LF. Acid clearance during sleep in the pathogenesis of reflux esophagitis. *Digestive Disease and Sciences*. 1981; 26: 423-427.
52. Johnston N, Dettmar PW, Bishwokarma B, Lively MO, Koufman JA. Activity/stability of human pepsin: Implications for reflux attributed laryngeal disease. *Laryngoscope*. 2007; 11: 1036-1039.
53. Schneider JH, Kuper M, Konigsrainer A, Brucher B. Transient lower esophageal sphincter relaxation in morbid obesity. *Obesity Surgery*. 2009; 19: 595-600.
54. Stein HJ, Barlow AP, DeMeester TR, Hinder RA. Complications of gastroesophageal reflux disease: Role of the lower esophageal sphincter, esophageal acid and acid/alkaline exposure, and duodenogastric reflux. *Annals of Surgery*. 1992; 216: 35-43.
55. Emerenziani S, Sifrim D. Gastroesophageal reflux and gastric emptying, revisited. *Current Gastroenterology Report*. 2005; 7: 190-195.
56. Parkman HP, FriedenberG FK, Fisher RS. Disorders of gastric emptying. In: Yamada T, Alpers DH, Kalloo AN, Kaplowitz N, Owyang C, Powell DW eds, *Gastroenterology* 5th Edition. West Sussex, UK: Wiley-Blackwell; 2009: 903-35.
57. Nind G, Chen W-H, Protheroe R, et al. Mechanisms of gastroesophageal reflux in critically ill mechanically ventilated patients. *Gastroenterology*. 2005; 128: 600-606.
58. Schallom M, Chang Y-H, Tricomi S, Metheny NA. A pilot study of pepsin in tracheal and oral secretions in mechanically ventilated tube fed patients. Accepted for publication. *American Journal of Critical Care*.
59. Nagler R. Persistent gastroesophageal reflux induced during prolonged gastric intubation. *New England Journal of Medicine*. 1963; 269: 495-500.
60. Ibanez J, Penafiel A, Raurich JM, Marse P, Jorda R, Mata F. Gastroesophageal reflux in intubated patients receiving enteral nutrition: Effect of supine and semirecumbent positions. *Journal of Parenteral and Enteral Nutrition*. 1992; 16: 419-22.

61. Gomes GF, Pisani JC, Macedo ED, Campos AC. The nasogastric feeding tube as a risk factor for aspiration and aspiration pneumonia. *Current Opinion in Clinical Nutrition and Metabolic Care*. 2003; 6: 327-33.
62. Dotson RG, Robinson RG, Pingleton SK. Gastroesophageal reflux with nasogastric tubes. Effect of nasogastric tube size. *American Journal of Respiratory and Critical Care Medicine*. 1994; 149: 1659-62.
63. Ferrer M, Bauer T, Torres A, Hernandez C, Piera C. Effect of nasogastric tube size on gastroesophageal reflux and microaspiration in intubated patients. *Annals of Internal Medicine*. 1999; 130: 991-4.
64. Ibanez J, Penafiel A, Marse P, Jorda R, Raurich JM, Mata F. Incidence of gastroesophageal reflux and aspiration in mechanically ventilated patients using small-bore nasogastric tubes. *Journal of Parenteral and Enteral Nutrition*. 2000; 24:103-6.
65. Russell GN, Yam PCI, Tran J, Innes P, Thomas SD, Berry PD. et al. Gastroesophageal reflux and tracheobronchial contamination after cardiac surgery: Should a nasogastric tube be routine? *Anesthesia Analgesia*. 1996; 83: 228-32.
66. Manning BJ, Winter DC, McGreal G, Kirwan WO, Redmond HP. Nasogastric intubation causes gastroesophageal reflux in patients undergoing elective laparotomy. *Surgery*. 2001; 130: 788-91.
67. Coben RM, Weintraub A, DiMarino AJ Jr, Cohen S. Gastroesophageal reflux during gastrostomy feeding. *Gastroenterology*. 1994; 106: 13-8.
68. Balan KK, Vinjamuri S, Maltby P, Bennett J, Woods S, Playfer JR, Critchley M. Gastroesophageal reflux in patients fed by percutaneous endoscopic gastrostomy (PEG): Detection by a simple scintigraphic method. *American Journal of Gastroenterology*. 1998; 93:946-9.
69. Douzinas EE, Andrianakis I, Livaditi O, Bakos D, Flevari K, Goutas N, et al. Reasons of PEG failure to eliminate gastroesophageal reflux in mechanically ventilated patients. *World Journal of Gastroenterology*. 2009; 15: 5455-60.
70. Roy P-M, Person B, Souday V, Kerkeni N, Dib N, Asfar P. Percutaneous radiologic gastrostomy versus nasogastric tube in critically ill patients. *Clinical Nutrition*. 2005; 24: 321-5.
71. Douzinas EE, Tsapalos A, Dimitrakopoulos A, Diamanti-Kandarakis E, Rapidis AD, Roussos C. Effect of percutaneous endoscopic gastrostomy on gastroesophageal reflux in mechanically-ventilated patients. *World Journal of Gastroenterology*. 2006; 12: 114-8.

72. Lee T-H, Shiun Y-C. Changes in gastroesophageal reflux in patients with nasogastric tube followed by percutaneous endoscopic gastrostomy. *Journal of the Formosan Medical Association*. 2011; 110: 115-9.
73. Nguyen NQ, Fraser RJ, Bryant LK, Chapman M, Holloway RH. Diminished functional association between proximal and distal gastric motility in critically ill patients. *Intensive Care Medicine*. 2008; 34: 1246-55.
74. Ochi M, Tominaga K, Tanaka F, Tanigawa, T, Shiba M, Watanabe T, et al. Effect of chronic stress on gastric emptying and plasma ghrelin levels in rats. *Life Sciences*. 2008; 82: 862-8.
75. Zheng J, Dobner A, Babygirija R, Ludwig K, Takahashi T. Effects of repeated restraint stress on gastric motility in rats. *American Journal of Physiology- Regulatory Integrative Comparative Physiology*. 2009; 296: R1358-65.
76. De Winter BY, De Man JG. Interplay between inflammation, immune system and neuronal pathways: Effect on gastrointestinal motility. *World Journal of Gastroenterology*. 2010; 16:5523-35.
77. Stengel, A, Wang L, Tache Y. Stress-related alterations of acyl and desacyl ghrelin circulating levels: Mechanisms and functional implications. *Peptides*. 2011; 32: 2208-17.
78. Schindlbeck NE, Lippert M, Heinrich C, Muller-Lissner SA. Intragastric bile acid concentrations in critically ill, artificially ventilated patients. *American Journal of Gastroenterology*. 1989; 84: 624-8.
79. Dive A, Michel I, Galanti L, Jamart J, Vander Borght T, Installe E. Gastric acidity and duodenogastric reflux during nasojejunal tube feeding in mechanically ventilated patients. *Intensive Care Medicine*. 1999; 25: 574-80.
80. Wilmer A, Tack J, Frans E, Dits H, Vanderschueren S, Gevers A, Bobbaers H. Duodenogastroesophageal reflux and esophageal mucosal injury in mechanically ventilated patients. *Gastroenterology*. 1999; 116: 1293-9.
81. Farrell S, McMaster C, Gibson D, Shields MD, McCallion WA. Pepsin in bronchoalveolar lavage fluid: A specific and sensitive method of diagnosing gastro-oesophageal reflux-related pulmonary aspiration. *Journal of Pediatric Surgery*, 2006; 41: 289-293.
82. Raghavendran K, Nemzek J, Napolitano LM, Knight PR. Aspiration-induced lung injury. *Critical Care Medicine*. 2011; 39: 818-826.
83. Marik PE. Pulmonary aspiration syndromes. *Current Opinion in Pulmonary Medicine*. 2011; 17: 148-154.

84. Ohrui T, Yamaya M, Suzuki T, et al. Mechanisms of gastric juice-induced hyperpermeability of the cultured human tracheal epithelium. *Chest*. 1997; 111: 454-459.
85. Blumin JH, Merati AL, Toohill RJ. Duodenogastroesophageal reflux and its effect on extraesophageal tissues: A review. *Ear, Nose & Throat Journal*. 2008; 87: 234-237.
86. Johnston N, Wells CW, Samuels TL, Blumin JH. Pepsin in nonacidic refluxate can damage hypopharyngeal epithelial cells. *Annals of Otolaryngology, Rhinology & Laryngology*. 2009; 118: 677-685.
87. Nader-Djalal N, Knight PR, Thusu K, et al. Reactive oxygen species contribute to oxygen-related lung injury after acid aspiration. *Anesthesia Analgesia*. 1998; 87: 127-133.
88. Rotta AT, Shiley KT, Davidson BA, et al. (2004). Gastric acid and particulate aspiration injury inhibits pulmonary bacterial clearance. *Critical Care Medicine*. 2004; 32: 747-754.
89. Beck-Schimmer B, Rosenberger DS, Neff SB, et al. Pulmonary aspiration: New therapeutic approaches in the experimental model. *Anesthesiology*. 2005; 103: 556-566.
90. Hutson AD, Davidson BA, Raghavendran K, et al. Statistical prediction of the type of gastric aspiration lung injury based on early cytokine/chemokine profiles. *Anesthesiology*. 2006; 104: 73-79.
91. Raghavendran K, Davidson BA, Hutson AD, et al. Predictive modeling and inflammatory biomarkers in rats with lung contusion and gastric aspiration. *The Journal of Trauma Injury, Infection, and Critical Care*. 2009; 67: 1182-1198.
92. Bregeon F, Papazian L, Delpierre S, et al. Role of proinflammatory activity contained in gastric juice from intensive care unit patients to induce lung injury in a rabbit aspiration model. *Critical Care Medicine*. 2008; 36: 3205-3212.
93. Farhath S, He Z, Nakhla T, et al. Pepsin, a marker of gastric contents, is increased in tracheal aspirates from preterm infants who develop bronchopulmonary dysplasia. *Pediatrics*. 2008; 121: 253-259.
94. Ward C, Forrest IA, Brownless IA, et al. Pepsin like activity in bronchoalveolar lavage fluid is suggestive of gastric aspiration in lung allografts. *Thorax*. 2005; 60: 872-874.
95. Stovold R, Forrest IA, Corris PA, et al. Pepsin, a biomarker of gastric aspiration in lung allografts. *American Journal of Respiratory and Critical Care Medicine*. 2007; 175: 1298-1303.
96. Metheny NA, Davis-Jackson J, Stewart BJ. Effectiveness of an aspiration risk-reduction protocol. *Nursing Research*. 2010; 59: 18-25.

97. Torres A, Serra-Batlles J, Ros E, et al. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. *Annals of Internal Medicine*. 1992; 116: 540-543.
98. Kollef MH. Ventilator-associated pneumonia: A multivariate analysis. *Journal of the American Medical Association*. 1993; 270: 1965-1970.
99. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomized trial. *The Lancet*. 1999; 354: 1851-1858.
100. van Nieuwenhoven CA, Vandenbroucke-Grauls C, van Tiel FH, et al. Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: A randomized study. *Critical Care Medicine*. 2006; 34: 396-402.
101. Keeley L. Reducing the risk of ventilator-acquired pneumonia through head of bed elevation. *Nursing in Critical Care*. 2007; 12: 287-294.
102. Alexiou VG, Ierodiakonou V, Dimopoulos G, Falagas ME. Impact of patient position on the incidence of ventilator-associated pneumonia: A meta-analysis of randomized controlled trials. *Journal of Critical Care*. 2009; 24: 515-522.
103. Grap MJ, Munro CL, Bryant S, Ashtiani B. Predictors of backrest elevation in critical care. *Intensive and Critical Care Nursing*. 2008; 19: 68-74.
104. Rose L, Baldwin I, Crawford T. The use of bed-dials to maintain recumbent positioning for critically ill mechanically ventilated patients (The RECUMBENT study): Multicentre before and after observational study. *International Journal of Nursing Studies*. 2010; 47: 1425-1431.
105. Helman DL, Sherner III JH, Fitzpatrick TM, Callender ME, Shorr AF. Effect of standardized orders and provider education on head-of-bed positioning in mechanically ventilated patients. *Critical Care Medicine*. 2003; 31: 2285-2290.
106. Veterans Health Administration and Department of Defense, Patient Safety Center of Inquiry. Patient care ergonomics resource guide: Safe bariatric patient handling and toolkit. Available at <http://www.visn8.va.gov/visn8/patientsafetycenter/safePtHandling/toolkitBariatrics.asp> Accessibility verified May 2013.
107. Metehny NA, Schallom ME, Edwards SJ. Effect of gastrointestinal motility and feeding tube site on aspiration risk in critically ill patients: A review. *Heart & Lung*. 2004; 33: 131-45.

108. Metheny NA, Stewart J, Nuetzel G, Oliver D, Clouse RE. Effect of feeding-tube properties on residual volume measurements in tube-fed patient. *Journal of Parenteral and Enteral Nutrition*. 2005; 29: 192-197.
109. Ridley EJ, Davies AR. Practicalities of nutrition support in the intensive care unit: The usefulness of gastric residual volume and prokinetic agents with enteral nutrition. *Nutrition*. 2011; 27: 509-12.
110. Landzinski J, Kiser TH, Fish DN, Wischmeyer PE, MacLaren R. Gastric motility function in critically ill patients tolerant vs intolerant to gastric nutrition. *Journal of Parenteral and Enteral Nutrition*. 2008; 32: 45-50.
111. Cohen J, Aharon A, Singer P. The paracetamol absorption test: A useful addition to the enteral nutrition algorithm? *Clinical Nutrition*. 2000; 19: 233-6.
112. Kesek DR, Akerlind L, Karlsson T. Early enteral nutrition in the cardiothoracic intensive care unit. *Clinical Nutrition*. 2002; 21: 303-7.
113. Mentec H, Dupont H, Bocchetti M, Cani P, Ponche F, Bleichner G. Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications. *Critical Care Medicine*. 2001; 29: 1955-61.
114. McClave SA, Lukan JK, Stefater JA, Lowen CC, Looney SW, Matheson PJ, et al. Poor validity of residual volumes as a marker for risk of aspiration in critically ill patients. *Critical Care Medicine*. 2005; 33: 324-30.
115. Metheny NA, Schallom L, Oliver DA, Clouse RE. Gastric residual volume and aspiration in critically ill patients receiving gastric feedings. *American Journal of Critical Care*. 2008;17:512-20.
116. Poulard F, Dimet J, Martin-Lefevre L, Bontemps F, Fiancette M, Clementi E, et al. Impact of not measuring residual gastric volume in mechanically ventilated patients receiving early enteral feeding: A prospective before-after study. *Journal of Parenteral and Enteral Nutrition*. 2010; 34:125-30.
117. Montejo JC, Minambres E, Bordeje L, Mesejo A, Acosta J, Heras A, et al. Gastric residual volume during enteral nutrition in ICU patients: the REGANE study. *Intensive Care Medicine*. 2010; 36: 1386-93.
118. MacLaren R, Kiser TH, Fish DN, Wischmeyer PE. Erythromycin vs metoclopramide for facilitating gastric emptying and tolerance to intragastric nutrition in critically ill patients. *Journal of Parenteral and Enteral Nutrition*. 2008; 32: 412-9.
119. Soulsby CT, Khela M, Yazaki E, Evans, DF, Hennessy E, Powell-Tuck J. Measurements of gastric emptying during continuous nasogastric infusion of liquid feed: Electric impedance tomography versus gamma scintigraphy. *Clinical Nutrition*. 2006; 25: 671-80.

120. Chapman MJ, Besanko LK, Burgstad CM, Fraser RJ, Bellon M, O'Connor S, et al. Gastric emptying of a liquid nutrient meal in the critically ill: relationship between scintigraphic and carbon breath test measurement. *Gut*. 2011; 6: 1336-43.
121. Ritz MA, Fraser R, Edwards N, Di Matteo AC, Chapman M, Butler R, et al. Delayed gastric emptying in ventilated critically ill patients: Measurement by ¹³C-octanoic acid breath test. *Critical Care Medicine*. 2001; 29: 1744-9.
122. Deane AM, Zaknic AV, Summers MJ, Chapman MJ, Lange K, Ritz MA, et al. Intrasubject variability of gastric emptying in the critically ill using a stable isotope breath test. *Clinical Nutrition*. 2010; 29: 682-6.
123. Murray CDR, Martin NM, Patterson M, Taylor SA, Ghatei MA, Kamm MA, et al. Ghrelin enhances gastric emptying in diabetic gastroparesis: A double blind, placebo controlled, crossover study. *Gut*. 2005; 54: 1693-8.
124. Bouvet L, Mazoit J-X, Chassard D, Allaouchiche B, Bosselli E, Benhamou D. Clinical assessment of the ultrasonographic measurement of antral area for estimating preoperative gastric content and volume. *Anesthesiology*. 2011. 114; 1086-1092.
125. Perlas A, Davis L, Khan M, Mitsakakis N, Chan VWS. Gastric sonography in the fasted surgical patient: A prospective descriptive study. *Anesthesia Analgesia*. 2011; 113: 93-97.
126. Varma R, Nelson L. Prophylactic nasogastric decompression after abdominal surgery. *Cochrane Database of Systematic Reviews*. 2010; issue 3.
127. Kearns PJ, Chin D, Mueller L, Wallace K, Jensen WA, Kirsch CM. The incidence of ventilator-associated pneumonia and success in nutrient delivery with gastric versus small intestinal feeding: A randomized clinical trial. *Critical Care Medicine*. 2000; 28: 1742-6.
128. Neumann DA, DeLegge MH. Gastric versus small-bowel tube feeding in the intensive care unit: A prospective comparison of efficacy. *Critical Care Medicine*. 2002; 30:1 436-8.
129. Montejo JC, Grau T, Acosta J, et al. Multicenter, prospective, randomized, single-blind study comparing the efficacy and gastrointestinal complications of early jejunal feeding with early gastric feeding in critically ill patients. *Critical Care Medicine*. 2002; 30: 796-800.
130. Heyland DK, Drover JW, MacDonald S, Novak F, Lam M. Effect of postpyloric feeding on gastroesophageal regurgitation and pulmonary microaspiration: Results of a randomized controlled trial. *Critical Care Medicine*. 2001; 29: 1495-1501.
131. Montecalvo MA, Steger KA, Farber HW, Smith BF, Dennis RC, Fitzpatrick GF, et al. Nutritional outcome and pneumonia in critical care patients randomized to gastric versus

- jejunal tube feedings. The Critical Care Research Team. *Critical Care Medicine*. 1992; 20: 1377-87.
132. Hsu C-W, Sun S-F, Lin S-L, Kang S-P, Chu K-A, Lin C-H, Huang H-H. Duodenal versus gastric feeding in medical intensive care unit patients: A prospective, randomized, clinical study. *Critical Care Medicine*. 2009; 37: 1866-72.
133. Metheny NA, Stewart BJ, McClave SA. Relationship between feeding tube site and respiratory outcomes. *Journal of Parenteral and Enteral Nutrition*. 2011; 35: 346-55.
134. Lucey BC, Gervais DA, Titton RL, O'Hare F, Hahn PF, Maher M, Mueller PR. Enteric feeding with gastric decompression: Management with separate gastric accesses. *American Journal of Roentgenology*. 2004; 183: 387-90.
135. Seidner DL. Preventing enteral tube feeding-associated aspiration: Something no one should get blue in the face over. *Nutrition in Clinical Practice*. 2002; 17: 140-1.
136. Chen Y-C, Chou S-S, Lin L-H, Wu L-F. The effect of intermittent nasogastric feeding on preventing aspiration pneumonia in ventilated critically ill patients. *Journal of Nursing Research*. 2006; 14: 167-79.
137. Bonten MJM, Gaillard CA, van der Hulst R, et al. Intermittent enteral feeding: The influence on respiratory and digestive tract colonization in mechanically ventilated intensive-care-unit patients. *American Journal of Respiratory and Critical Care Medicine*. 1996; 154: 394-9.
138. Bowling TE, Cliff B, Wright JW, Blackshaw PE, Perkins AC, Lobo DN. The effects of bolus and continuous nasogastric feeding on gastro-oesophageal reflux and gastric emptying in healthy volunteers: A randomized three-way crossover pilot study. *Clinical Nutrition*. 2008; 27: 608-13.
139. Shimoyama Y, Kusano M, Kawamura O, et al. High-viscosity liquid meal accelerates gastric emptying. *Neurogastroenterology Motility*. 2007; 19: 879-86.
140. Kanie J, Suzuki Y, Iguchi A, Akatsu H, Shimokata H. Prevention of gastroesophageal reflux using an application of half-solid nutrients in patients with percutaneous endoscopic gastrostomy feeding. Letters to the editor. *Journal of the American Geriatrics Society*. 2004; 52: 466-7.
141. Nishiwaki S, Araki H, Shirakami Y, et al. Inhibition of gastroesophageal reflux by semi-solid nutrients in patients with percutaneous endoscopic gastrostomy. *Journal of Parenteral and Enteral Nutrition*. 2009; 33: 513-9.
142. Adachi K, Furuta K, Morita T, et al. Half-solidification of nutrient does not decrease gastro-esophageal reflux events in patients fed via percutaneous endoscopic gastrostomy. *Clinical Nutrition*. 2009; 28: 648-51.

143. Tack J. Gastric motor and sensory function. *Current Opinion in Gastroenterology*. 2009; 25: 557-65.
144. Fraser RJL, Bryant L. Current and future therapeutic prokinetic therapy to improve enteral feed intolerance in the ICU patient. *Nutrition in Clinical Practice*. 2010; 25: 26-31.
145. Ohno T, Mochiki E, Kuwano H. The roles of motilin and ghrelin in gastrointestinal motility. *International Journal of Peptides*. 2010; 2010:1-6.
146. De Smet B, Mitselos A, Depoortere I. Motilin and ghrelin as prokinetic drug targets. *Pharmacology & Therapeutic*. 2009; 123: 207-23.
147. Ritz MA, Chapman MJ, Fraser RJ, Finnis ME, Butler RN, Cmielewski P, et al. Erythromycin dose of 70 mg accelerates gastric emptying as effectively as 200 mg in the critically ill. *Intensive Care Medicine*. 2005; 31: 949-54.
148. Nguyen NQ, Chapman MJ, Fraser RJ, Bryant LK, Holloway, RH. Erythromycin is more effective than metoclopramide in the treatment of feed intolerance in critical illness. *Critical Care Medicine*. 2007; 35: 483-9.
149. Nguyen NQ, Chapman M, Fraser RJ, Bryant LK, Burgstad C, Holloway RH. Prokinetic therapy for feed intolerance in critical illness: One drug or two? *Critical Care Medicine*. 2007; 35: 2561-67.
150. Sallam HS, Chen JDZ. The prokinetic face of ghrelin. *International Journal of Peptides*. 2010; 2010: 1-11.
151. Greenwood-Van Meerveld B, Kriegsman M, Nelson R. Ghrelin as a target for gastrointestinal motility disorders. *Peptides*. 2011; 32: 2352-6.
152. Crona D, MacLaren R. Gastrointestinal hormone concentrations associated with gastric feeding in critically ill patients. *Journal of Parenteral and Enteral Nutrition*. 2011; 28 July online: 1-8.
153. Dezfulian C, Shojania K, Collard HR, Kim M, Matthay MA, Saint S. Subglottic secretion drainage for preventing ventilator-associated pneumonia: a meta-analysis. *The American Journal of Medicine*. 2005; 118: 11-18.
154. Leasure AR, Stirlen J, Lu SH. Prevention of ventilator-associated pneumonia through aspiration of subglottic secretions: A systematic review and meta-analysis. *Dimensions of Critical Care Nursing*. 2012; 31: 102-117.
155. Xin Y, Dai N, Zhao L, Wang J-G, Si J-M. The effect of famotidine on gastroesophageal and duodenogastroesophageal refluxes in critically ill patients. *World Journal of Gastroenterology*. 2003; 9: 356-358.

156. Moreira TV, McQuiggan M. Methods for the assessment of gastric emptying in critically ill, enterally fed adults. *Nutrition in Clinical Practice*. 2009; 24: 261-273.
157. American Association of Critical Care Nurses. Dye in Enteral Feedings: Clinical practice alert. Available at <http://www.aacn.org/wd/practice/content/dye-enteral-feedings-practice-alert.pcms?menu=practice>. Accessibility verified May 2013.
158. Sanko JS. Aspiration assessment and prevention in critically ill enterally fed patients. *Gastroenterology Nursing*. 2004; 27: 279-285.
159. Meert KL, Daphtary KM, Metheny NA. Detection of pepsin and glucose in tracheal secretions as indicators of aspiration in mechanically ventilated children. *Pediatric Critical Care Medicine*. 2002; 3: 19-22.
160. Badellino M, Buckman RF, Malaspina PJ, Eynon CA, O'Brien GM, Kueppers F. Detection of pulmonary aspiration of gastric contents in an animal model by assay of peptic activity in bronchoalveolar fluid. *Critical Care Medicine*. 1996; 24: 1881-1885.
161. Ufberg JW, Bushra JS, Patel D, Wong E, Karras DJ, Kueppers F. A new pepsin assay to detect pulmonary aspiration of gastric contents among newly intubated patients. *American Journal of Emergency Medicine*. 2004; 22: 612-614.
162. Samuels TL, Johnston N. Pepsin as a marker of extraesophageal reflux. *Annals of Otolaryngology, Rhinology & Laryngology*. 2010; 119: 203-208.
163. Metheny NA, Chang Y-H, Ye JS, et al. Pepsin as a marker for pulmonary aspiration. *American Journal of Critical Care*. 2002; 11: 150-154.
164. Metheny NA, Dahms TE, Chang Y-H, Stewart BJ, Frank PA, Clouse RE. Detection of pepsin in tracheal secretions after forced small-volume aspirations of gastric juice. *Journal of Parenteral and Enteral Nutrition*. 2004; 28: 79-84.
165. Krishnan U, Mitchell JD, Messina I, Day AS, Bohane TD. Assay of tracheal pepsin as a marker of reflux aspiration. *Journal of Pediatric Gastroenterology and Nutrition*. 2002; 35: 303-308.
166. Neubert H, Gale J, Muirhead D. Online high-flow peptide immunoaffinity enrichment and nanoflow liquid chromatography/tandem mass spectrometry: Assay development for total salivary pepsin/pepsinogen. *Clinical Chemistry*. 2010; 56: 1-11.
167. Potluri S, Friedenber F, Parkman HP et al. Comparison of a salivary/sputum pepsin assay with 24-hr esophageal pH monitoring for detection of gastric reflux into the proximal esophagus, oropharynx, and lung. *Digestive Diseases and Sciences*. 2003; 48(9):1813-1817.

168. Kim TH, Lee KJ, Yeo M et al. Pepsin detection in the sputum/saliva for the diagnosis of gastroesophageal reflux disease in patients with clinically suspected atypical gastroesophageal reflux disease symptoms. *Digestion*. 2008; 77: 201-206.
169. Knight J, Lively MO, Johnston N, Dettmar PW, Koufman JA. Sensitive pepsin immunoassay for detection of laryngopharyngeal reflux. *Laryngoscope*. 2005; 115: 1473-1478.
170. Sole ML, Penoyer DA, Bennett M, Bertrand J, Talbert S. Oropharyngeal secretion volume in intubated patients: The importance of oral suctioning. *American Journal of Critical Care*. 2011; 20: 141-5.
171. DeKeyser FG, Pugh LC. Assessment of the reliability and validity of biochemical measures. *Nursing Research*. 1990; 39: 314-317.
172. Sessler CN, Gosnell MS, Grap MJ et al. The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit practice. *American Journal of Respiratory and Critical Care Medicine*. 2002; 166: 1338-1344.
173. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: Reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *Journal of the American Medical Association*. 2003; 289: 2983-2991.
174. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II; A severity of disease classification system. *Critical Care Medicine*. 1985; 13: 818-829.
175. Oh TE, Hutchinson R, Short S, Buckley T, Lin E, Leung D. Verification of the Acute Physiology and Chronic Health Evaluation scoring system in a Hong Kong intensive care unit. *Critical Care Medicine*. 1993; 21: 698-705.
176. Del Bufalo C, Morelli A, Bassein L, et al. Severity scores in respiratory intensive care: APACHE II predicted mortality better than SAPS II. *Respiratory Care*. 1995; 40: 1042-1047.
177. Beck DH, Taylor BL, Millar B, Smith GB. Prediction of outcome from intensive care: A prospective cohort study comparing Acute Physiology and Chronic Health Evaluation II and II prognostic systems in a United Kingdom intensive care unit. *Critical Care Medicine*. 1997; 25: 9-15.
178. Bergstrom, N., Braden, B.J., Laguzza, A., & Holman, V. The Braden scale for predicting pressure sore risk. *Nursing Research*. 1997; 36: 205-210.
179. World Health Organization. BMI Classification. http://apps.who.int/bmi/index.jsp?introPage=intro_3.html. Accessibility verified May 2013.

180. Sona CS, Zack JE, Schallom ME, et al. The impact of a simple, low-cost oral care protocol on ventilator-associated pneumonia rates in a surgical intensive care unit. *Journal of Intensive Care Medicine*. 2009; 24: 54-62.
181. Peridex Chlorhexidine gluconate mouthwash , Peridex (Chlorhexidine Gluconate 0.12% Oral Rinse).
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019028s020lbl.pdf.
Accessibility verified May 2013.
182. Grap MJ, Munro CL, Hummell RS, et al. Effect of backrest elevation on the development of ventilator-associated pneumonia. *American Journal of Critical Care*. 2005; 14:3 25-333.
183. Ballew C, Buffmire MV, Fisher C, et al. Factors associated with the level of backrest elevation in a thoracic cardiovascular intensive care unit. *American Journal of Critical Care*. 2011; 20: 395-399.
184. Hagsisawa S, Ferguson-Pell M. Evidence supporting the use of two-hourly turning for pressure ulcer prevention. *Journal of Tissue Viability*. 2000; 17: 76-81.
185. Peterson MJ, Schwab W, van Oostrom JH, Gravenstein N, Caruso LJ. Effects of turning on skin-bed interface pressures in healthy adults. *Journal of Advanced Nursing*. 2010; 66; 1556-1564.
186. McGuinness J, Persaud-Roberts S, Marra S, et al. How to reduce hospital-acquired pressure ulcers on a neuroscience unit with a skin and wound assessment team. *Surgical Neurology International*. 2012; 3: 138-142.
187. Still MD, Cross LC, Dunlap M, et al. The turn team: A novel strategy for reducing pressure ulcers in the surgical intensive care unit. *Journal of American College of Surgeons*. 2013; 216: 373-379.
188. Shahin ESM, Dassen T, Halfens RJG. Incidence, prevention and treatment of pressure ulcers in intensive care patients: A longitudinal study. *International Journal of Nursing Studies*. 2009; 46: 413-421.
189. Manzano F, Perez A-M, Colmenero M, et al. Comparison of alternating pressure mattresses and overlays for prevention of pressure ulcers in ventilated intensive care patients: a quasi-experimental study. *Journal of Advanced Nursing*. 2013, e-pub.
190. Silverwood S, Haddock M. Reduction of musculoskeletal injuries in intensive care nurses using ceiling-mounted patient lifts. *Dynamics*. 2006; 17: 19-21.
191. Chhokar R, Engst C, Miller A, et al. The three-year economic benefits of a ceiling lift intervention aimed to reduce healthcare worker injuries. *Applied Ergonomics*. 2005: 36; 223-229.

192. Alamgir H, Yu S, Fast C, et al. Efficiency of overhead ceiling lifts in reducing musculoskeletal injury among carers working in long-term care institutions. *Injury*. 2008; 39; 570-577.
193. Sole M, Mehta D, Bennett M, et al. Pepsin and salivary amylase in oral and tracheal secretions: A pilot study. *Critical Care Medicine*. 2012; 40 (12S); abstract 449.
194. Hughes TAT, Wiles CM. Palatal and pharyngeal reflexes in health and in motor neuron disease. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1996; 61: 96-98.
195. Saita N, Fukuda K, Koukita Y, et al. Relationship between gagging severity and its management in dentistry. *Journal of Oral Rehabilitation*. 2013; 40: 106-111.
196. Hoesch RE, Lin E, Young M. et al. Acute lung injury in critical neurological illness. *Critical Care Medicine*. 2012; 40: 587-593.
197. Reignier J, Mercier E, LeGoouge A, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical and early enteral feeding a randomized controlled trial. *Journal of the American Medical Association*. 2013; 309: 249-256.
198. Alhazzani W, Alenezi F, Jaeschke RZ, Moayyedi P, Cook DJ. Proton pump inhibitors versus histamine 2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: A systematic review and meta-analysis. *Critical Care Medicine*. 2013; 41: 693-705.
199. Oelschlager BK, Chang L, Pope CE, Pellegrini CA. Typical GERD symptoms and esophageal pH monitoring are not enough to diagnose pharyngeal reflux. *Journal of Surgical Research*. 2005; 128: 55-60.
200. Yuksel ES, Vaezi MF. New developments in extraesophageal reflux disease. *Gastroenterology & Hepatology*. 2012; 8: 590-599.
201. Kagawa R, Ikebe K, Enoki K, et al. Influence of hypertension on pH of saliva in older adults. *Oral Diseases*. 2012; doi:10.1111/odi.12043.
202. Muralidharan D, Fareed N, Pradeep PV, et al. Qualitative and quantitative changes in saliva among patients with thyroid dysfunction prior to and following the treatment of the dysfunction. *Oral Medicine*. 2013; 1-7 (in press).
203. Yuksel ES, Hong S-K S, Strugala V, et al. Rapid salivary pepsin test: Blinded assessment of test performance in gastroesophageal reflux disease. *Laryngoscope*. 2012; 122: 1312-1316.

204. Chow M CM, Kwok S-M, Luk H-W, et al. Effect of continuous oral suctioning on the development of ventilator-associated pneumonia: A pilot randomized controlled trial. *International Journal of Nursing Studies*. 2012.
205. Weiss CH, Moazed F, DiBardina D, et al. Bronchoalveolar lavage amylase is associated with risk factors for aspiration and predicts bacterial pneumonia. *Critical Care Medicine*. 2013; 41: 765-773.