Pneumonia in the Critically Ill Hospitalized Patient

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CASE PRESENTATION

Dr. Douglas Schultz: A 59-year-old white man with a three-month history of systemic lupus erythematosus and a history of insulin-dependent diabetes mellitus was admitted to the hospital with a three-day history of fever to 38.8°C and dysuria. Evaluation revealed a urinary tract infection with E. coli and benign prostatic hypertrophy. One month later, the patient underwent transurethral resection of the prostate. On the fourth postoperative day, he developed fever to 39.4°C, shortness of breath, weakness, confusion, and reported a slightly productive cough. His medications at the time included prednisone, 10 mg daily, and NPH insulin, 20 units subcutaneously daily.

On initial examination, the patient was found to be mildly short of breath with a respiratory rate of 32, blood pressure of 120/76 mm Hg, and a temperature of 39.3°C rectally. His only remarkable physical findings were crackles in the posterior aspect of the right lung in the upper two-thirds of the chest. The remainder of his lung examination was unremarkable and no new extrapulmonary findings were noted.

Laboratory evaluation showed a white blood cell count of 8,600 with 85 percent polys and 10 percent bands. Blood glucose was 347 mg/dl and arterial blood gases, while breathing room air, showed a pH of 7.4, Pco2 38 mm Hg, and Paco2 of 56 mm Hg. A chest radiograph (Fig 1) showed a right upper lobe infiltrate. Sputum was evaluated by Gram stain and showed copious white blood cells with Gram-negative rods. Sputum and blood cultures were obtained. The remainder of the laboratory data was unremarkable.

The patient was treated with a presumptive diagnosis of nosocomial Gram-negative pneumonia and therapy included intravenous hydration, oxygen via a 40 percent Venti-mask, and intravenous cefazidine. In addition, the patient received appropriate increases in steroid therapy for stress, and insulin coverage for hyperglycemia. Two days later, the patient was found to be more short of breath and he was transferred to Winthrop-University Hospital's intensive care unit for further care. On arrival, the patient had a blood pressure of 70 palpable. Arterial blood gases, with the patient breathing via 40 percent Venti-mask, showed a pH of 7.36, Pco2 = 22 mm Hg, and Paco2 = 42 mm Hg. At that time, his blood cultures from the other hospital were reported to show two strains of Pseudomonas aeruginosa. A repeat chest radiograph (Fig 2) showed diffuse infiltration of the right lung and faint infiltration at the left base.

The patient was then endotracheally intubated and placed on mechanical ventilation. Antibiotic therapy was directed towards Pseudomonas aeruginosa with amikacin added to ceftazidime. Bronchoscopy was performed with a protected specimen brush and the brush was cut into 1 ml of tryptic soy broth and cultured quantitatively, revealing greater than 10⁶ Pseudomonas aeruginosa per ml in pure culture.

The patient was treated with mechanical ventilation for a period of three weeks. His therapy also included supplemental oxygen, titrated to maintain oxygenation, and he had gradual improvement in his oxygenation status and control of his respiratory infection. After three weeks of mechanical ventilation, the patient was successfully extubated. His course had been complicated by diarrhea, felt to be related to antibiotic therapy and tube feedings, intermittent supraventricular tachycardia, tracheostomy for airway care, and intermittent return of fresh blood from his nasogastric tube, in spite of prophylaxis of intestinal bleeding with cimetidine. At the time of discharge from the intensive care unit, the patient was felt to have recovered from his pneumonia and all of his antibiotics were discontinued. Sputum cultures continued to reveal Pseudomonas aeruginosa, but no therapy was prescribed.

Approximately one week after discharge from the intensive care unit, the patient again developed dyspnea, cough productive of green sputum, and fever to 38.3°C. A repeat chest radiograph (Fig 3) demonstrated persistent infiltrates in the right chest along with...

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FIGURE 1. Chest radiograph demonstrating right-sided pneumonia developing postoperatively.
lung. The patient was subsequently intubated and ventilated using a high frequency oscillator. After 2 weeks, the patient was weaned off the ventilator and discharged from the hospital.

Dr. Alan M. Fein: Our patient exemplifies the close clinical relationship which ties severe infection to the adult respiratory distress syndrome (ARDS). The patient, a 59-year-old man with systemic lupus erythematosus and diabetes mellitus, who was receiving corticosteroids, presented with Gram-negative pneumonia which was uncontrolled by the prescribed antibiotics and he then developed septic ARDS. ARDS may be conceptualized as the pulmonary component of a generalized inflammatory injury, especially to the endothelium. When initiated by severe infection, it often progresses to involve a sequential fashion other major organ systems, including kidneys, gastrointestinal tract and liver leading to a syndrome of multisystem organ failure. ARDS may have both direct and indirect causes which often overlap. Pneumonia is the most common direct cause of the adult respiratory distress syndrome, particularly if it involves a large enough segment of parenchyma to severely impair the mechanical and gas exchange function of the lung.\(^1\) While viral pneumonia typically involves the lung parenchyma in a diffuse fashion, most other classes of organisms, including bacteria (most commonly), fungi and mycobacteria, also have this capability.\(^1\) *Pneumocystis carinii* has emerged as a common cause of severe hypoxic respiratory failure, usually in patients with AIDS.\(^2\)

Infection may also initiate ARDS indirectly by activation of systemic inflammation.\(^3\) Bacteria, viruses, fungi, or even traumatized tissue induce a similar systemic response characterized by hypermetabolism (even in the absence of blood stream invasion) and subsequent multorgan failure.\(^4,5\) The link between this systemic response, organ failure and infection is under complex and active investigation. Recent work has emphasized the central role of lymphocyte/macrophage-derived tumor necrosis factor (cachectin) and interleukin-1, in modulating the response to sepsis.\(^6\) Other potential mediators in this chain are activated neutrophils, complement and the various components of the thrombotic system, which may directly injure tissue and amplify inflammation.\(^3\)

Dr. Niederman: Is it possible to predict which septic patients will develop ARDS?

Dr. Fein: ARDS usually follows onset of the septic syndrome within 72 hours.\(^3\) While isolated bacteremia carries a relatively low risk for progressive lung injury (6-15 percent), when combined with shock and thrombocytopenia, the risk rises dramatically to 65 and 46 percent, respectively.\(^4,5\) Additional insults, such as hypertransfusion, aspiration or burns will increase the likelihood of sepsis leading to ARDS to approximately 50 percent.

At the present time, clinical signs in patients at risk are the best predictors of progressive lung injury.\(^4\) In a recent analysis combining injury severity score (ISS), individual risk factors and initial oxygenation, Pepe et al\(^8\) reported that ISS, numbers of transfusions, the presence of the septic syndrome and initial oxygenation best predicted ARDS, in that order. Our own data suggest that severity of presenting hypoxemia...
and metabolic acidosis are better predictors of progression to ARDS in septic patients than are any measurements of mediators in serum.9

In many studies, the measurement of plasma factors to predict ARDS has been disappointing.4,5,9 While various components of activated complement are elevated in septic patients, none has been shown to consistently predict progressive lung injury.10-12 Recently, a prospective study by Langlois and Gawryl13 demonstrated the terminal complement complex was increased by an average of 100 percent in septic patients who developed ARDS prior to the onset of clinical lung injury. While interesting, these findings await confirmation at other clinical centers. The neutrophil is also an important participant in the initial phases of lung injury.14 Despite this, our own data suggest that neither neutrophil turnover nor neutrophil chemoattractant activity can identify which septic patients will develop ARDS.9

**Dr. Niederman: How does sepsis affect the outcome of ARDS?**

**Dr. Fein:** Advances in the management of respiratory failure have reduced the number of patients who succumb to hypoxemia. Rather, deaths occurring 72 hours or more after the initial insult usually result from uncontrolled pulmonary sepsis.14 Nosocomial pneumonia is evident in more than 70 percent of patients with ARDS.15 Infection in a damaged lung potentially influences the outcome by several mechanisms. The additional septic burden further enhances the release of inflammatory mediators including tumor necrosis factor (TNF) and interleukin-1, directly potentiating organ damage and recruiting more neutrophils and macrophages to the lung. These effector cells release proteases and oxidants which promote colonization by micro-organisms and lead to disordered repair of connective tissue matrix and fibrosis. Among ARDS patients with infection, 67 percent died compared to only 7 percent of non-infected patients and those with nosocomial pneumonia may have an even higher mortality.14 Most infected patients have failure of other organ systems in addition to the lung.16

It is interesting that following the recovery from ARDS, our patient developed a second episode of respiratory failure, with recovery of both *Pseudomonas aeruginosa* and *Pneumocystis carinii*. Both of these organisms are indicators of a markedly compromised host. Host defense impairments are common in the multiorgan failure syndrome and clearly influence outcome.17 In our patient these compounded the already significant effects of systemic lupus erythematosus, diabetes, and corticosteroid therapy. Proteolytic enzymes, especially neutrophil elastase, are released into the alveolar lining fluid in ARDS.18 In addition to its effects on connective tissue matrix, elastase may inhibit ciliary function, and degrade immunoglobulin IgG and secretory IgA, thereby inhibiting bacterial clearance and phagocytosis.17,19,20 Likewise, the formation of pulmonary edema fluid may directly inhibit bacterial clearance by macrophages21 and washout surfactant, which has antimicrobial activity.22 While there is no mention in our patient of liver dysfunction, this is a frequent accompaniment of ARDS and multiorgan failure.23 Liver dysfunction limits clearance of gut bacteria, endotoxin and circulating inflammatory mediators such as TNF, thus enhancing injury.24 Iatrogenic factors may also impair host defenses. High inspired oxygen tensions used in the patient's treatment as well as corticosteroids, impair the phagocytic function of macrophages and neutrophils.20,24,25 It is clear that failure of multiple host defenses contributed to the second episode of acute respiratory failure which he sustained.

**Dr. Niederman:** The patient being discussed today had Gram-negative colonization of the tracheobronchial tree and Gram-negative pneumonia, two findings that are closely interrelated. In addition, the pathogenesis of airway colonization is related to many of the host impairments that our patient demonstrated. He had two episodes of pneumonia, both acquired in the hospital, and at the conclusion of the first episode, he continued to grow *Pseudomonas aeruginosa* in his lower airway, in the absence of clinical signs of infection. This represented airway colonization which had persisted after an initial pneumonic episode. While still colonized with *Pseudomonas aeruginosa*, he developed a second episode of pneumonia which was due to both *Pseudomonas aeruginosa* and *Pneumocystis carinii*. The features of interest in this case are the relationship of airway colonization to the subsequent occurrence of pneumonia, the mechanisms that allow risk factors to lead to colonization of the airway by Gram-negative bacteria, and reasons for persistent lower airway colonization by *Pseudomonas aeruginosa*.

Colonization of both the upper and lower respiratory tract are frequently associated with the occurrence of nosocomial pneumonia. Rates of Gram-negative colonization of the oropharynx are directly related to the severity of illness for a given patient. In a study by Johanson and colleagues,26 utilizing multiple cultures of the oropharynx, it was found that no more than 6 percent of normal individuals had oropharyngeal colonization by Gram-negative bacteria. However, as patients became progressively ill, the incidence of Gram-negative colonization of the upper airway increased, such that with multiple cultures, nearly three-quarters of the sickest patients in the hospital were colonized with enteric Gram-negative bacteria. The relevance of this finding to the occurrence of pneumonia was shown in a follow-up study of 213 intensive care unit patients, 26 of whom developed nosocomial
pneumonia. Among the patients with pneumonia, 22 of 26 had prior oropharyngeal colonization by Gram-negative bacteria, indicating a high co-association between upper airway colonization and the subsequent occurrence of parenchymal lung infection. The reason for the close relationship between airway colonization and pneumonia may be the result of two factors. First, once the airway is colonized by Gram-negative bacteria, these organisms are available for aspiration into the tracheobronchial tree. In addition, it is possible that patients who have become colonized in the oropharynx have host impairments which predispose not only to upper airway colonization, but also to lower airway colonization and subsequent pneumonia. Thus, colonization of both the upper and lower respiratory tract can be viewed as a "marker" of a seriously ill patient who has multiple impairments in respiratory host defenses.

The patient discussed today has multiple risk factors for both upper and lower airway colonization (Table 1). These included his serious degree of underlying illness, recent surgery, the use of multiple antibiotics, endotracheal intubation and tracheostomy, malnutrition, the use of corticosteroids, recurrent hypotensive episodes, and the use of histamine type-2 receptor blocking agents for the prophylaxis of gastrointestinal bleeding. Each of these factors increased the risk of airway colonization through a variety of mechanisms.

Antibiotics can increase the risk of infection by interfering with the normal flora in both the upper and lower respiratory tract. The normal upper respiratory tract rarely harbors Gram-negative bacteria and is usually colonized by Gram-positive organisms, particularly anaerobes, which may "interfere" with the growth of Gram-negative organisms. It has been conceptualized that the normal flora of the upper airway occupy bacterial binding sites in the oropharyngeal mucosa and, thereby, block subsequent colonization by Gram-negative bacteria. This type of interference can be eliminated with the use of systemic antibiotics. A similar mechanism may also apply in the lower airway, although in most individuals the lower airway does not have normal flora and is sterile.

Endotracheal intubation can increase the risk of upper and lower airway colonization and pneumonia. Patients with tracheostomy have nearly a 70 percent incidence of nosocomial pneumonia and this is largely related to two factors. First, patients with tracheostomy have the capacity for organisms to directly enter the lower respiratory tract, thereby bypassing upper airway defenses. In addition, the presence of a tracheostomy or an endotracheal tube may traumatize the tracheobronchial mucosa and alter its integrity, making it more susceptible to invasion and colonization.

Corticosteroids may predispose to colonization by interfering with a variety of host defense mechanisms. Histamine type 2 (H2) blockers similarly may predispose to colonization by the mechanisms to be discussed by Dr. Craven. In our own studies of mechanically ventilated patients, it has been observed that Pseudomonas species colonization of the lower airway was more common in patients receiving H2 blockers than in patients who did not receive this therapy.

The major pathogenetic mechanism that unifies many of the risk factors for upper and lower airway colonization involves the cell-cell interaction termed bacterial adherence. At multiple mucosal sites throughout the body, the binding of bacteria to the epithelial surface has been demonstrated to be an important mechanism that leads to colonization. In the respiratory tract, bacterial adherence has been demonstrated to mediate Gram-negative colonization of both the upper and the lower airway. Many of the risk factors for airway colonization have been shown to act by enhancing the ability of respiratory epithelial cells to bind bacteria, thereby allowing bacteria to establish a foothold on the respiratory mucosa (Table 1). Studies to date have demonstrated that general surgery, renal failure, malnutrition and cardiac bypass surgery all have the ability to make oropharyngeal epithelial cells express more binding sites for Gram-negative bacteria.

In studies by Johanson and colleagues, it has been demonstrated that patients whose lungs became colonized after general surgery had a serial rise in the ability of their buccal epithelial cells to bind bacteria. Such a serial rise was not observed in patients who did not develop colonization following general surgery. The mechanism whereby serious illness and systemic insult increase the number of binding sites on oral epithelial cells has been evaluated by the same investigators. In these studies, it was shown that certain
critically ill patients elaborate proteases in their salivary secretions which have the capacity to digest fibronectin from the cell surface. Fibronectin appears to be a blocking glycoprotein which covers epithelial cell receptors for Gram-negative bacteria. With the release of oral proteases, fibronectin is removed from the buccal epithelial surface, thereby exposing more epithelial receptors for subsequent bacterial binding. It is yet unknown whether similar mechanisms operate in the lower respiratory tract. However, it has been shown that patients with tracheostomy, colonized by *Pseudomonas aeruginosa*, had an overall higher degree of tracheal cell binding capacity than did tracheostomized patients who were not colonized by *Pseudomonas aeruginosa*. In addition, patients with the highest degree of tracheal cell adherence tended to have the highest levels of neutrophil elastase in their tracheal secretions. Thus, it is possible that proteases in high concentrations, in some manner mediated the increased adherence to tracheal epithelial cells that was seen in patients colonized in the lower airway by *Pseudomonas* species.

Malnutrition is one host factor that has been related to both colonization and increases in adherence to both oral and tracheal epithelial cells. Higuchi and colleagues demonstrated, in an animal model, that with progressive declines in animal weight, there was a serial rise in the ability of buccal epithelial cells to bind bacteria. In addition, among tracheostomy patients, those with the most severe nutritional impairment tended to have the highest degree of tracheal cell adherence. In patients with endotracheal intubation who were receiving mechanical ventilation, it has also been shown that patients who were severely malnourished had a greater likelihood to develop lower respiratory tract colonization by *Pseudomonas* species than intubated patients who were better nourished.

In studies of bacterial adherence, there has been the consistent observation, in normal individuals and in critically ill patients, that tracheal cells have a greater capacity to bind *Pseudomonas aeruginosa* than do buccal epithelial cells. The clinical relevance of these findings may relate to the occurrence of tissue "tropisms," or preferences, of *Pseudomonas aeruginosa* in the human respiratory tract. In other words, if *Pseudomonas aeruginosa* binds to tracheal cells more avidly than it binds to buccal cells, then possibly *Pseudomonas aeruginosa* would preferentially colonize the lower airway rather than the upper airway, if the organism has access to both sites simultaneously. Such a situation does exist in patients with tracheostomy and in patients with endotracheal intubation. In both of these populations, colonization studies have demonstrated that *Pseudomonas* species colonized the lower airway more frequently and persistently than the upper airway. The patient discussed today did not have bacterial adherence directly measured. However, it is likely that many clinical factors did increase his tracheal cell capacity to bind *Pseudomonas aeruginosa* and, thereby, led to persistent lower airway colonization by *Pseudomonas aeruginosa*. The persistence of colonization by *Pseudomonas aeruginosa* in such patient may be related to multiple factors. The patient was severely malnourished and if malnutrition increased tracheal cell binding capacity for bacteria, then *Pseudomonas* colonization would persist until the malnutrition was reversed. In addition, with colonization, airway inflammation is present and neutrophils in inflammatory secretions can release elastase which can, in turn, interfere with the local protective function of IgA and further predispose to airway colonization. A vicious circle of colonization begetting more colonization is quite likely in this circumstance.

In addition to more frequent and more persistent colonization of the lower airway rather than the oropharynx, the other expression of tissue "tropisms" in the human respiratory tract may be that the lower airway becomes colonized by *Pseudomonas* species independent of the upper airway. In mechanically ventilated patients, *Pseudomonas* species, in contrast to other Gram-negative bacteria, have the capacity to colonize the lower airway without first colonizing the upper airway. This finding of primary tracheobronchial colonization has been observed by several investigators. Schwartz et al have reported that while Enterobacteriaceae entered the trachea after initial oropharyngeal colonization, other organisms such as *Pseudomonas* species rarely were found in the upper airway before colonizing the lower airway. Pingleton et al have also observed that intubated patients may have primary tracheal colonization by Gram-negative bacteria.

At least three different factors influence the adherence of bacteria to cells. These include host cell variables, bacterial variables, and micro-environmental factors. Among host cell variables, the most important factors include the site of cellular origin and the type of host from which the cells are taken. Another cellular variable that may be important is the presence of cilia. Recently, it has been shown that *Pseudomonas aeruginosa* can bind directly to ciliary structures.

Bacterial variables are important because certain organisms have the capacity to bind epithelial cells while others do not. Specific features that enhance an organism's ability to bind to epithelial cells include the presence or absence of a capsule, the type of surface appendages present, and the nature of the exoproducts released by the bacteria. Certain *Pseudomonas* species do have the capacity to bind epithelial cells directly via their pili, which may serve
as bacterial adhesions that attach directly to the epithelial surface.\textsuperscript{47}

The micro-environment in which bacteria meet epithelial cells is also a determinant of adherence. For example, the composition of sputum, both its protease and mucin components, can influence whether or not bacteria bind epithelial cells. In addition, the pH of the epithelial surface may influence the ability of bacteria to bind.\textsuperscript{48} As mentioned previously, proteolytic components of sputum may alter the bacterial binding interaction.\textsuperscript{30} Mucins in sputum can serve as receptors for bacterial binding and thus have the capacity to competitively inhibit bacterial binding if they bind to bacteria, but not directly to cells. On the other hand, if mucins attach directly the cellular surface, then they may act as a receptor "bridge" for bacteria and further increase the capacity of the epithelium to bind bacteria.\textsuperscript{49} This may be particularly important in patients who have impaired mucociliary clearance where large quantities of mucins may adhere to the epithelial surface and, thereby, predispose to colonization.

Based on our understanding of bacterial adherence, it may become possible in the future to devise prophylactic strategies for airway colonization. As we better understand the nature of bacterial adherence, we may be able to develop vaccines with the use of adhesins as antigens and, thereby, form local antibody which can block bacterial binding. To the extent that mucins serve as cellular receptors for bacteria, the use of mucolytic or ciliokinetic agents may be helpful in modifying the risk of infection. In addition, our insight into bacterial adherence studies has shown that primary colonization of the lower airway by \textit{Pseudomonas aeruginosa} is possible. Consideration of this finding may be useful in the design of protocols that employ prophylactic antibiotics. As Dr. Craven will discuss, many protocols that are designed to prevent nosocomial pneumonia involve sterilization of the oropharynx and the gastrointestinal tract, under the presumption that these are the only sources of organisms that enter the lung. If \textit{Pseudomonas aeruginosa} can enter the tracheobronchial tree without first colonizing elsewhere, then prevention of infection by this organism may require the direct application of antibiotics to the lower airway, and not just to the oropharynx and gastrointestinal tract.

\textit{Dr. Niederman: Dr. Craven, can you discuss the scope and causes of the problem of nosocomial pneumonia?}\n
\textit{Dr. Craven:} Nosocomial pneumonia accounts for approximately 15 percent of hospital-acquired infections\textsuperscript{50} and is the leading cause of death from nosocomial infection.\textsuperscript{51} Rates of nosocomial pneumonia are considerably higher in intensive care unit patients compared to patients on hospital wards, and mechanically ventilated patients have a risk of pneumonia that is several fold higher than nonventilated patients.\textsuperscript{51,52,53} Celis et al\textsuperscript{52} examined 120 consecutive episodes of nosocomial pneumonia and found intubation increased the risk of nosocomial pneumonia approximately 7-fold. Cross and Roupe\textsuperscript{51} found rates of pneumonia in patients receiving mechanical ventilation via an endotracheal tube were increased 10-fold compared to patients with no respiratory therapy device.\textsuperscript{51} In the Study on the Efficacy of Nosocomial Infection Control (SENIC), only 1 percent of the patients were treated with continuous ventilatory support, but the rate of pneumonia was 21-fold higher than patients who were not receiving mechanical ventilation.\textsuperscript{52}

Gram-negative bacilli, such as \textit{Escherichia coli}, \textit{Klebsiella pneumoniae}, and \textit{Pseudomonas aeruginosa} are the most common types of bacteria causing nosocomial pneumonia. \textit{Staphylococcus aureus}, which can be methicillin-sensitive or resistant, accounts for a large portion of hospital-acquired pneumonia in some hospitals. Nosocomial pneumonia due to \textit{Legionella pneumophila} has been reported in certain geographic areas such as Pittsburgh, Burlington (Vermont), and Los Angeles. These infections are usually associated with cooling-tower reservoirs or hospital water which is heavily colonized with the organism. Anaerobes have been cultured from approximately 30 percent of infected patients, but appear to be less important than aerobic pathogens. Most nosocomial pneumonias are caused by more than one pathogen.

Fatality rates for patients with nosocomial pneumonia remain high in many series.\textsuperscript{53-56} Nosocomial pneumonia contributed to 60 percent of the fatal nosocomial infections in a study of 200 consecutive hospital deaths by Gross et al.\textsuperscript{53} Stevens et al\textsuperscript{54} reported fatality rates of 50 percent for intensive care unit patients with hospital-acquired pneumonia compared to 3.5 percent of patients without pneumonia and rates were higher for patients infected with \textit{Pseudomonas aeruginosa}. In our study of 233 mechanically ventilated patients, there was a 55 percent fatality rate for patients with pneumonia compared to a rate of 25 percent for patients without pneumonia.\textsuperscript{55} These data underscore the need for earlier recognition, treatment, and prevention.

\textit{Dr. Niederman: What are some of the risk factors for nosocomial pneumonia?}\n
\textit{Dr. Craven:} Aspiration of bacteria from the oropharynx is the primary route of entry into the lung, and a number of factors affect the type and number of bacteria that colonize the oropharynx.\textsuperscript{56,57} Most of us aspirate bacteria into our lower airways daily, but pneumonia does not develop.\textsuperscript{56} The development of pneumonia is not only related to the numbers and types of bacteria that are aspirated, but also ability of the lung's mechanical, humoral, and cellular defenses to contain and prevent infection.
Table 2—Factors That May Increase the Risk of Nosocomial Pneumonia by Altering Colonization, Increasing the Risk of Aspiration, or Impairing Host Defenses

<table>
<thead>
<tr>
<th>Host factors:</th>
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<tbody>
<tr>
<td>Age</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Coma</td>
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<tr>
<td>Underlying disease-chronic lung disease, congestive heart failure, diabetes mellitus, AIDS, systemic lupus, cancer, central nervous system diseases, seizures, head trauma, uremia, malnutrition</td>
</tr>
<tr>
<td>Drugs:</td>
</tr>
<tr>
<td>Heroin, cocaine, alcohol, sedatives, antibiotics, antacids, histamine type-2 blockers, steroids, cytotoxic drugs</td>
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<tr>
<td>Invasive Devices:</td>
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<tr>
<td>Intubation, tracheostomy, mechanical ventilation, nasogastric tube</td>
</tr>
<tr>
<td>Surgery:</td>
</tr>
<tr>
<td>Head and neck, chest, abdomen</td>
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</table>

Risk factors that may increase the risk of nosocomial pneumonia are summarized in Table 2. Host factors such as age and underlying disease may either allow more bacteria to enter the lung or impair removal of bacteria by various pulmonary host defense mechanisms. Drugs or medications may either alter consciousness or promote infection by impairing removal of pathogens from the lung. Invasive devices and surgery increase the risk of aspiration or removal of bacteria from the lung.

As mentioned, the use of an endotracheal tube may increase the risk of nosocomial pneumonia at least 6- to 21-fold compared to nonintubated patients. The presence of the endotracheal tube impairs removal of bacteria, allows leakage of pathogens around the cuff, and causes local trauma and inflammation (Table 3). The upper part of the tracheobronchial tree contains heavily ciliated epithelium and mucus that can trap and clear bacteria from the lung. The cilia beat hundreds of times per minute, in unison, to move mucus and bacteria out of the trachea. Colonization of the tracheobronchial tree may decrease or alter this activity, and increase the number of pathogens to be cleared by alveolar macrophages, polymorpho-nuclear leukocytes, humoral antibodies (IgM, IgG, IgA), and complement. In addition, the endotracheal tube can impair swallowing, and alter the host’s diet and thus his intestinal flora. The use of a nasogastric tube is also a widely unappreciated risk factor for pneumonia, that may increase the risk of nosocomial pneumonia by several different mechanisms (Table 3).

Dr. Niederman: Dr Craven, could you comment on the role of respiratory therapy equipment in the pathogenesis of pneumonia?

Dr. Craven: When a patient is mechanically ventilated, the lower respiratory tract may become colonized more readily with bacteria. In the 1960s, the Dallas group reported that ventilators with contaminated mainstream nebulizers could generate bacterial aerosols that infiltrated the terminal bronchioles and alveoli, resulting in a necrotizing Gram-negative pneumonia. Most ventilators now heat and humidify the inspiratory phase gas with humidifiers that do not generate significant bacterial aerosols.

While ventilators rarely infect patients, secretions from patients are a common source of bacterial contamination of the mechanical ventilator tubing and condensate present in the tubing. If the condensate is inadvertently flushed back into the patient, pneumonia can result, because the patient receives a large inoculum of bacteria in a volume of fluid which can be inoculated directly into the lungs, thereby overwhelming host defenses. Several devices have been advocated to remove condensate from the circuit. One of these devices, the heat moisture exchanger, eliminates the condensate problem, but may not provide optimal humidity to the patient.

In-line medication nebulizers are a potential source of bacterial aerosols that may penetrate to the terminal bronchioles and avoid host defenses. These devices may become contaminated by reflex of condensate from the tubing. Humidifying cascades appear to be an unlikely risk factor for pneumonia and ventilator circuit colonization. Humidifying cascades should be filled with sterile water and because of the high temperature in the cascade, bacterial growth of the most nosocomial pathogens is limited.

Dr. Niederman: Please explain how gastric colonization may serve as a risk factor for pneumonia and discuss how we could approach intestinal bleeding prophylaxis so as to minimize pneumonia risk.

Dr. Craven: First, let me briefly discuss the subject of stress ulcer prophylaxis. In contrast to the 1970s, when stress bleeding was a serious complication for intensive care patients, the incidence in the 1980s appears to be less frequent, perhaps because of improvements in mechanical ventilation, nutritional support, and early treatment of shock. For this reason,
it is critical to carefully assess the needs of each specific patient and the risk-benefit ratio of any prophylactic agent.

Many critically ill patients receive prophylaxis against stress bleeding with antacids which may neutralize gastric acid or H2-blockers that block gastric acid secretion. Antacids and/or H2-blockers such as cimetidine and ranitidine have been used for prophylaxis against stress bleeding in critically ill patients with variable effectiveness. The efficacy depends on the criteria used to assess stress bleeding, the doses administered, and the patient population studied. Antacids have been most effective in studies where they were administered every 2 hours to maintain gastric pH above 3.5. H2-blockers have been most effective in earlier studies of stress bleeding prophylaxis, and for critical care patients who have a moderate risk of bleeding. When macroscopic bleeding is used as the criterion for efficacy and when combining results of all studies, antacids and H2-blockers appear to have similar efficacy and appear more effective than placebo.

Prophylaxis against stress bleeding can also be achieved with sucrose octasulfate which acts by a different mechanism. In contrast to the potential effects of antacids and H2-blockers on gastric pH, sucrose octasulfate (sucralfate) activity is independent of hydrogen diffusion or neutralization. In addition, sucralfate has little buffering capacity and appears to act by adhesion to the mucosa, altering gastric mucus, increasing PGE2 in the gastric lumen, and by absorbing pepsin. In studies reported to date, sucralfate appears to provide protection against stress bleeding that is similar to antacids and H2-blockers. Although suspensions of sucralfate are only available in Europe, a useable preparation for critically ill patients can be made by putting the tablet in solution, making a suspension, and then flushing it down the nasogastric tube. It is very important that the sucralfate tablet not be crushed before adding the saline solution or sterile water, and that the nasogastric tube be flushed after the sucralfate is given, to avoid clogging the tube.

Let me now briefly discuss the role of nasogastric tubes and gastric colonization in the pathogenesis of oropharyngeal colonization and pneumonia. Gastric colonization may be an important prerequisite for retrograde colonization of the oropharynx and the development of nosocomial pneumonia. The bactericidal activity of hydrochloric acid (pH -1) and gastric secretions was first demonstrated in 1939 by Garrod. Normally, the stomach maintains near-sterility by its acid pH. Changes in the gastric flora may occur in patients with increased age, malnutrition, achlorhydria, or other gastrointestinal diseases.

Reduced gastric acid in the intubated intensive care unit patients may result from intrinsic disease of gastric acid production or from the use of antacids or histamine type 2-blockers which neutralize or block gastric acid secretion. Correlation between levels of bacteria in the gastric juice and treatment of patients with peptic ulcer disease with cimetidine was reported by Ruddell et al. du Moulin et al described gastric overgrowth with Gram-negative bacilli in mechanically ventilated patients and related these finding to increasing the gastric pH. These observations have been corroborated by other investigators. The level of gastric overgrowth noted in critically ill ventilated patients is a concern. Some patients with high gastric pH had colonization with Gram-negative bacilli that reached 100 million organisms/ml. Colonization was usually considerably lower when the pH was less than 3.5. Gastric overgrowth with aerobic Gram-negative bacilli was most common, but high numbers of Gram-positive bacteria and fungi may occur as well.

Several investigators have studied the time sequence of colonization. du Moulin et al showed that 52 of 58 post-surgical patients with respiratory failure had gastric and/or tracheal colonization with Gram-negative bacilli and a clear sequence of transmission could be demonstrated in 17 of 52 patients. In 11 (65 percent of the patients), gastric colonization preceded tracheal colonization. In a similar study, using pharyngeal and gastric specimens from 40 medical and surgical patients, Goularte et al showed a clear sequence of colonization in ten patients in whom four (40 percent) had gastric colonization that preceded colonization of the pharynx. Daschner et al reported retrograde colonization of the trachea from the stomach in 32 percent of 142 patients who were receiving stress ulcer prophylaxis and mechanical ventilation. When a nasogastric tube is in place, it may facilitate the transfer of bacteria from a colonized stomach to the oropharynx and organisms may then be aspirated into the lung.

The possible role of gastric colonization in the pathogenesis of pneumonia was supported in our prospective study of risk factors for pneumonia in mechanically ventilated patients. Overall, 21 percent of the 233 patients receiving mechanical ventilation developed pneumonia. Pneumonia occurred in 38 percent of 18 patients who received antacids and cimetidine, 36 percent of 48 patients who received cimetidine alone, and in 18 percent of 135 patients who received antacids alone. Although the numbers of patients with pneumonia in each group were small, H2-blockers with and without antacids were independently associated with the development of pneumonia (p = .01).

In a study of 153 critical care patients receiving antacids and/or cimetidine therapy, Donowitz et al showed that 59 percent of gastric cultures with a pH
of ≥4 were positive for Gram-negative bacilli. In contrast, only 14 percent of gastric cultures at a pH ≤ 4 were positive for these organisms (p < .001). As gastric pH increased, the proportion of specimens with Gram-negative bacilli rose, and those with normal flora decreased.

A more recent report of nosocomial pneumonia in mechanically ventilated patients receiving prophylaxis against stress bleeding concluded that rates of pneumonia directly correlated with increasing gastric pH. In patients whose gastric pH was < 3.4, the rate of pneumonia was 41 percent compared to a rate of 69 percent in patients who had a pH > 5.0.

Tube feeding and aspiration is particularly common in critically ill patients. Enteral feeding and preparations have a pH range from 6.4 to 7.0. Pingleton et al demonstrated gastric colonization in 100 percent of ventilated patients receiving enteral feeding without antacid or H2-blocker therapy, and 11 (63 percent) subsequently developed nosocomial pneumonia.

Two recent randomized trials of mechanically ventilated intensive care unit patients given stress ulcer prophylaxis with sucralfate compared to conventional agents, found lower rates of pneumonia in patients given sucralfate. In Tryba’s study, rates of pneumonia were increased 3-fold for patients receiving antacids compared to those given sucralfate. In the study by Driks et al, 61 patients were randomized to sucralfate and 69 patients to conventional therapy; antacids (N = 39), H2-blockers (N = 17), and antacids and H2-blockers (N = 13). Rates of pneumonia were 12 percent in the sucralfate group compared to 23 percent for patients treated with antacids and/or H2-blockers. Of note, pneumonia occurred in only 1 of the 17 patients who received an H2-blocker alone as prophylaxis against stress bleeding. The low rate of pneumonia in the H2-blocker alone group suggests the need for additional randomized trials to assess risk and benefit compared to sucralfate. The H2-blocker group was comprised mostly of medical intensive care unit patients who may be at less risk for pneumonia.

Driks et al also reported that qualitative and quantitative gastric colonization with Gram-negative bacilli was significantly lower in patients given sucralfate compared to patients given conventional therapy. Laggener et al also reported colonization was significantly lower in the patients who received sucralfate compared to patients who were treated with ranitidine. Although the changes in gastric colonization were most likely related to gastric pH, two recent reports have suggested that sucralfate may have intrinsic bactericidal activity. Dr. Niederman: In addition to careful attention to gastrointestinal bleeding prophylaxis, how can pneumonia be prevented in patients at risk?

Dr. Craven: Another approach to the prevention of pneumonia and other nosocomial infections has been selective decontamination of the oropharynx, and gastrointestinal tract with antibiotics. Stoutenbeek et al applied polymyxin B, tobramycin, and amphotericin B (PTA) paste four times daily in the oropharynx, along with the use of a solution of these antibiotics given via the nasogastric tube to eliminate colonization in the stomach and upper gastrointestinal tract. Systemic cefotaxime was also administered for variable periods to treat incubating infections. Using this regimen, nosocomial infections were reduced from 81 percent in 59 historic control subjects to 16 percent in 63 patients receiving the prophylactic antibiotic regimen, and “respiratory tract infection” was reduced from 59 percent in the control group compared to 8 percent for patients receiving prophylaxis.

Unertl et al administered a solution of polymyxin B, gentamicin, and amphotericin B to the nose, oropharynx, and stomach of 19 intubated patients who were expected to receive more than six days of mechanical ventilation and compared infection rates to 20 control patients. Colonization of the oropharynx and trachea were significantly lower (p < .001) in the group given antibiotic prophylaxis. Nine cases of pneumonia were identified in the control group compared to one case in the group given antibiotic prophylaxis.

In a more recent study of intensive care unit patients by Ledingham et al, selective decontamination with a regimen similar to that of Stoutenbeek et al reduced the number of respiratory infections 6-fold compared to historic control subjects (18 vs 3). There was also a significant reduction in the colonization rates with aerobic Gram-negative bacilli in the oropharynx and rectum of patients given prophylaxis compared to historical controls.

Flaherty et al randomized patients in a cardiac intensive care unit to receive sucralfate compared with selective decontamination of the oropharynx and stomach with gentamicin, nystatin, and polymyxin; no systemic third generation cephalosporin was included. Overall, rates of infection were 27 percent in the sucralfate group vs 12 percent in the selective decontamination group. Overall, there were five episodes of pneumonia in the sucralfate group compared to one in the antibiotic prophylaxis group. Patients in the sucralfate group had three Gram-negative pneumonias compared to none in the antibiotic group. Although there were no significant differences in ICU stay or fatality rates, antibiotic use was increased 3-fold in the sucralfate group. Antibiotic resistance was not observed, but the duration of the study was short.

With the exception of the study of Flaherty et al, most of the data on selective decontamination of the oropharynx and gastrointestinal tract has been tried...
in multiple trauma patients with results compared to historic controls. Of note is the absence of any change in fatality rates despite the marked decrease in nosocomial infections. In addition, it is not clear if selective decontamination will be applicable to chronically ill patients who may develop colonization with more resistant nosocomial pathogens. Although the selection of antibiotic-resistant organisms was not encountered in these studies, more data collected over a longer time period are needed to definitively assess the risks, benefits, and cost effectiveness of antibiotic prophylaxis in the intensive care unit patient.

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