Chapter 17. Prevention of Ventilator-Associated Pneumonia

Harold R Collard, MD
University of Colorado Health Sciences Center
Sanjay Saint, MD, MPH
University of Michigan School of Medicine

Introduction

Ventilator-associated pneumonia (VAP) is a leading cause of morbidity and mortality in the intensive care unit (ICU).[1] The incidence of VAP varies greatly, ranging from 6 to 52% of intubated patients depending on patient risk factors. The cumulative incidence is approximately 1-3% per day of intubation. Overall, VAP is associated with an attributable mortality of up to 30%. Attributable mortality approaches 50% when VAP is caused by the more virulent organisms that typify late-onset VAP (occurring 4 or more days into mechanical ventilation). The cost per episode of VAP is substantial, although specific data are lacking. The average cost per episode of nosocomial pneumonia is estimated at $3000 to $6000, and the additional length of stay for patients who develop VAP is estimated at 13 days.[1,2]

VAP is typically categorized as either early-onset VAP (occurring in the first 3-4 days of mechanical ventilation) or late-onset VAP. This distinction is important microbiologically. Early-onset VAP is commonly caused by antibiotic-sensitive community-acquired organisms (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus*). Late-onset VAP is commonly caused by antibiotic-resistant nosocomial organisms (eg, *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, *Acinetobacter* species, and *Enterobacter* species). Most episodes of ventilator-associated pneumonia (VAP) are thought to develop from the aspiration of oropharyngeal secretions containing potentially pathogenic organisms. Aspiration of gastric secretions may also contribute, though likely to a lesser degree. Tracheal intubation interrupts the body's anatomic and physiologic defenses against aspiration, making mechanical ventilation a major risk factor for VAP.

This chapter reviews 4 practices that carry the potential to reduce the incidence of VAP in patients receiving mechanical ventilation. They are: variation in patient positioning, continuous aspiration of subglottic secretions, selective digestive tract decontamination, and the use of sucralfate.

Subchapter 17.1. Patient Positioning: Semi-recumbent Positioning and Continuous Oscillation

Background

Aspiration of gastric secretions likely contributes to the development of VAP.[1] Semi-recumbent positioning of mechanically ventilated patients may help reduce the incidence of gastroesophogeal reflux and lead to a decreased incidence of VAP. Immobility in critically ill patients leads to atelectasis and decreased clearance of bronchopulmonary secretions. Both of these sequelae may lead to increased risk of VAP. Continuous rotation and movement of critically ill patients (termed continuous oscillation) may thus help prevent such changes.

<u>Semi-recumbent positioning</u>

Practice Description

Semi-recumbent positioning is generally defined as elevation of the head of the bed to 45 degrees. This is generally achieved in a hospital bed with patients' feet remaining parallel to the floor (ie, the entire bed is not tilted) but this is not explicitly described in the published trials. Semi-recumbency is generally continued for the duration of mechanical ventilation.

Opportunities for Impact

Outside of select medical centers that have studied this practice, semi-recumbent positioning has not been widely adopted as the standard of care. Thus, such an intervention would have enormous opportunity for impact should it prove beneficial.

Study Designs

There have been three trials of semi-recumbent patient positioning and its effect on the incidence of VAP.[3-5] Two of these studies measured aspiration events using nuclear medicine techniques, the other was a randomized trial with the primary outcome being VAP. In the one randomized trial, 86 patients were randomized at the time of intubation to semi-recumbent body position (45 degrees) or supine body position (0 degrees).[3] All patients received the same general critical care (eg, sterile endotracheal suctioning, stress ulcer prophylaxis with sucralfate if tolerating oral medications, no ventilator tubing changes, no selective digestive tract decontamination).

Study Outcomes

In the one randomized clinical trial, VAP was clinically defined as a new and persistent infiltrate on chest radiography, plus two of the following: temperature of >38.3C, leukocyte count >12,000/mm^3 or <4000/mm^3, purulent tracheal secretions.[3] Microbiologic confirmation required the above criteria be met and the isolation of pathogenic bacteria from an endotracheal aspirate or bronchoscopic procedure. Mortality was reported at time of discharge from the ICU. Both studies of the frequency of aspiration measured radioisotope counts (counts per minute) of endotracheal aspirates at various time points before during and after semi-recumbent positioning.[4,5]

Evidence for Effectiveness of the Practice

Only one randomized clinical trial of semi-recumbent patient positioning in mechanically ventilated patients has been published to date (see Table17.1.1). Semi-recumbent positioning was associated with a statistically significant reduction in both clinically and microbiologically-diagnosed VAP.[3] There was no significant difference in mortality. These findings corroborate earlier studies that demonstrated decreased frequency of gastroesophogeal reflux with semi-recumbent positioning,[4,5] and an independent association of supine positioning with the development of VAP.[6]

Potential for Harm

No adverse effects were observed in patients randomized to semi-recumbent positioning.[3] However, patients were excluded if they had any of the following conditions: recent abdominal or neurologic surgery (<7 days), shock refractory to vasoactive therapy, and previous recent endotracheal intubation (<30 days).

Costs and Implementation

The cost of semi-recumbent positioning is negligible and implementation is simple but will require health care provider education.

<u>Continuous oscillation</u>

Practice Description

Continuous oscillation utilizes mechanical beds that employ either rotating platforms or alternating inflation/deflation of mattress compartments to turn patients from side to side. These beds achieve 40 to 60 degrees of tilt and can cycle every 5-30 minutes as programmed. In general, in published trials, continuous oscillation was started within 24 hours of admission to the ICU and continued until discharge.

Opportunities for Impact

Continuous oscillation is infrequently applied to critically ill patients. Thus, this intervention would have significant opportunity for impact should it prove beneficial.

Study Designs

A meta-analysis of six randomized controlled trials evaluated the effect of continuous oscillation on clinical outcomes, including pneumonia, in critically ill patients.[7] The vast majority of patients were mechanically ventilated but the absolute percentage is not reported in most trials. Five of the six trials included were limited to surgical and/or neurologic patients. A subsequent randomized controlled trial included 103 medical and surgical patients.[8] In most cases, continuous oscillation was compared to standard critical care practice of rolling patients every two hours.

Study Outcomes

The definition of VAP varied among trials but was generally clinical and required a new infiltrate on chest radiography, fever, and leukocytosis. Microbiologic confirmation was not consistently obtained. Mortality was recorded at time of ICU discharge.

Evidence for Effectiveness of the Practice

The role of continuous oscillation in the prevention of VAP is unclear (see Table 17.1.1). A meta-analysis of six randomized controlled trials on this subject found a statistically significant reduction in the risk of pneumonia.[7] Five of these studies were limited to surgical and/or neurologic patients. The sixth study, which included primarily medical patients, failed to find any significant effect.[9] A subsequent randomized controlled trial of medical and surgical patients also failed to find any benefit.[8]

Potential for Harm

There were no significant risks of continuous oscillation in any of the randomized trials. Inadvertent disconnection of intravenous lines, increased ventricular ectopy, and patient intolerance were reported, but not quantified. Conscious patients tolerated the procedure poorly.

Costs and Implementation

The incremental cost of specialized beds capable of continuous oscillation has been estimated at approximately $100 per day.[9] A significant reduction in VAP incidence and length of stay could result in cost savings.

Comment

Both semi-recumbent positioning and continuous oscillation are relatively low-cost, low-risk interventions. The one randomized trial to date of semi-recumbent positioning shows it to be an effective method of reducing VAP. While it has not proven to provide a mortality benefit, semi-recumbent positioning is a safe and straightforward intervention whose effectiveness should be confirmed by additional randomized clinical trials. Continuous oscillation is less clearly beneficial, although it may be effective in certain subgroups of patients (eg, surgical, neurologic). It also deserves continued study.

Table 17.1.1. Patient positioning*

Study Design	Study Design, Outcomes	Pneumonia or Aspiration	Mortality
Semi-recumbent positioning			
Randomized controlled trial of semi-recumbent patient positioning in 86 mechanically ventilated patients. Primary outcome was VAP. (Drakulovic, 1999)[3]	Level 1, Level 1	RR 0.24 (p=0.003)	RR 0.64 (p=0.289)
Two-period crossover trial of semi-recumbent patient positioning in 15 mechanically ventilated patients. Primary outcome was pulmonary aspiration. (Orozco-Levi, 1995)[4]	Level 3, Level 2	RR 0.65 (p<0.01)	–
Randomized two-period crossover trial of semi-recumbent patient positioning in 15 mechanically ventilated patients. Primary outcome was pulmonary aspiration. (Torres, 1992)[5]	Level 3, Level 2	RR 0.23 (p=0.036)	–
Continuous oscillation			
Randomized controlled trial of continuous oscillation in 103 critically ill medical and surgical patients (90% mechanically ventilated). Primary outcomes included pneumonia. (Traver, 1995)[8]	Level 1, Level 1	RR 0.62 (p=0.21)	RR 0.85 (p>0.05)
Meta-analysis of 6 randomized controlled trials of continuous oscillation in critically ill surgical or stroke patients (majority mechanically ventilated). (Choi, 1992)[7]	Level 1A, Level 1	RR 0.50 (p=0.002)	No significant difference (data not reported)
Randomized controlled trial of continuous oscillation in 86 critically ill medical patients (majority mechanically ventilated). Primary outcomes included pneumonia. (Summer, 1989)[9]	Level 1, Level 1	RR 0.57 (p=0.40)	RR 0.93 (p>0.05)

* RR indicates relative risk; VAP, ventilator-associated pneumonia.

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Subchapter 17.2. Continuous Aspiration of Subglottic Secretions

Background

Ventilator-associated pneumonia (VAP) frequently develops from the aspiration of oropharyngeal secretions containing potentially pathogenic organisms.[1] Tracheal intubation interrupts the body's anatomic and physiologic defenses against aspiration, making mechanical ventilation a major risk factor for VAP. The accumulation of contaminated oropharyngeal secretions above the endotracheal tube cuff may contribute to the risk of aspiration.[1] Removal of these pooled secretions through suctioning of the subglottic region, termed continuous aspiration of subglottic secretions (CASS), may reduce the risk of developing VAP.

Practice Description

Continuous aspiration of subglottic secretions requires intubation with specially designed endotracheal tubes (see Figure 17.2.1). These endotracheal tubes contain a separate dorsal lumen that opens into the subglottic region, allowing for aspiration of any pooled secretions. The amount of secretions is monitored (usually daily) and the patency of the suction lumen is tested frequently (every few hours). In studies of the impact of this practice, aspiration has been applied from time of intubation to time of extubation. One of the studies tested manual aspiration performed hourly instead of continuous mechanical aspiration.[2]

Opportunities for Impact

Continuous aspiration of subglottic secretions is an uncommon practice. The opportunities for impact are therefore significant should this practice prove beneficial in lowering rates of VAP.

Study Designs

There have been three randomized controlled trials of CASS to date.[2-4] (Table 17.2.1) Two have included both medical and surgical patients requiring mechanical ventilation for greater than 72 hours and one included only post-cardiac surgery patients. All three studies randomized patients to CASS or standard care. Attempts were made to control for additional, potentially effective preventive strategies such as patient positioning, frequency of ventilator circuit changes, type of stress ulcer prophylaxis used, and administration of antibiotics.

Study Outcomes

All trials reported development of VAP and mortality at the time of extubation, ICU or hospital discharge. VAP was generally defined as a new radiographic infiltrate plus two of the following: fever, leukocytosis/leukopenia, or purulent tracheal aspirate. Microbiologic confirmation was not consistently obtained. Time to development of VAP was also reported. Mortality was reported at time of discharge from the hospital.

Evidence for Effectiveness of the Practice

One of the three trials found a statistically significant decrease in the incidence of VAP with CASS when compared to standard treatment, while a second study showed a strong trend (See Table 17.2.1).[2,3] All three trials reported a statistically significant delay in the time to development of VAP, ranging from 48 hours to 8 days. Two trials found a decreased incidence of VAP caused by *Staphylococcus aureus* and *Hemophilus influenzae*, but no change was observed in the incidence of VAP caused by *Pseudomonas aeruginosa* or *Enterobacteriaceae*.[3,4] No difference in mortality was observed in any of the trials.

Potential for Harm

There is minimal potential for harm to patients from the application of CASS and no adverse patient events were reported in over 150 patients.[4]

Costs and Implementation

The cost and cost-effectiveness of CASS have not been examined. The direct costs appear minimal. Hi-Lo Evac tubes cost approximately 25% more than standard endotracheal tubes, putting the estimated cost of each unit at less than $1.[2] The cost-savings per episode of VAP prevented could therefore be substantial. Implementation would largely be a matter of making the specialized endotracheal tubes available and providing staff training. The mechanical suctioning apparatus would require frequent monitoring by nursing or respiratory therapy to insure adequate function.

Comment

Continuous aspiration of subglottic secretions is a promising strategy for the prevention of VAP. Two randomized controlled trials have suggested a decrease in the rate of VAP in patients requiring prolonged (>3 days) mechanical ventilation (only one trial was statistically

significant). The third trial showed no difference, but the patient population in this trial included many short-term intubations (mean duration of 36 hours) and was restricted to patients undergoing cardiac surgery. Larger randomized controlled trials are needed to address the impact of CASS more definitively.

Another interesting observation is the delay in the development of VAP and the decreased incidence of *Staphylococcus aureus* and *Hemophilus influenzae*. This suggests that CASS may provide most of its benefit by preventing early VAP caused by community-acquired organisms, and its use could therefore be targeted to those patients requiring mechanical ventilation for intermediate periods of time (ie, those at greatest risk for early VAP).

Figure 17.2.1. Diagram of continuous aspiration of subglottic secretions (copied with permission)[3]
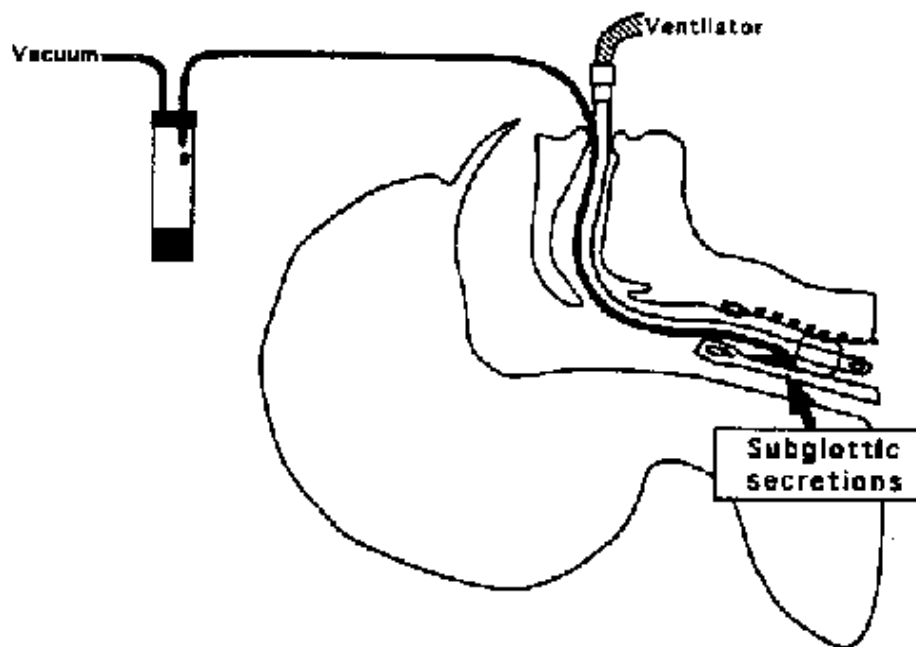
Table 17.2.1. Randomized trials of continuous aspiration of subglottic secretions*

Study Description	Study Outcomes	Relative Risk of Pneumonia (95% CI)	Relative Risk of Mortality (95% CI)
Kollef, 1999[4]: 343 patients undergoing cardiac surgery and requiring mechanical ventilation	Level 1	0.61 (0.27-1.40)	0.86 (0.30-2.42)
Valles, 1995[3]: 153 patients requiring prolonged mechanical ventilation	Level 1	0.47 (0.21-1.06)	1.09 (0.72-1.63)
Mahul, 1992[2]: 145 patients requiring mechanical ventilation for more than 3 days	Level 1	0.46 (0.23-0.93)	1.14 (0.62-2.07)

* CI indicates confidence interval.

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Subchapter 17.3. Selective Digestive Tract Decontamination

Background

Selective digestive tract decontamination (SDD) involves the use of non-absorbable antibiotics topically applied to the gastrointestinal tract in an effort to sterilize the oropharynx and stomach. The goal is to decrease the pathogenicity of aspirated secretions and thereby reduce the incidence of VAP.

Practice Description

Most studies have used a combination of topical polymixin, tobramycin or gentamicin, and amphotericin applied to the oropharynx (by hand) and the stomach (by nasogastric tube).[1] About half of the studies also included a short (3-4 day) course of systemic intravenous antimicrobial therapy, most commonly ceftriaxone. In general, topical antibiotics were applied several times daily from the time of intubation until extubation (or shortly thereafter).

Opportunities for Impact

SDD is not widely used in the United States.[1] The Centers for Disease Control and Prevention and the American Thoracic Society's guidelines published in the 1990s do not recommend its routine use.[2,3] Given the frequency and morbidity of VAP, if the practice is beneficial substantial opportunity for patient safety enhancement exists.

Study Designs

There have been over 30 randomized controlled trials and seven meta-analyses of SDD (see Table 17.3.1).[4-10] A representative meta-analysis identified 33 randomized trials of SDD using a structured search of the literature that met the authors' methodologic inclusion criteria: measurement of clinical outcomes (including VAP and mortality), inclusion of unselected patient populations, and mechanical ventilation in at least half of patients.[1] As with several of the other meta-analyses, individual trials in this particular meta-analysis were grouped into those that used topical antibiotics only and those that used topical and systemic antibiotics. This meta-analysis was unique in that the investigators obtained individual patient data for the majority of patients (4343 (76%) of the 5727 patients involved).[1]

Study Outcomes

All meta-analyses reported risk of VAP and mortality at hospital or ICU discharge. Individual study outcomes also included number of days intubated, length of ICU stay, duration of antibiotic therapy, time to onset of VAP, and cost. Several meta-analyses performed subgroup analysis to assess the importance of statistical methods (eg, quality of randomization, blinding, VAP definition) and clinical factors (eg, Acute Physiology and Chronic Health Evaluation (APACHE) score).

Evidence for Effectiveness of the Practice

All seven meta-analyses report substantial reduction in the risk of VAP with the use of SDD (see Table 17.3.1). Four of seven meta-analyses report a statistically significant reduction in mortality.[4-6,8] Four of seven meta-analyses separately analyzed trials using topical antibiotics only and those using topical and systemic antibiotics.[4,6,8,9] All four revealed a statistically significant mortality benefit with combined topical and systemic prophylaxis and no mortality benefit with topical prophylaxis alone.[1,6,8,9] However, these four meta-analyses did reveal a significant decrease in VAP incidence in those given topical antibiotics only compared to the placebo group.[4,6,8,9] Several of the meta-analyses included subgroup analyses to assess the benefit of SDD in patients categorized by type of illness (surgical, medical) and severity of illness (APACHE score), with conflicting results.[4,6]

Potential for Harm

There were no significant adverse events reported in most trials, although allergic reactions to the antibiotic preparations have been uncommonly noted. The primary long-term concern with the widespread use of SDD is the development of antibiotic resistance.[11-13] The data are unclear regarding the impact of SDD on the emergence of resistant organisms, and no study has demonstrated an impact of increased bacterial resistance on morbidity or mortality.

Costs and Implementation

The cost of implementing SDD appears minimal in most trials, but there have been no in depth reviews of the subject. Several trials have found that patients receiving SDD had lower

total antibiotic costs.[14-16] Overall hospital costs also may be lower, mediated through the decreased rate of VAP.[17]

Comment

SDD is a very promising method of reducing VAP and ICU-related mortality. The data supporting a significant reduction in risk of VAP and short-term mortality with SDD using topical and short-term intravenous antibiotics are strong. SDD is a relatively non-invasive intervention and the additional financial cost is minimal. What remains to be determined is the long-term effect of SDD on antibiotic resistance patterns, and the impact of such effect on morbidity and mortality. Research into the impact of SDD on the emergence of antibiotic resistance should be strongly encouraged.

Table 17.3.1. Meta-analyses of selective digestive tract decontamination*

Study Design	Pneumonia (95% CI)	Mortality (95% CI)
Nathens, 1999[6]: 21 randomized controlled trials of antibiotic prophylaxis used to decrease nosocomial respiratory tract infections; dual analysis of medical and surgical patients	Medical: OR 0.45 (0.33-0.62) Surgical: OR 0.19 (0.15-0.26)	Medical Overall: OR 0.91 (0.71-1.18) Topical/IV: OR 0.75 (0.53-1.06) Topical: OR 1.14 (0.77-1.68) Surgical Overall: OR 0.70 (0.52-0.93) Topical/IV: OR 0.60 (0.41-0.88) Topical: OR 0.86 (0.51-1.45)
D'Amico, 1998[1]: 33 randomized controlled trials from of antibiotic prophylaxis used to decrease nosocomial respiratory tract infections; dual analysis of topical and systemic antibiotics combined and topical antibiotics alone	Overall: not reported Topical/IV: OR 0.35 (0.29-0.41) Topical: OR 0.56 (0.46-0.68)	Overall: OR 0.88 (0.78-0.98) Topical/IV: OR 0.80 (0.69-0.93) Topical: OR 1.01 (0.84-1.22)
Hurley, 1995[5]: 26 randomized controlled trials of antibiotic prophylaxis used to decrease nosocomial respiratory tract infections	Overall: OR 0.35 (0.30-0.42)	Overall: OR 0.86 (0.74-0.99)
Kollef, 1994[7]: 16 randomized controlled trials of antibiotic prophylaxis used to decrease nosocomial respiratory tract infections	Overall: RD 0.145 (0.116-0.174)	Overall: RD 0.019 (-0.016-0.054)
Heyland, 1994[8]: 25 randomized controlled trials of antibiotic prophylaxis used to decrease nosocomial respiratory tract infections; performed subgroup analyses	Overall: RR 0.46 (0.39-0.56) Topical/IV: RR 0.48 (0.39-0.60) Topical: RR 0.43 (0.32-0.59)	Overall: RR 0.87 (0.79-0.97) Topical/IV: RR 0.81 (0.71-0.95) Topical: RR 1.00 (0.83-1.19)
SDD Trialists' Collaborative Group, 1993[9]: 22 randomized controlled trials of antibiotic prophylaxis used to decrease nosocomial respiratory tract infections; performed subgroup analyses	Overall: OR 0.37 (0.31-0.43) Topical/IV: OR 0.33 (0.27-0.40) Topical: OR 0.43 (0.33-0.56)	Overall: OR 0.90 (0.79-1.04) Topical/IV: OR 0.80 (0.67-0.97) Topical: OR 1.07 (0.86-1.32)
Vandenbroucke-Grauls, 1991[10]: 6 randomized controlled trials of antibiotic prophylaxis used to decrease nosocomial respiratory tract infections	Overall: OR 0.12 (0.08-0.19)	Overall: OR 0.70 (0.45-1.09)

* CI indicates confidence interval; RD, risk difference, RR, relative risk; and OR, odds ratio.

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Subchapter 17.4. Sucralfate and Prevention of VAP

Background

Aspiration of gastric secretions may contribute to the development of VAP. It has been observed that gastric colonization by potentially pathogenic organisms increases with decreasing gastric acidity, leading to the hypothesis that pH-altering drugs may cause increased rates of VAP.[1] H_2-antagonist therapy, widely used in mechanically-ventilated patients for stress ulcer prophylaxis (see Chapter 34), significantly elevates gastric pH. Sucralfate, an alternative prophylactic agent that does not affect gastric pH, may allow less gastric colonization with potentially pathogenic organisms than H_2-antagonists and therefore prevent some cases of VAP.

Practice Description

In general, 1 g of sucralfate suspension is given through a nasogastric tube every four to six hours. When H_2-antagonists are used, their dosing and frequency vary. A representative study used 50 mg of ranitidine intravenously every eight hours, dose adjusted for creatinine clearance.[2] Stress ulcer prophylaxis is usually started upon initiation of mechanical ventilation and continued until extubation (Chapter 34).

Opportunities for Impact

Stress ulcer prophylaxis is usually given to critically ill ventilated patients. A large cohort study of over 2000 critically ill patients suggests that the majority receive H_2-antagonists (71.8%) followed by sucralfate (7.0%) and combination therapy (15.4%) or other single agents (omeprazole, antacids, prostaglandins).[3] There is, therefore, significant opportunity for impact should sucralfate prove to lower rates of VAP and improve survival.

Study Designs

There have been over 20 randomized controlled trials of stress ulcer prophylaxis using sucralfate, H_2-antagonists, and other therapies in critically ill patients. Seven meta-analyses have been published to date.[2,4-10] The individual trials and meta-analyses have significant variation in methodology. In general, the individual trials randomized critically ill patients to sucralfate, H_2-antagonists, other agents such as antacids and pirenzepine, or placebo. The majority of patients included in these studies required mechanical ventilation. Various drug-drug, drug-placebo combinations were compared, and the rates of VAP and mortality were recorded.

Study Outcomes

Most trials report development of VAP and mortality as primary endpoints. There is significant variation in the definition of VAP used in these trials. In the largest and most recent randomized trial, VAP was defined as a new radiographic infiltrate plus two of the following: temperature of >38.5°C or <35.0°C, leukocyte count >10,000/mm^3 or <3000/mm^3, purulent sputum, and isolation of pathogenic bacterial from an endotracheal aspirate.[8] Mortality was reported at time of discharge from the ICU.

Evidence for Effectiveness of the Practice

The results of the seven meta-analyses and one recent large randomized controlled trial are inconclusive (see Table 17.4.1). The two largest meta-analyses to date suggest a decreased incidence of VAP with sucralfate compared to H_2-antagonists,[4,6] and one reports a statistically significant mortality benefit with sucralfate.[6] A recent randomized controlled trial of 1200 ventilated patients reports no significant difference between the two therapies in terms of VAP or mortality.[8]

Potential for Harm

Sucralfate therapy has been associated with a statistically significant increased risk of clinically important gastrointestinal bleeding when compared to H_2-antagonists.[8] Clinically important bleeding developed in 3.8% of patients receiving sucralfate compared with 1.7% of patients receiving H_2-antagonists (relative risk for H_2-antagonist = 0.44, 95% CI: 0.21-0.92).[8] Gastrointestinal bleeding in critically ill patients has an attributable mortality of approximately 12.5%.[8] While previous meta-analyses have suggested little difference in rates of gastrointestinal bleeding between the various prophylactic agents,[6] these results from a large randomized trial are convincing. There are very few adverse effects from sucralfate therapy aside from constipation, rare nausea and vomiting and very rare bezoar formation and aluminum intoxication.[11] Sucralfate administration has been associated with transmission of vancomycin resistant enterococcus, likely due to increased manipulation of patients' nasogastric tubes.[12] Unlike parenteral H_2-blockers, sucralfate mandates nasogastric tube placement in intubated patients. The drug can also lead to decreased absorption of other medications.

Costs and Implementation

Several studies have looked at the cost-effectiveness of stress ulcer prophylaxis.[13,14] Based on decision analysis, the cost per episode of gastrointestinal bleeding averted in high-risk patients is several thousand dollars greater with H_2-antagonists than with sucralfate.[13] This cost difference remains significant even if H_2-antagonists are assumed to be 50% more effective. There are no reliable data comparing overall costs from the actual clinical trials. The mean cost, largely driven by prolonged length of stay, is significantly higher for patients who bleed than for those who do not ($70,000 vs. $15-20,000), implying that in patients at high risk for GI bleeding (eg, mechanically ventilated patients, those with a coagulopathy), stress ulcer prophylaxis may be cost-neutral or even cost-saving (see also Chapter 34).[14] Implementation of sucralfate use would be largely an issue of staff education as administration is relatively uncomplicated.

Comment

The data supporting stress ulcer prophylaxis with sucralfate instead of H_2-antagonists to prevent VAP are inconclusive, and the theoretical contribution of increased gastric colonization with potentially pathogenic organisms to the development of VAP is unproven. There are data both supporting and refuting a decreased incidence of VAP with sucralfate. Most investigators have found at least a trend toward decreased incidence of VAP with sucralfate, and larger studies are warranted. The greatest benefit from sucralfate may be the prevention of late-onset VAP in patients requiring long-term ventilation.[15] Any increased risk of gastrointestinal bleeding with sucralfate therapy in these patients may be offset by the decreased risk of VAP. Until the data are more definitive, however, when stress ulcer prophylaxis is deemed appropriate (Chapter 34), the

use of H$_2$-blockers seems preferable to sucralfate because of the former's superiority in preventing clinically important gastrointestinal bleeding.

Table 17.4.1. Studies of stress ulcer prophylaxis

Study Design	Design, Outcomes	Pneumonia* (95% CI)	Mortality* (95% CI)
Meta-analysis of randomized controlled trials comparing ranitidine with placebo, sucralfate with placebo and ranitidine with sucralfate for the prevention of pneumonia in critically ill patients. (Messori, 2000)	Level 1A, Level 1	ranitidine vs. sucralfate: 1.35 (1.07-1.70) ranitidine vs. placebo: 0.98 (0.56-1.72) sucralfate vs. placebo: 2.21 (0.86-5.65)	not reported
Multicenter randomized, blinded, placebo-controlled trial of sucralfate with ranitidine in 1200 critically ill mechanically ventilated patients. Endpoints were gastrointestinal bleeding, VAP and mortality. (Cook, 1998)	Level 1, Level 1	ranitidine vs. sucralfate: 1.18 (0.92-1.51)	ranitidine vs. sucralfate: 1.03 (0.84-1.26)
27 randomized trials of stress ulcer prophylaxis in critically ill patients. The majority of patients were mechanically ventilated. Endpoints were gastrointestinal bleeding, pneumonia and mortality. (Cook, 1996)	Level 1A, Level 1	sucralfate vs. H_2-antagonist: 0.77 (0.60-1.01) H_2-antagonist vs. placebo: 1.25 (0.78-2.00)	sucralfate vs. H_2-antagonist: 0.73 (0.54-0.97)
14 randomized trials of stress ulcer prophylaxis in critically ill patients. (Tryba, 1995)	Level 1A, Level 1	sucralfate vs. H_2-antagonist/ antacid: 0.67 (p<0.05)	not reported
6 (outcome VAP) and 7 (outcome mortality) randomized trials of stress ulcer prophylaxis in critically ill patients. (Cook, 1995)	Level 1A, Level 1	sucralfate vs. H_2-antagonist/ antacid: 0.50 (0.21-0.79)	sucralfate vs. H_2-antagonist: 0.71 (0.49-1.04) sucralfate vs. antacid: 0.70 (0.52-0.94)
14 randomized trials of stress ulcer prophylaxis in critically ill patients. Endpoints were gastrointestinal bleeding and pneumonia. (Tryba. 1991)	Level 1A, Level 1	sucralfate vs. H_2-antagonist: 0.50 (0.32-0.78) sucralfate vs. antacid: 0.40 (0.24-0.69)	sucralfate vs. H_2-antagonist/ antacid: 0.81 (NA)

Table 17.4.1. Studies of stress ulcer prophylaxis (cont.)

9 randomized trials of stress ulcer prophylaxis in critically ill patients. (Tryba, 1991)	Level 1A, Level 1	sucralfate vs. H_2-antagonist/ antacid: 0.48 (p<0.05)	sucralfate vs. H_2-antagonist/ antacid: 0.72 (p<0.05)
8 randomized trials of stress ulcer prophylaxis in critically ill patients studying the rate of pneumonia with different drug regimens. (Cook, 1991)	Level 1A, Level 1	sucralfate vs. H_2-antagonist/ antacid: 0.55 (0.28-1.06) H_2-antagonist/antacid vs. placebo: 0.42 (0.17-1.11)	not reported

* Point estimates reflect odds ratio or relative risk.

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Final Comment to Chapter 17

Ventilator-associated pneumonia is common, costly, and morbid. This chapter confirms that there are several low-risk interventions that carry the potential to reduce the frequency of this complication. Further research will be needed to confirm the benefit of promising practices (eg, semi-recumbency or continuous aspiration of subglottic secretions) or fully allay concerns regarding practices that have potential for harm (eg, antibiotic resistance with selective decontamination).