Gastric Colonization by Gram-Negative Bacilli and Nosocomial Pneumonia in the Intensive Care Unit Patient

Evidence for Causation

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The purpose of this article is to assess critically the evidence for a causal relationship between gastric colonization by Gram-negative bacilli and nosocomial pneumonia in the intensive care unit. Articles were found using MEDLINE search and citations in relevant articles. Nine diagnostic tests of causation were applied and analysis showed that the major tests were satisfied. The strongest evidence comes from randomized controlled trials of selective gut decontamination and stress ulcer prophylaxis in intensive care units. These studies confirm that the incidence of nosocomial pneumonia correlates directly with the rate of gastric colonization by Gram-negative bacilli. Further support comes from other tests of causation such as strength and consistency of association, temporal relationship, and dose-response gradient. The data reviewed suggest that gastric colonization with Gram-negative bacilli plays a causal role in the development of nosocomial pneumonia in the intensive care unit patient. This relationship impacts on future studies of pathogenesis and prevention of this potentially lethal infection.


Tests of Causation

Is There Evidence from True Experiments in Humans?

Strong evidence for a causal relationship between gastric colonization with bacterial pathogens and nosocomial pneumonia comes from randomized controlled trials carried out in the ICU. Evidence is derived from studies of interventions that alter the Gram-negative bacillary content of the stomach and then demonstrate a concordant change in the incidence of pneumonia. For example, if gastric colonization with pathogenic Gram-negative bacilli is implicated as a causal factor in the development of nosocomial pneumonia, then elimination of such organisms from the stomach by selective decontamination of the digestive tract should lower the incidence of pneumonia. Kerver et al performed such a study. Ninety-six surgical ICU patients requiring intensive care for more than five days were randomly allocated to a control group or a study group that received oral

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nonabsorbable topical antibiotics (ie, tobramycin, amphotericin B, and polymyxin B through the nasogastric tube and applied to the buccal mucosa) plus systemic cefotaxime for five to eight days. Excluding *Escherichia coli*, Gram-negative bacillary colonization of the digestive tract in the study group was reduced to 0 percent as assessed by fecal cultures. As a result, 40 patients in the control group vs six patients in the experimental group developed lower respiratory tract infections. When overall mortality in the two groups was examined, there were no differences found. However, if mortality due to infection is examined, eight deaths occurred in the control group compared with two in the experimental group.

The patients in both study groups were comparable in age, sex, duration of ICU stay, and APACHE score (severity of illness score). There was no comment on any prior underlying medical illness (especially respiratory or neurologic diseases) or length of mechanical ventilation, both of which increase the risk for pneumonia and could potentially be confounders. Other confounding variables not controlled for were the use of enteral feeds and H2 antagonists/antacids. The administration of parenteral cefotaxime in addition to an oral antibiotic regimen also confuses the interpretation of results. It is difficult to know whether any observed changes in outcome measures were due to the topical, nonabsorbable antibiotics or the systemic parenteral antibiotics. The criteria used to determine infection were not strictly defined nor were outcome assessments evaluated in a blinded fashion. Given the aforementioned potential for bias and the various confounding variables, the statistically significant results should be accepted cautiously.

However, further studies have validated the findings of Kerver et al. Ulrich et al. evaluated a diverse population of ICU patients and randomly allocated them to a control group or an experimental group. The latter received gastrointestinal and oropharyngeal decontamination with polymyxin E, norfloxacin, and amphotericin B plus systemic antibiotic prophylaxis with trimethoprim. The results showed a statistically and clinically significant reduction in the incidence of Gram-negative bacillary respiratory, urinary, and line-related infections: a total of 95 infections by Gram-negative bacilli and 29 episodes of respiratory tract infection in the control group compared with nine infections by Gram-negative bacilli and seven episodes of pneumonia in the experimental group. Mortality rates from acquired infections as well as overall mortality rates were also significantly reduced (p<0.02).

Ledingham and others also prospectively studied the use of topical antibiotics in ICU patients using a consecutive control group design. All patients admitted to a general ICU over 16 months were evaluated and patients seen in the first eight months formed the control group. Patients seen in the second eight-month period received selective decontamination of the digestive tract with polymyxin E, tobramycin, and amphotericin B together with systemic cefotaxime for four days. Although use of a consecutive control group has inherent weaknesses, this type of study design was used to eliminate patient-to-patient contamination. Again, the experimental group showed a marked reduction in colonization of the stomach by Gram-negative bacilli as well as a decrease in the incidence of infection.

Based on the studies cited, there appears to be consistent evidence that by reducing or eliminating Gram-negative bacilli in the digestive tract, the incidence of nosocomial pneumonia (as well as other infections due to Gram-negative bacilli) is reduced significantly. However, interpreting such data from the point of view of a causal hypothesis is confusing as it is not clear how each component of the intervention decontamination therapy (gastrointestinal decontamination, oropharyngeal decontamination or systemic antibiotics) contributes to a reduction in infectious episodes. The greatest support for a causal hypothesis would come from studies showing that gastric decontamination alone resulted in a lower rate of pneumonia. However, this is not the case. Stoutenbeek et al. found no difference in infection rates between multiple trauma patients treated with intestinal decontamination alone compared with control cases. When oropharyngeal and intestinal decontamination were combined, there was a significant reduction in secondary colonization and infection of the respiratory tract by Gram-negative bacilli. (Secondary infections were infections that developed during or after systemic antibiotic therapy.) No differences in early ICU infections caused primarily by Gram-positive organisms were noted until a systemic antibiotic was added prophylactically on admission to the ICU. In those patients who received systemic antibiotics plus oropharyngeal and intestinal decontamination, there was an overall pulmonary infection rate of 5 percent compared with a historic control group with a 59 percent infection rate (p<0.001).

Further studies have also attempted to define the role of each component of decontamination therapy. Brun-Buisson et al. evaluated the efficacy of intestinal decontamination alone (no systemic antibiotics) on intestinal colonization and infection in the ICU. This prospective randomized study showed that intestinal decontamination alone was effective in decreasing colonization and infection rates with multiresistant strains of Gram-negative bacilli that were predominant in their ICU at the time the study was initiated. However, there was no impact on the overall rate of nosocomial infections, including pneumonia. Thirty-
three percent of the control group developed infections vs 32 percent of the treated group. All patients had received povidone-iodine solution applied to their oropharynx, but the efficacy of this solution in achieving oropharyngeal decontamination is not known.

Lastly, Unertl and others\textsuperscript{44} again demonstrated in a randomized controlled trial of topically administered antibiotics that intestinal and oropharyngeal decontamination without systemic antibiotics is efficacious in reducing both colonization and infection of the respiratory tract. In the control group, tracheal colonization occurred in 19 patients compared with 11 in the treatment group (p<0.01). Nine patients in the control group developed pneumonia compared with one in the treatment group (p<0.01). However, the treatment had no impact on mortality rates.

In summary, data from studies of selective decontamination of the digestive tract provide evidence for a causal hypothesis. Intestinal decontamination appears to lower the incidence of subsequent respiratory infections. The role of parenteral antibiotics in combination with topical antibiotics remains controversial.\textsuperscript{15} The rationale for their use is twofold: (1) to treat any infection already contracted before admission to the ICU and (2) to prevent infection until effective decontamination can be achieved by topical antibiotics (usually three to four days).\textsuperscript{16} Nevertheless, concerns have been raised about the possibility of overgrowth of resistant organisms.

Studies of gastric alkalinization therapy provide further evidence of a causal association. In a prospective study, Daschner et al\textsuperscript{17} examined the influence of stress ulcer prophylaxis on gastric flora and the subsequent development of nosocomial pneumonia in ICU patients. They demonstrated that the higher the gastric pH, the greater the colony counts for Gram-negative bacilli isolated from the stomach. This association seemed to be correlated with a higher incidence of pneumonia.

Craven et al\textsuperscript{8} looked at risk factors for both nosocomial pneumonia and case-fatality in 233 ICU patients. Variables significantly associated by univariate analysis with these outcomes were then entered in a stepwise logistic regression model. The use of cimetidine, an H\textsubscript{2} antagonist, remained a significant risk factor for the development of pneumonia.

This correlation was further studied in 1987 when Driks et al\textsuperscript{18} examined incidence rates of nosocomial pneumonia in mechanically ventilated patients given sucralfate as compared with those given antacids or H\textsubscript{2} blockers. Sucralfate is a mucosal protective agent that has been proven efficacious in preventing gastric bleeding without reducing levels of acidity in the stomach.\textsuperscript{19,20} One hundred thirty ICU patients were randomized to receive either sucralfate or H\textsubscript{2} antagonist or antacids. There was no obvious selection bias and strict diagnostic criteria for pneumonia were used along with blinded assessment of chest roentgenograms to further reduce any observer bias. Patients in both groups were similar with respect to age, underlying disease, previous use of antibiotics, and severity of illness. Six patients originally treated with sucralfate crossed over to the antacid/H\textsubscript{2} antagonist group and two of them subsequently developed pneumonia.

Results showed that patients in the sucralfate group had a higher proportion of gastric aspirates with pH <4 (p<0.001) and a significantly lower number of Gram-negative bacilli in culture specimens (p<0.05) than did patients in the antacid/H\textsubscript{2} antagonist group. Pneumonia occurred in 11.5 percent of the sucralfate group and 23.2 percent of the antacid/H\textsubscript{2} blocker group (p=0.11). However, of the 17 patients treated with H\textsubscript{2} antagonists alone, only one (5.9 percent) developed pneumonia compared with 15 (29 percent) of 52 patients treated with antacids or antacids plus H\textsubscript{2} antagonists. Excluding crossover patients, incidence rates reached a statistically significant difference: 9.1 percent vs 23.2 percent (p=0.05). The mortality rate in the sucralfate group (including crossover patients) was 29.5 percent vs 46.4 percent in the antacid/H\textsubscript{2} blocker group (p<0.07). The investigators concluded the following: “Although our results fell short of statistical significance when they were analyzed according to intention to treat, they suggest that agents that elevate gastric pH increase the risk of nosocomial pneumonia in patients receiving ventilation by favoring gastric colonization with Gram-negative bacilli.” Although the results were not statistically significant, they certainly appear to be clinically significant. What can one conclude from this study? Sucralfate does not raise the gastric pH nor does it promote bacterial overgrowth to the extent that gastric alkalinization therapy does. This study shows a trend toward a lower incidence of pneumonia and lower mortality rates in patients whose gastric pH is not altered and who are not extensively colonized by Gram-negative bacilli.

Tryba\textsuperscript{22} also studied the use of sucralfate and antacids in 100 mechanically ventilated ICU patients who were prospectively randomized to antacid or sucralfate therapy. Thirty-nine patients were excluded after randomization because of primary thoracic trauma or pneumonia. Strict diagnostic criteria and blinded assessments were used to diagnose lower respiratory tract infection. Those treated with sucralfate had a higher proportion of gastric aspirates with a pH <4. ICU-acquired pneumonia developed in 3 of 29 patients in the sucralfate group and 11 of 12 patients in the antacid group (p<0.05). However, such a difference may have been due to the presence of confounding variables such as underlying medical illness, use of enteral feeds, and use of prophylactic antibiotics. The
investigators did not comment on these variables. Also, the presence of such a large exclusion group after randomization offers the potential for bias. Nevertheless, these findings tend to corroborate those of Dricks et al.18

Whether sucralfate reduces the incidence of nosocomial pneumonia is not yet settled and further studies are needed to validate this hypothesis. In fact, one other possible explanation is that sucralfate may have antibacterial properties of its own. Both Tryba and Mantey-Stiers24 and Daschner et al17 have examined the antibacterial effect of sucralfate in gastric juice. The rate of bacterial growth in simulated gastric juice is markedly diminished by sucralfate, independent of its effect on pH. Nevertheless, it is clear that the lower the gastric pH, the lower the colony count of Gram-negative bacilli, and this appears to be associated with a lower incidence of nosocomial pneumonia.

Is the Association Strong?

Strength refers to the magnitude of the difference between the incidence of pneumonia in groups with and without gastric colonization by Gram-negative bacilli. Trials of selective decontamination of the digestive tract demonstrated a fourfold to sixfold reduction in lower respiratory tract infections in the experimental populations compared with control populations. Since the estimates of the strength of this association were generated in a number of instances by randomized trials, this adds further support to the hypothesis.

Is the Association Consistent from Study to Study?

A thorough review of the published literature revealed only one study that did not support the premise that the stomach acts as a reservoir for Gram-negative bacilli that in turn can cause pneumonia. Driks et al25 examined the role of gastric colonization in nosocomial respiratory infections in 40 neurosurgical patients. Endotracheal and nasogastric aspirates plus oropharyngeal swabs were sampled daily and colonization and infection rates were studied. Gram-negative bacilli were recovered from nasogastric aspirates of only 11 patients with the amount of microbial growth directly related to increases in gastric pH. There was a statistically significant relationship between Gram-negative bacilli isolated from both the stomach and the trachea, but the sequence of transmission (stomach to trachea) was documented in only one case. Fifteen patients subsequently developed pneumonia. The investigators concluded that gastric colonization was not a significant risk factor for tracheal colonization or pneumonia.

There are several reasons that explain why the study of Reusser et al26 may have shown discordant results. First of all, the study population was different; the average age of the neurosurgical patients was 34 years. There was no mention of any underlying disease state but given the average age, they probably had few other significant medical problems. This population would differ substantially from others studied in medical/surgical ICUs. Among other factors, bacterial adherence and subsequent colonization are related to patient age and severity of underlying illness.29 This might explain why gastric colonization rates were so low in this study. Ten patients had identical strains of Gram-negative bacilli isolated from both gastric and endotracheal aspirates. Given that there were so few patients with Gram-negative bacilli in their stomach, it is not surprising that the investigators were able to document the sequence of transmission in only one patient. Of those patients with gastric colonization with Gram-negative bacilli, it is impossible to tell how many subsequently developed pneumonia. Therefore, from the data presented, we cannot make any comment on the relationship between gastric colonization and nosocomial pneumonia. All other investigators, using different strategies and in different settings, consistently demonstrated an association between gastric colonization and nosocomial pneumonia.

Is the Temporal Relationship Correct?

Much has been done to define the temporal sequence in the pathogenesis of ICU-acquired pneumonia. In 1972, Johanson and colleagues30 completed a prospective cohort study of 213 patients in a medical ICU to determine the frequency of colonization of the respiratory tract with Gram-negative bacilli and the relationship of such colonization to nosocomial pneumonia. Sequential cultures from the posterior oropharynx and from tracheal aspirates confirmed a temporal relationship. Forty-five percent of the patients became colonized with Gram-negative bacilli. Of these, pneumonia developed in 23 percent while only 3.3 percent of the noncolonized patients developed pneumonia.

Although there was no mention of gastric colonization, this study supported the general concept that prior colonization of the upper respiratory tract with Gram-negative bacilli is associated with subsequent lower respiratory tract infection. However, there were some design flaws in this study. It was not stated whether the organisms isolated from the oropharynx were the same as the organisms that caused infection. Strict diagnostic criteria were not adhered to nor was there a blinded assessment of outcomes. Both of these represent potential sources of bias. Also, the investigators failed to comment on or control for concomitant therapy or interventions such as use of enteral feeds or gastric alkalization. Such cointervention could represent confounding variables. Nevertheless, the association between colonization of the upper respi-
ratory tract and subsequent pneumonia was very strong (RR = 6.6).

The work of Johanson et al was further substantiated by a study done by Kerver and colleagues. They showed that in 66 percent of bacteriologically documented lower respiratory tract infections, pathogens had been isolated previously from endotracheal aspirates.

Subsequent studies have demonstrated consistently the association between colonization and infection and have attempted to implicate the stomach as a reservoir for Gram-negative bacilli. Schwartz et al27 studied daily cultures from rectal, hypopharyngeal, and tracheal sites in 20 ICU patients. Enterobacteriaceae were commonly isolated from rectal cultures before they colonized the trachea. However, nonenterobacteriaceae (e.g., Pseudomonas and Acinetobacter) were rarely found in such sites prior to their appearance in the trachea, suggesting that colonizing enterobacteriaceae originate from the patient's endogenous gut flora while nonenterobacteriaceae came from environmental sources. Pseudomonas is commonly isolated from hospital personnel, water supplies, or other environmental sources. Whether bacteria are endogenous or exogenous in origin, the stomach may ultimately act as a reservoir for these organisms, especially if the normal acidity of the stomach is altered.20

In 1978, Atherton and White29 suggested that the stomach acted as a reservoir for colonization of the esophagus, mouth, and nasopharynx, and subsequently the trachea. They described ten mechanically ventilated patients with paralytic ileus who developed microbial overgrowth of the stomach. In six patients, the same Gram-negative bacilli were subsequently found in the trachea and in three patients the sequence of transmission from the stomach to the trachea was clearly documented.

In a study of 142 critically ill patients who were being mechanically ventilated and given gastric alkalization therapy, Daschner and colleagues17 demonstrated that gastric colonization preceded tracheal colonization in 32 percent of the patients.

DuMoulin et al30 further demonstrated this sequence. They examined the gastric and respiratory tract flora of 60 ICU patients, all of whom were receiving antacids or cimetidine. In 52 patients, one or more organisms were cultured from the upper airway and the stomach. Thirty-one of these patients subsequently developed Gram-negative bacillary pneumonia and in 11 of the cases, the causative organisms were clearly of gastric origin. Pneumonia did not occur in the eight patients whose gastric and airway flora were different. It was also noted that the gastric pH correlated with increased numbers of Gram-negative bacilli. However, there were some problems with the study design. Again, strict diagnostic criteria were lacking, no blinded assessments were done, and potential confounders were not controlled for. Despite these concerns, this study further contributes to the theory that colonizing Gram-negative bacilli originate in the patient's endogenous flora, possibly the stomach, and that the maintenance of high gastric pH is associated with increasing numbers of Gram-negative bacilli in the stomach.

Is There a Dose-Response Gradient?

Donowitz et al31 showed that in 153 ICU patients receiving antacids or H2 antagonists, Gram-negative bacilli were recovered from 59 percent of gastric specimens when gastric pH was >4 and from only 14 percent when gastric pH was <4. They also demonstrated graphically that as the gastric pH rose, so did gastric colonization with Gram-negative bacilli. The study of Daschner et al17 showed a relationship between the incidence of pneumonia and the gastric pH. The higher the pH, the more Gram-negative bacilli that were isolated from the stomach and the greater the incidence of pneumonia. Such a biologic gradient would further support the causal hypothesis.

Does the Association Make Epidemiologic Sense?

A causal relationship between gastric colonization and nosocomial pneumonia is compatible with the current understanding of the distribution and determinants of this disease.

Does the Association Make Biologic Sense?

Application of this criterion is more relevant to nonhuman experimental data. Certainly this association concurs with our current understanding of bacterial adherence, colonization, and pathogenesis of pneumonia.

Is the Association Specific?

According to Trout,1 limitation of the association to "a single putative cause and a single effect" allows one to satisfy this particular diagnostic test. This is difficult when dealing with a subject as complex as pneumonia.

To date and to our knowledge, there are no data to

| Table 1—Diagnostic Tests of Causation |
|-------------------------------|------------------|
| Tests*                        |                  |
| 1. Is there evidence from true experiments in humans? | |
| 2. Is the association strong? | |
| 3. Is the association consistent from study to study? | |
| 4. Is the temporal relationship correct? | |
| 5. Is there a dose-response gradient? | |
| 6. Does the association make epidemiologic sense? | |
| 7. Does the association make biologic sense? | |
| 8. Is the association specific? | |
| 9. Is the association analogous to a previously proved causal association? | |

*Listed in order of decreasing importance.
support a specific causal relationship between gastric colonization with Gram-negative bacilli and nosocomial pneumonia. In fact, studies of selective decontamination therapy have demonstrated that a reduction in numbers of Gram-negative bacilli in the digestive tract results in a reduction in all infections that may be caused by Gram-negative bacilli (i.e., urinary tract, line-related, intra-abdominal). These results could be interpreted as suggesting that the association is specific to nosocomial infection in general but not to a specific site of infection.

Is the Association Analogous to a Previously Proved Causal Relationship?

This has been referred to by Trout as the "last and least" of the diagnostic tests. Data on infections in cancer patients, particularly those with hematologic malignant neoplasms who are undergoing remission induction therapy, suggest the gut as a reservoir and potential source of organisms that lead to infection in these patients.4

In summary, subjecting the current literature dealing with the association between gastric colonization with Gram-negative bacilli and nosocomial pneumonia to the nine tests outlined above (Table 1) provides strong evidence for a causal relationship. First and foremost, there is good evidence from true experiments in humans, the strongest evidence coming from randomized controlled trials on selective decontamination of the digestive tract and on gastric alkalinization therapy. The association is a strong one as shown by selective decontamination studies that virtually eliminate Gram-negative bacilli from the digestive tract with a resulting fourfold to sixfold reduction in the incidence of pneumonia. The association is consistent as it is described repeatedly in many of the studies already mentioned. The temporal relationship between gastric colonization and nosocomial pneumonia has been elucidated in a number of descriptive studies, and a dose-response gradient in terms of increasing gastric pH leading to increased gastric colonization appears to be linked to a rise in the incidence of pneumonia. Given what has been described previously in the literature, the causal relationship between gastric colonization and nosocomial pneumonia makes both biologic and epidemiologic sense. However, to date there is no evidence to support a specific association, although a somewhat analogous association has been demonstrated in patients with infection and hematologic malignant neoplasms.

In conclusion, gastric colonization with Gram-negative bacilli appears to play a causal role in the development of nosocomial pneumonia in the ICU patient. The significance of this relationship lies in its implications for management strategies that it offers: to reduce the burden of nosocomial pneumonia, gastric colonization with Gram-negative bacilli must be prevented or eliminated. Naturally occurring defense mechanisms that prevent gastrointestinal colonization should be maintained or augmented. These include normal anatomy and motility, secretions, cell desquamation, and finally the indigenous and mostly anaerobic flora of the gut. Consideration of such a strategy offers many new research questions. Do motility-enhancing agents play a role in decreasing gastric colonization and cephalad transmission of organisms? Does the presence of a nasogastric tube increase the risk of pneumonia? How does the use of prophylactic, broad-spectrum antibiotics affect gastric colonization? What is the effect of enteral feeds on gastric colonization? Would acidifying the enteral feed (pH = 3.5) prevent or eliminate gastric colonization? Also, gastric alkalinization therapy and selective decontamination of the digestive tract require further investigation. Further studies should evaluate not only these issues, but other interventions that impact on gastric colonization in an attempt to further reduce the burden of illness from nosocomial pneumonia.

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