Nosocomial Pneumonia in Mechanically Ventilated Patients Receiving Antacid, Ranitidine, or Sucralfate as Prophylaxis for Stress Ulcer

A Randomized Controlled Trial

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Objective: To assess three anti-stress ulcer prophylaxis regimens in mechanically ventilated patients for bacterial colonization, early- and late-onset nosocomial pneumonia, and gastrointestinal bleeding.

Design: Randomized controlled trial.

Patients: Consecutive eligible patients with mechanical ventilation and a nasogastric tube. Of 258 eligible patients, 244 were assessable.

Setting: Medical and surgical intensive care units.

Intervention: At intubation, patients were randomly assigned to receive one of the following: antacid (a suspension of aluminum hydroxide and magnesium hydroxide), 20 mL every 2 hours; ranitidine, 150 mg as a continuous intravenous infusion; or sucralfate, 1 g every 4 hours.

Measurements: Using predetermined criteria, the incidence of gastric bleeding, gastric colonization, early-onset pneumonia, and late-onset pneumonia was assessed in patients intubated for more than 24 hours.

Results: Of 244 assessable patients, macroscopic gastric bleeding was observed in 10%, 4%, and 6% of patients assigned to receive sucralfate, antacid, and ranitidine, respectively (P > 0.2). The incidence of early-onset pneumonia was not statistically different among the three treatment groups (P > 0.2). The incidence of late-onset pneumonia was not statistically different among the three treatment groups (P > 0.2). Among the 213 patients observed for more than 4 days, late-onset pneumonia was observed in 5% of the patients who received sucralfate compared with 16% and 21% of the patients who received antacid or ranitidine, respectively (P = 0.022). Mortality was not statistically different among the three treatment groups. Patients who received sucralfate had a lower median gastric pH (P < 0.001) and less frequent gastric colonization compared with the other groups (P = 0.015). Using molecular typing, 84% of the patients with late-onset gram-negative bacillary pneumonia were found to have gastric colonization with the same bacteria before pneumonia developed.

Conclusion: Stress ulcer prophylaxis with sucralfate reduces the risk for late-onset pneumonia in ventilated patients compared with antacid or ranitidine.


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Intensive care patients are at risk for bleeding from stress ulcers of the upper gastrointestinal tract (1). Despite the decline of this complication over the last two decades (2), certain patients, such as those requiring prolonged mechanical ventilation, remain at high risk and may benefit from stress ulcer prophylaxis (1, 3-5).

Over the last few years, studies have shown that agents that raise the gastric pH may promote proliferation of bacteria in the stomach, particularly gram-negative bacilli that may originate in the duodenum (6-10). Passive esophageal reflux and microaspiration of the gastric content along the endotracheal tube may lead to the colonization of the trachea and then to pneumonia (6, 7, 10-18). Thus, concerns have arisen that the risk for nosocomial pneumonia may outweigh the benefit of stress ulcer prophylaxis when agents raising the gastric pH are used.

Scuralfate is a complex salt of sucrose sulfate and aluminum hydroxide that appears to be as effective as antacids or histamine-2 (H2) antagonists for stress ulcer prophylaxis (2, 19, 20) but by mechanisms of action that do not result in clinically relevant gastric pH modification. Several studies have documented that gastric colonization is less frequent and of a lesser magnitude in ventilated patients treated with this agent compared with antacids or H2-antagonists (8, 21-23). However, whether this would result in a decreased risk for nosocomial pneumonia is controversial (18, 24) because a reduction was found in some (21-23, 25) but not all (17, 21-23, 25-29) comparative studies. Methodologic differences among these studies might explain these conflicting findings (18). For example, small numbers of patients for analysis (17, 26), low risk for pneumonia in the study patients (27, 28), periods of observation that were too brief (28), insufficient dosages of the agents that raise pH (27, 29), and wide use of enteral feeding (17) might account for the absence of reduction in the incidence of pneumonia noted in some studies. On the other hand, differences in the distribution of the baseline characteristics among the patients (22, 23), the grouping of patients receiving antacids and H2-antagonists, and analysis of subgroups of patients not randomly assigned to a treatment group (21, 25) may have biased the studies in which sucralfate was associated with lower rates of pneumonia. In addition, in two of these latter studies, the reduction of pneumonia devel-
Table 1. Characteristics of Study Patients*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Antacid (n = 81)</th>
<th>Ranitidine (n = 80)</th>
<th>Sucralfate (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>26/55</td>
<td>26/54</td>
<td>27/56</td>
</tr>
<tr>
<td>Age, y</td>
<td>46 ± 17.9†</td>
<td>52.2 ± 18.1</td>
<td>46.4 ± 17.5</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>17.4 ± 9.2</td>
<td>16.8 ± 8.6</td>
<td>17.2 ± 8.6</td>
</tr>
<tr>
<td>Glasgow score</td>
<td>9.5 ± 5.4</td>
<td>9.4 ± 5.2</td>
<td>9.2 ± 5.2</td>
</tr>
<tr>
<td>Admitted from community, n (%)</td>
<td>52 (64)</td>
<td>49 (61)</td>
<td>59 (71)</td>
</tr>
<tr>
<td>Received antibiotic therapy, n (%)</td>
<td>22 (27)</td>
<td>18 (23)</td>
<td>15 (18)</td>
</tr>
<tr>
<td>With bronchoaspiration before or during intubation, n (%)</td>
<td>13 (16)</td>
<td>14 (18)</td>
<td>14 (17)</td>
</tr>
<tr>
<td>With tracheostomy, n (%)</td>
<td>1 (1)</td>
<td>3 (4)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>In surgical ICU, n (%)</td>
<td>44 (54)</td>
<td>41 (51)</td>
<td>46 (55)</td>
</tr>
<tr>
<td>Requiring emergency surgery, n (%)</td>
<td>30 (37)</td>
<td>28 (35)</td>
<td>33 (40)</td>
</tr>
<tr>
<td>Had surgical intervention lasting more than 4 hours, n (%)</td>
<td>19 (23)</td>
<td>15 (19)</td>
<td>14 (17)</td>
</tr>
<tr>
<td>With trauma, n (%)</td>
<td>28 (35)</td>
<td>29 (36)</td>
<td>35 (42)</td>
</tr>
<tr>
<td>With thoracic trauma, n</td>
<td>17</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>With neurosurgical intervention, n</td>
<td>10</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>With abdominal intervention, n</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>With surgery (other than trauma), n (%)</td>
<td>16 (20)</td>
<td>12 (15)</td>
<td>11 (13)</td>
</tr>
<tr>
<td>Abdominal, n</td>
<td>4</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Neurosurgery, n</td>
<td>4</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Thoracic, n</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Other, n</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>In medical ICU, n (%)</td>
<td>37 (46)</td>
<td>39 (49)</td>
<td>37 (45)</td>
</tr>
<tr>
<td>With cardiac disease, n (%)</td>
<td>9 (11)</td>
<td>12 (15)</td>
<td>11 (13)</td>
</tr>
<tr>
<td>With cardiac arrest, n</td>
<td>5</td>
<td>9</td>
<td>7</td>
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<tr>
<td>With pulmonary disease, n</td>
<td>19 (23)</td>
<td>17 (21)</td>
<td>15 (18)</td>
</tr>
<tr>
<td>Pneumonia on admission, n</td>
<td>9</td>
<td>7</td>
<td>6</td>
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<tr>
<td>Obstructive lung disease, n</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>ARDS, n</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Other, n</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>With other medical conditions, n (%)</td>
<td>9 (11)</td>
<td>10 (13)</td>
<td>11 (13)</td>
</tr>
<tr>
<td>Neurologic disease, n</td>
<td>7</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Miscellaneous, n</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>During the study period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days at risk with tracheostomy, n</td>
<td>65</td>
<td>25</td>
<td>46</td>
</tr>
<tr>
<td>Days at risk with endotracheal tube, n</td>
<td>452</td>
<td>408</td>
<td>434</td>
</tr>
<tr>
<td>Patients with enteral feeding, n (%)</td>
<td>22 (27)</td>
<td>20 (25)</td>
<td>23 (28)</td>
</tr>
</tbody>
</table>

* APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = the adult respiratory distress syndrome; ICU = intensive care unit.
† Values are expressed as mean ± SD.

opposing in patients treated with sucralfate compared to other treatment did not reach the usual 0.05 level of significance (21, 23).

Furthermore, previous studies did not distinguish between pneumonia occurring early or late after intubation. This may be important because it is likely that early-onset pneumonia may be related to the introduction of bacteria in the trachea at the time of intubation (30-32), a process that is not expected to be influenced by the type of anti-stress ulcer prophylaxis.

Therefore, we compared three anti-stress ulcer prophylaxis regimens (antacid, ranitidine, and sucralfate) in a large group of ventilated patients for the occurrence of bacterial colonization, early and late-onset nosocomial pneumonia, and overt gastrointestinal bleeding.

Methods

Patients

The Centre Hospitalier Universitaire Vaudois is a 1100-bed hospital serving both as a municipal facility and a tertiary referral center. During a 2-year period (January 1989 to January 1991), all patients admitted to the adult medical and surgical intensive care units who were receiving mechanical ventilation and had a nasogastric tube in place were eligible for the study. Exclusion criteria were as follows: active upper gastrointestinal bleeding; treatment with antacids, H₂-blockers, or sucralfate during the preceding 48 hours; creatinine levels greater than 200 μmol/L; esogastric surgery; cardiac surgery; or organ transplantsations. Patients likely to be extubated within 24 hours were also excluded.

At intubation, patients were stratified into five categories according to the following underlying conditions: trauma (surgical intensive care unit), intervention after surgery (surgical intensive care unit), cardiac disease (medical intensive care unit), pulmonary disease (medical intensive care unit), and other medical conditions (medical intensive care unit). Randomization was done using a random permutable table to generate a random treatment list. Treatment regimens were included in opaque, sealed envelopes. The patients were assigned to one of the following anti-stress ulcer prophylactic regimens: 1) antacid, a hospital-made suspension containing 5.4% aluminum hydroxide and 1.5% magnesium hydroxide with a buffer capacity of 1.2 mEq/mL, administered every 2 hours—the standard dose of 20 mL was doubled if the gastric pH (tested with pH-indicator strips [Merck and Co., Darmstadt, Germany] before each administration) was less than 4.0; 2) ranitidine (Zantac, Glaxo, Bern, Switzerland) administered as a continuous intravenous infusion of 150 mg/d (100 mg/d if the blood creatinine level was between 150 and 200 μmol/L); or 3) sucralfate (Ulcogant, Merck and Co., Zürich, Switzerland) administered every 4 hours as 1 gram of suspension diluted in 20 mL of sterile water.

After antacid or sucralfate was administered, the nasogastric...
tubewasflushedwith10mLofsterilewaterandclampedfor 30 minutes.

Each prophylactic regimen was continued until extubation unless interrupted earlier for any of the following predetermined reasons: an increase of the blood creatinine level to more than 200 μmol/L, removal of the nasogastric tube, moribund state, discharge from the intensive care units, or side effects likely to be related to the stress ulcer regimen.

Data Collection and Definitions

For all eligible patients, demographic characteristics, diagnosis, underlying diseases, physical signs, laboratory tests, and medications were recorded prospectively by one of the investigators. However, only patients eventually intubated for more than 24 hours were followed and included in the final analysis. Glasgow coma and Acute Physiology and Chronic Health Evaluation (APACHE II) scoring systems were used to assess the severity of the acute illness. The adult respiratory distress syndrome was defined by the following criteria: acute bilateral diffuse pulmonary infiltrates and severe hypoxemia without evidence of cardiogenic edema.

Gastric aspirates were examined for the macroscopic presence of blood (“coffee ground material” or fresh blood). The severity of gastric hemorrhage was assessed by clinical criteria (physical signs, blood transfusion requirements, and outcome). Chest radiographs were obtained on a daily basis or more often if clinically indicated. They were interpreted by a pneumologist who had knowledge of all relevant data except for the patient’s stress ulcer prophylactic regimen, gastric pH, or colonization data.

Criteria for the diagnosis of ventilator-associated pneumonia were predetermined and derived from those of Salata and colleagues: presence of a new or progressive infiltrate on the chest radiograph consistent with pneumonia, without other obvious cause, and associated with conditions A or B or both, defined as follows. Condition A refers to any of the following findings: pleural fluid or blood culture positive for an organism also isolated in the tracheal aspirate, radiographic cavitation, or histopathologic evidence of pneumonia. Condition B includes at least two of the following: tracheal aspirates with more than 25 leukocytes per low-power field (×100) on a Gram stain, new leukocytosis defined as a leukocyte count greater than 10 × 10⁹/L with an increase of at least 25% over baseline, or body temperature greater than 38.5 °C with an increase of at least 1 °C above baseline. The latter two criteria were considered only when other causes for these findings were excluded.

Pneumonia was considered to be caused by a pathogen when it was cultured in high counts as the sole or predominant microorganism in the tracheal aspirate culture.

Using the criteria of Langer and colleagues, early-onset and late-onset pneumonia were diagnosed if they occurred during the first 4 days of or 4 days after the initiation of mechanical ventilation, respectively. Consequently, only patients observed for more than 4 days could be evaluated for the development of late-onset pneumonia. A second episode of pneumonia was diagnosed when it was clearly temporally distinct from the first episode and when it involved other areas of the lungs.

Pneumonia was attributed to a given anti-stress ulcer prophylactic regimen if it developed during treatment or within 2 days after extubation or treatment interruption.

Death was considered to be directly related to nosocomial pneumonia when it occurred during the episode and when no other major contributing cause was present.

Bacteriologic Investigations and pH Measurements

Gastric and tracheal aspirates and oropharyngeal swabs were obtained twice daily and cultured quantitatively (gastric juice) or semi-quantitatively in aerobic conditions. Aerobic bacteria were identified by standard microbiologic methods. Cultures for Chlamydia species, Legionella pneumophila, or Mycoplasma pneumoniae were not done. Blood or pleural fluid cultures were ordered by the primary care physician according to the clinical situation. Gastric pH was measured twice a day using a pH meter (except in 11 patients for whom values were derived only from pH-indicator strips [Merck and Co.]). A cut-off value of 4.0 for median pH was chosen for further analysis within the three treatment groups because it has been shown to be a critical value for the growth of gram-negative bacilli in the stomach.

Colonization was defined by the presence of one microorganism at a given site on at least two occasions. A patient was considered to have gastric colonization with high counts when quantitative culture of at least one specimen was more than 10⁵ CFU/mL. The amount of bacteria in the oropharynx and trachea was assessed semi-quantitatively using the four-quadrants streak-plate method and was considered high when bacteria were present up to the third or fourth quadrant.

The pattern of colonization was examined by comparing bacterial strains of the same species isolated from two or more sites. For this purpose, strains were kept at −20 °C when isolated for the first time at a given site. Strains of the same species were considered identical when the biotype and the antibiotic susceptibility patterns were identical. In addition,
was attributed to the treatment. In the ranitidine group, one patient developed leukopenia and another patient developed a rash. Removal of the nasogastric tube, withdrawal of supportive care, or discharge from the hospital was the other reason for premature protocol interruption. Five patients in the antacid group, 5 patients in the ranitidine group, and 8 patients in the sucralfate group had these characteristics. In addition, protocol violation prompted interruption of treatment in 7 patients in the antacid group, 4 patients in the ranitidine group, and 3 patients in the sucralfate group.

For patients in whom the protocol was interrupted, the total number of assessable days before interruption was not statistically different among the three groups ($P > 0.2$).

### Macroscopic Gastrointestinal Bleeding

Macroscopic gastrointestinal bleeding was observed in three (4%) patients treated with antacid (at days 3, 3, and 18 with median pH values of 7.4, 5.1, and 6.0, respectively), in five (6%) patients treated with ranitidine (at days 2, 2, 3, 4, and 6, with median pH values of 6.0, 7.0, 8.1, 4.2, and 5.3, respectively) and in eight (10%) patients treated with sucralfate (at days 2, 2, 3, 5, 8, 12, and 23 with median pH values of 5.0, 7.0, 7.4, 7.0, 3.5, 3.5, 6.1, and 5.4, respectively) ($P > 0.2$). This led the physicians in charge to modify the anti-stress ulcer prophylaxis regimen in 1, 2, and 3 patients in the antacid, ranitidine, and sucralfate groups, respectively. No pneumonia was observed in these six patients either before or after the treatment was modified.

Blood transfusions were required in one patient treated with ranitidine and in one patient treated with sucralfate. One patient treated with sucralfate died as a direct result of the bleeding.

### Gastric pH

A total of 669, 653, and 602 gastric specimens were obtained in the groups treated with antacid, ranitidine, and sucralfate, respectively. This corresponds to 1.3, 1.5, and 1.4 gastric specimens per patient per day in each group.

Median gastric pH values of patients treated by sucralfate were lower than those in patients treated with antacid or ranitidine ($P < 0.001$) (Figure 1). The medians of these values were 7.10, 5.27, and 4.30 for the

### Table 2. Gastric Colonization with Gram-negative Bacilli in Relation to Median Gastric pH

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment Group</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antacid (n=76)</td>
<td>Ranitidine (n=75)</td>
</tr>
<tr>
<td>Gastric colonization</td>
<td>1/3 (33)</td>
<td>2/8 (25)</td>
</tr>
<tr>
<td>High-count colonization</td>
<td>1/3 (33)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Patients with a pH greater than 4.0, n/n (%)</td>
<td>37/73 (51)</td>
<td>36/65 (55)</td>
</tr>
<tr>
<td>Gastric colonization</td>
<td>25/73 (34)</td>
<td>27/65 (42)</td>
</tr>
<tr>
<td>High-count colonization</td>
<td>26/74 (35)</td>
<td>27/63 (37)</td>
</tr>
</tbody>
</table>

Categorical variables were analyzed by the chi-square test for association. Continuous variables were analyzed by one-way analysis of variance or the nonparametric Kruskall Wallis test. The effect of continuous variables on a categorical variable was assessed using logistic regression analysis.

### Results

During the study period, 758 patients were admitted to the medical intensive care unit and 2408 patients were admitted to the surgical intensive care unit. Of 450 eligible patients during the study period, 375 were randomly assigned to a treatment group and 258 were eventually intubated for more than 24 hours. Fourteen were unassessable because of missing data (4, 3, and 7 were admitted to the surgical intensive care unit. Of 450

ribosomal RNA gene restriction fragment length analysis (ribotyping) was done for *Escherichia coli* and *Pseudomonas aeruginosa* strains when bacteria were isolated from the stomach, trachea, and throat of one patient (36). *EcoRI, BamHI, PstI, SphI* or *SmaI* restriction enzymes were used to digest the DNA of *P. aeruginosa*, whereas *BamHI, EcoRI, PstI* or *BglII* were used with *E. coli* DNA. Appropriate controls showed that the method accurately discriminated between strains of different origin (37). A retrograde colonization from the stomach to the trachea was assumed when a particular organism was first isolated from the stomach (and not from the throat) and subsequently recovered in the trachea.

### Statistical Analysis

Categorical variables were analyzed by the chi-square test for association. Continuous variables were analyzed by one-way analysis of variance or the nonparametric Kruskall Wallis test. The effect of continuous variables on a categorical variable was assessed using logistic regression analysis.

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Antacid (n=76)</th>
<th>Ranitidine (n=75)</th>
<th>Sucralfate (n=75)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric colonization</td>
<td>1/3 (33)</td>
<td>2/8 (25)</td>
<td>10/35 (29)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>High-count colonization</td>
<td>1/3 (33)</td>
<td>0 (0)</td>
<td>2/35 (6)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Patients with a pH greater than 4.0, n/n (%)</td>
<td>37/73 (51)</td>
<td>36/65 (55)</td>
<td>3/40 (28)</td>
<td>0.065</td>
</tr>
<tr>
<td>Gastric colonization</td>
<td>25/73 (34)</td>
<td>27/65 (42)</td>
<td>11/40 (28)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>High-count colonization</td>
<td>26/74 (35)</td>
<td>27/63 (37)</td>
<td>13/75 (28)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

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The protocol had to be interrupted before extubation in 23 (28%) of the patients in the antacid group, 19 (24%) of the patients in the ranitidine group, and 17 (20%) in the sucralfate group. Renal insufficiency developed in 5, 8, and 6 patients in the antacid, ranitidine, and sucralfate groups, respectively. In the antacid group, 6 patients developed diarrhea or ileus, which
patients receiving antacid, ranitidine, and sucralfate, respectively.

Bacterial Colonization

Of the 244 patients, 224 were assessable for colonization with gram-negative bacilli.

Of the 46 patients with a median pH lower than 4.0, 13 (28%) had gastric colonization with gram-negative bacilli compared with 86 (48%) of the 178 patients with a pH greater than 4.0 ($P = 0.003$). If colonization with high counts is considered, 3 of 46 patients with a median pH lower than 4.0 had gastric colonization compared with 63 of 178 patients with a pH greater than 4.0 ($P = 0.011$). Tracheal colonization with high counts was also lower in patients who had a gastric pH lower than 4.0 (7 of 46 patients) than in patients with a gastric pH greater than 4.0 (55 of 178 patients) ($P = 0.053$).

Gastric colonization in each treatment group was associated with a higher pH. In the patients with a gastric pH lower than 4.0, no apparent difference was found in the gastric colonization rates among the treatment groups, but only a few of these patients were in the antacid or ranitidine groups (Table 2). In the patients with a gastric pH greater than 4.0, 37 of 73 patients in the antacid group and 36 of 65 patients in the ranitidine group had gastric colonization, compared with $13$ of 40 patients in the sucralfate group ($P = 0.065$). When patients with low and high gastric pH values were pooled in each treatment group, the proportion of patients who had gastric colonization with gram-negative bacilli and gastric colonization with a gram-negative bacilli concentration greater than $10^6$ CFU/mL was lower in the sucralfate group (13 of 75 patients) than in patients with a gastric pH greater than 4.0 (55 of 178 patients) ($P = 0.053$).

The proportion of patients with tracheal colonization was not different in the antacid (24 of 76 patients) and sucralfate groups (22 of 75 patients) but was lower than in the ranitidine group (36 of 73 patients) ($P = 0.022$) (Table 3). The proportion of patients with oropharyngeal colonization was lower in the sucralfate group than in the other two groups ($P = 0.19$) (Table 3).

Ventilator-associated Pneumonia

Overall, 53 episodes of pneumonia were observed in the 244 patients. In the antacid group, 18 (22%) patients developed 20 episodes of pneumonia. In the ranitidine group, 21 (26%) patients developed 22 episodes of pneumonia, and in the sucralfate group, 10 (12%) patients developed 11 episodes of pneumonia ($P = 0.063$). Early-onset pneumonia represented 45% of all pneumonia episodes; late-onset pneumonia represented 55% of all episodes.

Early-onset pneumonia developed in 9 of 81 (11%) patients in the antacid group, 8 of 80 (10%) patients in the ranitidine group, and 7 of 83 (8%) patients in the sucralfate group ($P = 0.2$). Staphylococcus aureus, Streptococcus pneumoniae, and Haemophilus influenzae, alone or in combination, accounted for 54% of the cases of early-onset pneumonia, whereas gram-negative bacilli were present in only 17% of these episodes (Table 4).

Thirty-one patients were extubated (5 in the antacid group, 4 in the ranitidine group, and 3 in the sucralfate group) or died (7 in the antacid group, 8 in the ranitidine group, and 4 in the sucralfate group) before 4 days of observation and could not be analyzed for the development of late-onset pneumonia. No statistical difference in underlying characteristics of these patients was found among the treatment groups. Of the 213 patients observed for more than 4 days, late-onset pneumonia was diagnosed in 11 of 69 (16%) patients in the antacid group, 14 of 68 (21%) patients in the ranitidine group, and 4 of 76 (5%) patients in the sucralfate group ($P = 0.022$). Three of the four cases of late-onset pneumonia observed in the sucralfate group were diagnosed on day 5, whereas pneumonia continued to be observed during the following days in the other two groups (Figure 2).

Although no statistically significant difference in the median age of the patients was found among the groups, patients on ranitidine were approximately 12% older than the patients receiving antacid or sucralfate. A logistic regression analysis using age and treatment as predictors showed that late-onset pneumonia was not related to age ($P = 0.149$).

All but one patient with late-onset pneumonia caused by gram-negative bacilli had a median gastric pH greater than 4.0 before the episode. When analyzing only patients with a gastric pH greater than 4.0, the incidence of late-onset pneumonia was not statistically different among the treatment groups ($P = 0.089$).

Gram-negative bacilli were shown in 19 of 29 (66%) episodes of late-onset pneumonia (see Table 4). Of the 19 patients with late-onset gram-negative bacillary pneumonia, 84% (16 patients) had gastric colonization with bacteria of the same species before pneumonia developed, including the three patients of the sucralfate group who had a gastric pH greater than 4.0. In contrast, the overall gastric colonization rate with gram-negative bacilli was only 50% in the 182 patients who were followed for more than 4 days and did not have gram-negative pneumonia ($P = 0.009$). Moreover, 53% of the 19 patients with gram-negative pneumonia had gastric colonization with counts higher than $10^6$ CFU/mL before the episode, compared with 24% of the 182 patients without gram-negative pneumonia ($P = 0.017$).

Of the 16 patients with gram-negative pneumonia and previous gastric colonization, the bacteria isolated from the stomach and trachea in 14 patients had the same biotype and antibiotic susceptibility pattern and the
same ribotype (done in 10 patients). In one case, the strains differed by only 1 of 46 bands on ribotyping. In the last case, the two isolates differed only by the susceptibility to the antibiotic the patient was receiving. The tracheal strain was isolated 5 days after the gastric strain; it resisted the antibiotic but had the same ribotype as the gastric strain. Ribotypes of bacteria of the same species differed among patients, except for two patients (who were not hospitalized simultaneously) who harbored strains of *P. aeruginosa* with a similar ribotype.

Ribotypes were not done for six patients because the bacterial species were unique to each patient during the study period, were isolated on multiple occasions from one patient, and were only rarely encountered in our intensive care units. Therefore, based only on the species and the antibiotic susceptibility pattern, we assumed that the strains isolated at the different sites were identical.

Of the four patients with late-onset pneumonia caused by *Staphylococcus aureus*, three had gastric colonization before the episodes, and two had high counts. The median gastric pH was greater than 4.0 in all four cases.

### Mortality

The overall mortality rate in patients with pneumonia was 32% compared with 35% in patients without pneumonia. The data on mortality in the three treatment groups are shown in Table 5. No statistically significant difference in the mortality rates during hospitalization or ventilation therapy was found among the three treatment groups. Mortality in the patients with pneumonia was 10% in the sucralfate group, compared with 29% in the antacid group and 45% in the ranitidine group (*P = 0.147*). In patients with late-onset pneumonia, the mortality rate was 0% in the sucralfate group, 27% in the antacid group, and 36% in the ranitidine group (*P > 0.2*). All four patients who died as a direct result of pneumonia had late-onset pneumonia. One patient receiving sucralfate died on day 8 as a direct result of a hemorrhage caused by a stress ulcer. Autopsy showed a massive erosive gastritis. The median gastric pH since intubation was 3.6; during the 2 days before the hemorrhage, it was 2.3. No statistical difference in the occurrence of other causes of death was found in the three groups. The other causes of death were cerebral damage (46%), cardiac failure (17%), respiratory insufficiency (15%), multiple organ failure (10%), and miscellaneous disorders (6%).

### Discussion

Although it is recognized that the duration of intubation is an important risk factor for the development of ventilator-associated pneumonia (38-40), no study comparing stress ulcer regimens has analyzed when the pneumonic episodes had developed in the study patients. This is of special importance because ventilator-associated pneumonia developing early or late after intubation differs in the bacterial species that are recovered from the trachea (30-32) and are therefore likely to be related to different pathophysiologic mechanisms. In pneumonia that develops during the first few days after intubation, the spectrum of bacteria mostly includes oropharyngeal species thought to have been introduced in the trachea before or at the time of intubation (30, 32). Therefore, early-onset pneumonia is unlikely to depend much on the gastric pH modifications induced by therapy with the various anti-stress ulcer medications initiated after intubation. Our study confirmed this. Early-onset pneumonia showed the same frequency in the three treatment groups, were associated mainly with *H. influenza*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*, and represented 45% of all pneumonic episodes. In contrast, pneumonia that develops after a few days of intubation is most frequently associated with aerobic gram-negative bacilli (21, 32, 38); several studies have docu-
mented that up to 30% to 40% of these bacteria originate in the stomach (6-8, 14, 16, 41, 42). The gastric pH has been shown to greatly affect the bacterial colonization of the stomach (7, 21, 43). Therefore, the effect of various anti-stress ulcer medications on the gastric pH should primarily influence the incidence of those cases of pneumonia that develop only a few days after intubation. Our study confirmed this.

Late-onset pneumonia developed significantly more frequently in patients treated with antacid or ranitidine than in those treated with sucralfate. It can be argued that the diagnosis of pneumonia has been established on the basis of clinical criteria only, a method that has been shown to have a good sensitivity but suboptimal specificity. However, the overall incidence of pneumonia found in our study was low, and similar or even lower than that found in studies of similar patients investigated with bronchoscopy and protected brush specimens (44, 45). It is therefore unlikely that pneumonia was grossly overdiagnosed. More importantly, the patients of the three groups were analyzed blindly according to predetermined criteria, and possible misdiagnoses should have been distributed equally among the groups.

Thus, because the groups were similar in their underlying characteristics, we postulate that the higher rates of late-onset pneumonia observed in patients treated with antacid or ranitidine were most likely a result of the gastric pH elevation induced by these agents. This theory is supported by the gastric pH measurements and colonization data. Patients receiving antacid or ranitidine had higher median gastric pH values and higher rates and magnitudes of gastric colonization than did patients receiving sucralfate; this was also reported by others (21, 43). Detailed microbiologic investigations, including molecular typing, disclosed that in two thirds of the episodes of late-onset pneumonia, tracheal aspirates grew gram-negative bacilli, which were found in the stomach before pneumonia developed, often in large quantities. These results strongly suggest that the increased gastric pH and the subsequent gastric and tracheal colonization were the main factors accounting for the increased rates of late-onset pneumonia in the antacid and ranitidine groups compared with the sucralfate group. This is also consistent with recent data that have established a relation among duodenal reflux, gastric pH greater than 3.5, and subsequent bacterial colonization of the lower respiratory tract (10).

It is noteworthy that half of the patients receiving sucralfate had median gastric pH values greater than 4.0, a phenomenon already described by others (22, 46, 47) and attributed to gastric exocrine “failure” in severely ill patients. However, among these patients, those receiving sucralfate still had a lower rate of gastric colonization than those receiving antacids or ranitidine. This has also been observed by others (22) and may be related to an intrinsic antibacterial action of sucralfate (8, 48, 49). The importance of this finding remains to be determined, and in our study no statistically significant difference in the incidence of late-onset pneumonia was found among the three groups when only patients with a gastric pH greater than 4.0 were considered. Therefore, the lower incidence of late-onset pneumonia in the sucralfate group appears to be mainly associated with the fact that half of the patients receiving this drug were able to maintain a low gastric pH and thus suppress bacterial growth.

Although the colonization rates of the oropharynx and the trachea were also lower in the patients receiving sucralfate than in the other two groups, this did not reach statistical significance for all comparisons among groups. This may be related to the definition of colonization we used, which has created a high background because during the entire study period, only two positive cultures for gram-negative bacilli were required to
be estimated at 10% to 15% (32, 40) and was even lower
cause the mortality directly caused by pneumonia can
appeared to be lower in the patients treated with sucral­
81) (n = 80) 83)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Antacid</th>
<th>Ranitidine</th>
<th>Sucralfate</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death during hospitalization, n (%)</td>
<td>32 (40)</td>
<td>27 (34)</td>
<td>25 (30)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Death during mechanical ventilation, n (%)</td>
<td>17 (21)</td>
<td>16 (20)</td>
<td>9 (11)</td>
<td>0.16</td>
</tr>
<tr>
<td>Death in patients with pneumonia, n/n (%)</td>
<td>5/18 (29)</td>
<td>9/21 (45)</td>
<td>1/10 (10)</td>
<td>0.15</td>
</tr>
<tr>
<td>Death in patients with early-onset pneumonia, n/n (%)</td>
<td>2/9* (22)</td>
<td>4/8* (50)</td>
<td>1/7* (14)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Death in patients with late-onset pneumonia, n/n (%)</td>
<td>3/11* (27)</td>
<td>5/14* (36)</td>
<td>0/4* (0)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Death directly related to pneumonia, n</td>
<td>1†</td>
<td>38</td>
<td>0</td>
<td>0.16</td>
</tr>
<tr>
<td>Death caused by gastric hemorrhage, n</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>&gt;0.2</td>
</tr>
</tbody>
</table>

* None of the four patients with early- and late-onset pneumonia died.
† Late-onset pneumonia.

meet the criteria for colonization. However, in two
studies similar to ours (21, 23), statistically significant
differences were found in the colonization rates of the
gastric and tracheal and oropharyngeal sites among pa­
tients receiving sucralfate and those receiving a pH-raising agent. Moreover, our study found that the rate of
tracheal colonization with high bacterial counts was
statistically lower in patients with a gastric pH lower
than 4.0, suggesting again that the beneficial effect of
sucralfate is essentially obtained in the subgroup of
patients able to maintain a low gastric pH. Our results
also agree with a recent study (10) that showed a cor­
relation between organisms recovered from the lower
respiratory tract and those from the stomach, but not
with those found in the oropharynx.

Our study confirms and extends the findings of others
(21–23, 25) who found fewer cases of pneumonia in
patients receiving sucralfate than in those receiving pH-elevating agents. It shows that only patients who re­
cieve prolonged mechanical ventilation and are able to
maintain a low gastric pH will benefit more from stress ulcer prophylaxis with sucralfate than with agents rais­
ing the gastric pH. The clear identification of these two
conditions helps explain some of the conflicting results
observed in other comparative trials (18). Thus, because
a reduction in the risk for developing pneumonia can
only be expected in a few patients, only studies of large
randomized groups that include a high proportion of
patients ventilated for prolonged periods can be ex­
pected to show a statistically significant difference in
the development of pneumonia. These conditions were
not fulfilled by several previous studies (17, 21, 26, 28).
Moreover, insufficient dosages of the pH-raising agents
or wide use of enteral nutrition (20, 50) may result in
gastric pH values similar to those in patients receiving
sucralfate and patients receiving pH-raising agents. This
may also account for the absence of differences in rates
of pneumonia observed in some studies (17, 27, 29).

The crude mortality rate of patients in intensive care
units who require prolonged mechanical ventilation,
such as the patients included in our study, is between
30% and 40% (32, 40). Although the mortality rate ap­
ppeared to be lower in the patients treated with sucral­
fate, the differences from the other two groups were not
statistically significant. This was not unexpected be­
because the mortality directly caused by pneumonia can
be estimated at 10% to 15% (32, 40) and was even lower
in our study. Therefore, a much larger study would be
necessary to observe a statistically significant reduction
in the overall mortality.

Although the efficacy of various prophylactic regi­
mens in the prevention of bleeding from stress ulcers has
been controversial, a meta-analysis of 42 randomized
and prospective studies involving 4490 patients (51)
showed that antacids and H2-antagonist drugs were su­
perior to placebo or no therapy in reducing the risk for
gastrointestinal bleeding. In comparative studies, sucral­
fate appeared to be as effective as antacids and H2­
antagonists (20). In our study, the rate of macroscopic
gastrointestinal bleeding was not statistically different
from that of the three treatment groups. One of the
patients treated with sucralfate died as a direct result of
a hemorrhage caused by stress ulcers, but this has also
been described in patients treated with pH-elevating
agents (2).

In conclusion, stress ulcer prophylaxis with sucralfate
was not found to be less effective in preventing gastric
hemorrhage in mechanically ventilated patients com­
pared with prophylaxis with ranitidine and antacid. Su­
cralfate reduces the risk for developing late-onset pneu­
monia by its ability to maintain a low gastric pH and
reduce gastric bacterial colonization in many patients.
However, half of mechanically ventilated patients re­
cieving this drug have median gastric pH values greater
than 4.0 and will not benefit from this "protective"
effect. It may be indicated that these patients should be
identified by monitoring their gastric pH because addi­
tional strategies, such as digestive decontamination (32,
52–59) or keeping the patient in a moderate upright
position (60), may also be considered to prevent pneu­
monia of gastric origin in those patients ventilated for
prolonged periods.

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