

*Current Concepts*

## THE PREVENTION OF VENTILATOR-ASSOCIATED PNEUMONIA

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**N**OSOCOMIAL pneumonia is a leading cause of death from hospital-acquired infections, with an associated crude mortality rate of approximately 30 percent.<sup>1</sup> Ventilator-associated pneumonia refers specifically to nosocomial bacterial pneumonia that has developed in patients who are receiving mechanical ventilation. Ventilator-associated pneumonia that occurs within 48 to 72 hours after tracheal intubation is usually termed early-onset pneumonia; it often results from aspiration, which complicates the intubation process.<sup>2</sup> Ventilator-associated pneumonia that occurs after this period is considered late-onset pneumonia. Early-onset ventilator-associated pneumonia is most often due to antibiotic-sensitive bacteria (e.g., oxacillin-sensitive *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*), whereas late-onset ventilator-associated pneumonia is frequently caused by antibiotic-resistant pathogens (e.g., oxacillin-resistant *Staph. aureus*, *Pseudomonas aeruginosa*, acinetobacter species, and enterobacter species).<sup>3-5</sup>

The pathogenesis of ventilator-associated pneumonia usually requires that two important processes take place: bacterial colonization of the aerodigestive tract and the aspiration of contaminated secretions into the lower airway (Fig. 1).<sup>6</sup> Therefore, the strategies aimed at preventing ventilator-associated pneumonia usually focus on reducing the burden of bacterial colonization in the aerodigestive tract, decreasing the incidence of aspiration, or both.

The presence of invasive medical devices is an important contributor to the pathogenesis and development of ventilator-associated pneumonia. Many patients have nasogastric tubes that predispose them

to gastric reflux and increase the potential for aspiration. Endotracheal tubes facilitate bacterial colonization of the tracheobronchial tree and lower-airway aspiration of contaminated secretions through mucosal injury, the pooling of contaminated secretions above the endotracheal-tube cuff, and elimination of the cough reflex.<sup>6</sup> The ventilator circuit and respiratory-therapy equipment may also contribute to the pathogenesis of ventilator-associated pneumonia if they become contaminated with bacteria, which usually originate in the patient's secretions.<sup>6,7</sup>

When ventilator-associated pneumonia occurs, treatment usually consists of supportive care and the administration of antibiotics. Several studies have suggested that the mortality attributable to ventilator-associated pneumonia, particularly late-onset infection with antibiotic-resistant pathogens, is greater than 10 percent.<sup>4,8,9</sup> This figure implies that approximately one third of the deaths among patients with ventilator-associated pneumonia (attributable mortality, 10 percent; crude mortality, 30 percent) are due to the infection and two thirds are due to underlying diseases. However, other investigators have not found associated attributable mortality from ventilator-associated pneumonia after controlling for confounding factors.<sup>10</sup> More recently, the importance of adequate initial treatment with antibiotics has been recognized; such treatment may influence the estimates of attributable mortality.<sup>11-13</sup> Recent studies suggest that patients with suspected ventilator-associated pneumonia should initially be treated with a broad-spectrum antibiotic regimen aimed at covering all likely bacterial pathogens.<sup>11-13</sup> This regimen should subsequently be narrowed, according to the results of cultures of respiratory secretions and the sensitivity profiles of the bacteria.<sup>13</sup> In addition to higher mortality rates, ventilator-associated pneumonia is associated with prolonged hospitalizations and increased medical costs.<sup>6,10</sup>

## GENERAL PREVENTIVE STRATEGY

To help prevent ventilator-associated pneumonia, clinicians caring for patients who are receiving mechanical ventilation should participate in programs aimed at its prevention. These programs may be part of a more general local effort directed at preventing nosocomial infections. A program to prevent ventilator-associated pneumonia should incorporate readily available methods whose efficacy and cost effectiveness are supported by clinical studies, local experience, and the views of experts in the field.<sup>7</sup> To increase the likelihood of their acceptance and success,

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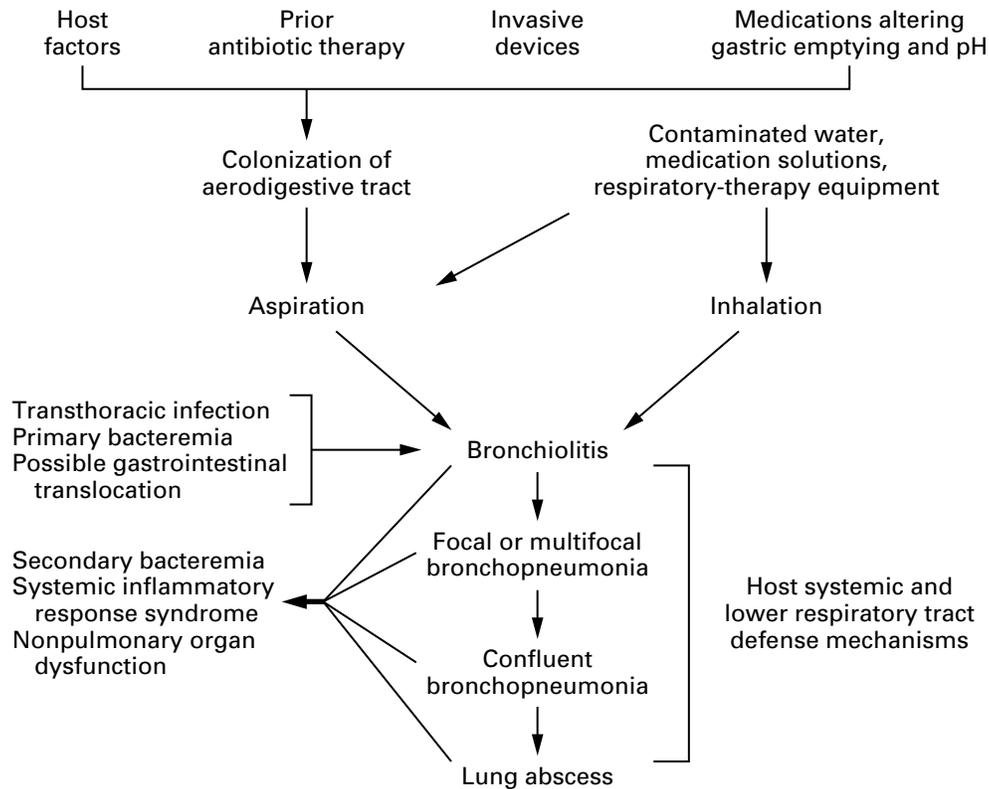


Figure 1. Pathogenesis of Ventilator-Associated Pneumonia.

TABLE 1. STEPS IN THE DEVELOPMENT AND IMPLEMENTATION OF A PROGRAM TO PREVENT VENTILATOR-ASSOCIATED PNEUMONIA.

1. Identify the prevention of ventilator-associated pneumonia as a high-priority task.
2. Establish a tracking mechanism for ventilator-associated pneumonia and other nosocomial infections.
3. Obtain base-line data on the incidence of ventilator-associated pneumonia through standard charting methods.<sup>16,17</sup>
4. Assemble key persons from the local medical community and outside consultants to develop the preventive program.
5. Base the program on medical evidence, reviews of similar programs at other institutions, the opinions of local and outside experts, and the availability of local resources.<sup>15-18</sup>
6. Establish program leadership by an individual or a group that will ensure that the program is updated regularly and will be held accountable for the program's acceptance.
7. Provide hospital staff and admitting physicians with a summary of the program. Organize in-service educational programs for hospital personnel.
8. Implement the program and track rates of ventilator-associated pneumonia.
9. Periodically review the rates of ventilator-associated pneumonia to ascertain the effectiveness of the program and to assess compliance with its recommendations.
10. Update the program to reflect new information, new technology, or changing patterns of disease.

such efforts should be tailored to the characteristics of the individual hospital. Several resources are available to assist in the development of this type of preventive program.<sup>7,14-18</sup>

The benefits derived from a program to prevent ventilator-associated pneumonia can be demonstrated in terms of both improved clinical outcomes and reduced costs of medical care.<sup>15-18</sup> Among the most important elements of this strategy are the presence of a dedicated person or group that takes charge of the process and a mechanism for tracking rates of nosocomial infection (Table 1). The following clinical recommendations, summarized in Tables 2 and 3, can guide the development of a program to prevent ventilator-associated pneumonia.

#### NONPHARMACOLOGIC STRATEGIES

##### Effective Hand Washing and the Use of Protective Gowns and Gloves

Hand washing is widely recognized as an important but underused measure to prevent nosocomial infections.<sup>19</sup> If strict hand-washing techniques, combined with other measures to control infection, fail to control an outbreak of ventilator-associated pneumonia attributed to a specific high-risk pathogen, the respiratory-therapy equipment or aerosol solu-

**TABLE 2.** RECOMMENDATIONS FOR THE NONPHARMACOLOGIC PREVENTION OF VENTILATOR-ASSOCIATED PNEUMONIA.

PREVENTION STRATEGY	RECOMMENDED FOR CLINICAL USE	GRADE*	ASSOCIATED REDUCTION IN MORTALITY	RECOMMENDED BY CDC†	REFERENCE
<b>Effective strategies</b>					
Removal of nasogastric or endotracheal tube as soon as clinically feasible	Yes	C	No	Yes	Tablan et al. <sup>7</sup>
Use of a formal infection-control program	Yes	C	No	Yes	Boyce et al., <sup>15</sup> Joiner et al., <sup>16</sup> Kelleghan et al., <sup>17</sup> Gaynes and Solomon <sup>18</sup>
Adequate hand washing between patient contacts	Yes	B	No	Yes	Doebbeling et al. <sup>19</sup>
Semirecumbent positioning of the patient	Yes	B	No	Yes	Torres et al. <sup>20</sup>
Avoidance of unnecessary reintubation	Yes	C	Yes	NSA	Torres et al. <sup>21</sup>
Provision of adequate nutritional support	Yes	C	No	NSA	Niederman et al. <sup>22</sup>
Avoidance of gastric overdistention	Yes	B	No	Yes	Tablan et al. <sup>7</sup>
Oral (non-nasal) intubation	Yes	D	No	No	Rouby et al. <sup>23</sup>
Scheduled drainage of condensate from ventilator circuits	Yes	C	No	Yes	Craven et al. <sup>24</sup>
Continuous subglottic suctioning	Yes‡	A	No	No	Valles et al. <sup>25</sup>
Maintenance of adequate pressure in endotracheal-tube cuff	Yes	C	No	Yes	Rello et al. <sup>26</sup>
<b>Ineffective strategies</b>					
Routine changes of ventilator circuit	No	A	No	No	Kollef <sup>27</sup>
Dedicated use of disposable suction catheters	No	A	No	No	Tablan et al., <sup>7</sup> Kollef et al. <sup>28</sup>
Routine changes of in-line suction catheter	No	B	No	NSA	Kollef et al. <sup>28</sup>
Daily changes of heat and moisture exchangers	No	A	No	Yes	Kollef et al., <sup>29</sup> Djedaini et al. <sup>30</sup>
Chest physiotherapy	No	A	No	No	Hall et al. <sup>31</sup>
<b>Strategies of equivocal or undetermined effectiveness</b>					
Use of protective gowns and gloves	Yes‡	B	No	Yes‡	Tablan et al., <sup>7</sup> Klein et al. <sup>32</sup>
Humidification with heat and moisture exchanger	Yes§	A	No	Yes§	Kirton et al. <sup>33</sup>
Humidification with heat and moisture exchanger with bacteriologic filter	—	U	—	NSA	—
Postural changes	Yes‡¶	B	No	No	Tablan et al. <sup>7</sup>

\*The grading scheme is as follows: A, supported by at least two randomized, controlled investigations; B, supported by at least one randomized, controlled investigation; C, supported by nonrandomized, concurrent-cohort investigations, historical-cohort investigations, or case series; D, supported by randomized, controlled investigations of other nosocomial infections; U, undetermined or not yet studied in clinical investigations.

†CDC denotes Centers for Disease Control and Prevention, and NSA not specifically addressed. CDC recommendations are described by Tablan et al.<sup>7</sup>

‡This strategy is recommended for specific groups of patients described in the studies cited.

§This strategy is recommended for clinical use but has not been clearly established to reduce the incidence of ventilator-associated pneumonia.

¶The effectiveness of this strategy requires confirmation in larger clinical trials before it can be generally accepted.

tions are probably contaminated. The use of protective gowns and gloves has also been found to reduce the rate of acquired nosocomial infections in children.<sup>32</sup> However, their use appears to be most effective when directed at specific antibiotic-resistant pathogens, such as vancomycin-resistant enterococci. Therefore, the use of protective gowns and gloves is not recommended for the routine prevention of ventilator-associated pneumonia.

### Semirecumbent Positioning of Patients

Aspiration of upper-airway secretions is common even in healthy adults. Patients receiving mechanical ventilation should be placed in a semirecumbent position to reduce the occurrence of aspiration.<sup>20</sup> In addition, measures to reduce unplanned extubation (e.g., appropriate use of physical and chemical restraints and securing of the endotracheal tube to the patient) and the need for subsequent reintubation

**TABLE 3.** RECOMMENDATIONS FOR THE PHARMACOLOGIC PREVENTION OF VENTILATOR-ASSOCIATED PNEUMONIA.

PREVENTION STRATEGY	RECOMMENDED FOR CLINICAL USE	GRADE*	ASSOCIATED REDUCTION IN MORTALITY	RECOMMENDED BY CDC†	REFERENCE
<b>Effective strategies</b>					
Avoidance of unnecessary antibiotics	Yes	C	No	Yes	Goldmann et al. <sup>14</sup>
Limitation of stress-ulcer prophylaxis to high-risk patients‡	Yes	B	No	NSA	Cook et al. <sup>34</sup>
Antibiotic-class rotation	Yes	C	No	NSA	Kollef et al. <sup>35</sup>
Chlorhexidine oral rinse	Yes§	B	No	NSA	Rumbak and Cancio, <sup>36</sup> DeRiso et al. <sup>37</sup>
Granulocyte colony-stimulating factor for neutropenic fever	Yes	D	No	NSA	Maher et al., <sup>38</sup> Mitchell et al. <sup>39</sup>
Antibiotics for neutropenic fever	Yes	D	No	NSA	Pizzo, <sup>40</sup> Gruppo Italiano Malattie Ematologiche Maligne dell' Adulto <sup>41</sup>
Vaccines against <i>Strep. pneumoniae</i> , <i>H. influenzae</i> type b strains, and influenza virus	Yes	D	No	NSA	Herceg, <sup>42</sup> Gross et al. <sup>43</sup>
<b>Ineffective strategies</b>					
Aerosolized antibiotic prophylaxis	No	B	No	No	Tablan et al. <sup>7</sup>
Selective digestive decontamination	No	A	No	No	Tablan et al., <sup>7</sup> Gastinne et al. <sup>44</sup>
<b>Strategies of equivocal or undetermined effectiveness</b>					
Routine parenteral prophylactic antibiotics for patients with coma	Yes¶	B	No	NSA	Sirvent et al. <sup>45</sup>
Combination antibiotic therapy	—	U	—	NSA	—
Prophylactic immune globulin	Yes¶	D	No	NSA	The Intravenous Immuno-globulin Collaborative Study Group <sup>46</sup>
Acidification of enteral feeding solutions	—	U	—	No	Tablan et al. <sup>7</sup>

\*The grading scheme is described in Table 2.

†CDC denotes Centers for Disease Control and Prevention, and NSA not specifically addressed. CDC recommendations are described by Tablan et al.<sup>7</sup>

‡High-risk patients are defined as those who require mechanical ventilation or have a coagulopathy.

§This strategy is recommended for specific groups of patients described in the studies cited.

¶The effectiveness of this strategy requires confirmation in larger clinical trials.

performed with the patient in the supine position may also be beneficial.<sup>21</sup>

**Avoidance of Large Gastric Volumes**

Although ventilator-associated pneumonia is commonly due to the aspiration of contaminated secretions into the lower airway, the origin of these infected inocula varies.<sup>6</sup> The stomach, upper airway, teeth, artificial airway, ventilator-circuit condensate, and nasal sinuses have all been implicated as potential sources of aspirated secretions. Unfortunately, the relative importance of these sites, particularly the stomach, as sources of the causative agents of pneumonia is uncertain, and this uncertainty has resulted in considerable controversy.<sup>6,47</sup> The issue is important because the provision of adequate nutritional support to patients receiving mechanical ventilation is thought to prevent the occurrence of ventilator-

associated pneumonia.<sup>22</sup> Therefore, it seems reasonable to administer nutritional support in a manner that minimizes the risk of bacterial colonization of the aerodigestive tract and subsequent aspiration.

Gastric overdistention should be avoided by reducing the use of narcotics and anticholinergic agents, monitoring gastric residual volumes after intragastric feedings, using agents that increase gastrointestinal motility (e.g., metoclopramide), and when necessary, supplying enteral nutrition through small-bore feeding tubes directed into the small bowel instead of the stomach.<sup>6,7</sup> However, the effectiveness of such interventions awaits validation in clinical trials.

**Oral (Non-Nasal) Intubation**

Prolonged nasal intubation (for more than 48 hours) should be avoided because of the association between nosocomial sinusitis and ventilator-associated

pneumonia.<sup>23</sup> Nosocomial sinusitis may predispose the patient to pneumonia through the aspiration of infected secretions from the nasal sinuses. Therefore, the preferred route of intubation is the oropharynx.

#### **Routine Maintenance of Ventilator Circuits**

Several clinical studies found no benefit from routinely changing ventilator-circuit tubing.<sup>27</sup> In large part, this lack of benefit appears to be due to the rapid bacterial colonization of such tubing, usually within 24 hours of its placement. Nevertheless, ventilator circuits occasionally require replacement because of overt soiling (e.g., with vomit or blood) or mechanical malfunction. Ventilator circuits should also be monitored regularly so that accumulated condensate in the tubing can be removed.<sup>24</sup> A high concentration of pathogenic bacteria is found in condensate fluid, which may cause pneumonia if aspirated. This condensate can also serve as a reservoir for nosocomial pathogens.

#### **Continuous Subglottic Suctioning**

Several lines of investigation have suggested that secretions that pool above inflated endotracheal-tube cuffs may be a source of aspirated material and thus ventilator-associated pneumonia.<sup>6,25</sup> Endotracheal tubes with a separate dorsal lumen above the cuff to suction pooled secretions from the subglottic space are now available.<sup>25</sup> These specialized endotracheal tubes should be part of an organized approach to preventing ventilator-associated pneumonia and should not be used in place of such efforts. The pressure of the endotracheal-tube cuff should be adequate to prevent the leakage of colonized subglottic secretions into the lower airway.<sup>26</sup>

#### **Type of Suction Catheter and Its Replacement**

Two types of suction-catheter systems are available: the open, single-use system and the closed, multiuse system. The risk of nosocomial pneumonia appears to be similar with both systems.<sup>7</sup> However, the main advantages attributed to the closed, multiuse catheters are lower costs and decreased environmental cross-contamination. Daily changes of in-line suction catheters are not necessary, which is another advantage of using closed, multiuse catheter systems instead of open, single-use systems, especially for patients who require prolonged ventilatory support.<sup>28</sup>

#### **Humidification with Heat and Moisture Exchangers**

Heat and moisture exchangers are attractive alternatives to heated-water humidification systems because of their passive operation (they do not require electricity or active heating elements) and their lower costs. More recent improvements in the performance characteristics of heat and moisture exchangers have made them safe and easy to use.

In theory, heat and moisture exchangers reduce

the incidence of ventilator-associated pneumonia by minimizing the development of condensate within ventilator circuits.<sup>33</sup> However, they should be considered primarily a cost-effective method of providing humidification to patients receiving ventilation if there are no contraindications (e.g., hemoptysis, copious or tenacious secretions, or difficulty discontinuing mechanical ventilation because of increased airway resistance). Moreover, certain heat and moisture exchangers can safely be left in place for up to one week, further increasing their cost effectiveness relative to that of heated-water humidification.<sup>29,30</sup>

#### **Postural Changes**

Patients who are confined to bed have an increased frequency of pulmonary and nonpulmonary complications.<sup>6</sup> Kinetic therapies that change the patient's position by means of specialized beds or medical devices are hypothesized to help prevent ventilator-associated pneumonia by improving the drainage of pulmonary secretions. However, the added expense of such devices and their lack of demonstrated effectiveness preclude a recommendation that they be used routinely at the present time.<sup>7</sup> Similarly, the routine use of chest physiotherapy for the prevention of ventilator-associated pneumonia should be avoided because of its lack of efficacy and the associated risks (e.g., arterial oxygen desaturation).<sup>31</sup>

### **PHARMACOLOGIC STRATEGIES**

#### **Stress-Ulcer Prophylaxis**

Patients receiving mechanical ventilation are at high risk for upper gastrointestinal hemorrhage from stress ulcers; they thus require preventive therapy.<sup>34</sup> The role of gastric pH in the pathogenesis of ventilator-associated pneumonia is controversial. Bacterial colonization of the stomach, enhanced by the administration of pH-lowering drugs (e.g., histamine H<sub>2</sub>-receptor antagonists and antacids), is thought to be an important source of pathogens that can cause pneumonia.<sup>6</sup> The administration of sucralfate into the stomach has been found to prevent bleeding from stress ulcers without lowering gastric pH. Several randomized trials have found that sucralfate is associated with lower rates of ventilator-associated pneumonia than are antacids or histamine H<sub>2</sub>-receptor antagonists.<sup>48</sup>

The choice of agent for prophylaxis against stress ulcers should depend on factors relating to the patient (e.g., the presence or absence of a nasogastric tube), the potential for unwanted drug interactions, and the local costs associated with providing the various forms of therapy.<sup>49</sup> In addition, because of the preliminary nature of the investigations and the potential for toxicity, routine acidification of enteral feeding solutions for the prevention of pneumonia should be avoided.<sup>7</sup>

### Administration of Antibiotics

Previous exposure to antibiotics is an important risk factor for ventilator-associated pneumonia because of the presence of antibiotic-resistant bacteria.<sup>9</sup> Colonization of the lower respiratory tract by antibiotic-resistant organisms such as *P. aeruginosa* and oxacillin-resistant *Staph. aureus* has been shown to be closely correlated with the subsequent development of overt pneumonia.<sup>50,51</sup> In an attempt to reverse the trend toward increasing rates of antimicrobial resistance among hospital-acquired infections, more effective strategies for using antibiotics have been advocated that restrict antibiotic use or offer guidelines for their administration.<sup>14,52</sup> Changing or rotating the antibiotic classes used for the treatment of suspected bacterial infections (i.e., avoiding the use of a single class of antimicrobial agents in an intensive care unit) may also reduce the rates of nosocomial pneumonia caused by antibiotic-resistant pathogens.<sup>35</sup> However, eliminating or reducing the unnecessary use of antibiotics should be the primary goal in preventing antibiotic-resistant nosocomial infections.<sup>14</sup>

### Combination Antibiotic Therapy

The routine use of combination antibiotic therapy has been advocated as a means of reducing the subsequent emergence of bacterial resistance. Unfortunately, rigorous clinical trials of this therapy have not been performed. The use of combination antibiotic therapy should be limited to clinical situations in which multiple pathogens or bacteria with antibiotic resistance are likely to be encountered. This strategy may reduce the likelihood that patients with ventilator-associated pneumonia will receive inadequate antibiotic therapy, which has been associated with detrimental outcomes.<sup>11-13</sup> However, the routine administration of prolonged courses of empirical combination therapy (i.e., therapy not supported by the results of clinical cultures) should be avoided, to minimize the subsequent development of antibiotic-resistant infections.

### Prophylactic Antibiotic Therapy

The use of aerosolized antibiotics for the prevention of ventilator-associated pneumonia has been abandoned because of its lack of efficacy and the subsequent emergence of antibiotic-resistant infections.<sup>7</sup> Similarly, the routine use of selective digestive decontamination has not gained acceptance in the United States, because of its lack of demonstrated effect on mortality, the emergence of antibiotic-resistant infections, and additional toxicity.<sup>7,44</sup>

The use of broad-spectrum parenteral antibiotics for the prevention of ventilator-associated pneumonia is also not recommended, because of the increasing frequency of antibiotic resistance among subsequent hospital-acquired infections. Nevertheless, one

recent investigation suggests that the administration of such therapy to patients with coma may reduce the incidence of ventilator-associated pneumonia.<sup>45</sup> Further investigations are required to determine the general applicability and safety of broad-spectrum parenteral antibiotic therapy for this indication before it can be accepted.

### Chlorhexidine Oral Rinse

Chlorhexidine is an antiseptic solution that has been used by dentists since 1959 for the control of dental plaque. Bacteria that have accumulated in dental plaque have been implicated as a source of pathogens in ventilator-associated pneumonia. Chlorhexidine has been shown to be effective in the control of ventilator-circuit colonization and pneumonia caused by antibiotic-resistant bacteria.<sup>36</sup> Oropharyngeal decontamination with chlorhexidine solution has also been shown to reduce the occurrence of ventilator-associated pneumonia in patients undergoing cardiac surgery.<sup>37</sup> The use of preventive oral washes with chlorhexidine seems reasonable in selected high-risk patients, given the ease of administration. However, overuse could result in colonization and superinfection with chlorhexidine-resistant pathogens.<sup>53</sup>

### Administration of Immune Globulin

One relatively large trial conducted in adult surgical patients found that standard immune globulin, as compared with placebo, reduced the overall incidence of nosocomial infection, and nosocomial pneumonia in particular.<sup>46</sup> However, because of its expense and potential side effects and the inconsistent findings of clinical trials, the use of immune globulin therapy should be limited to clinical trials or selected groups of high-risk patients.

### Prophylactic Treatment of Patients with Neutropenia

The presence of neutropenia is associated with an increased risk of both community-acquired and nosocomial infections. Granulocyte colony-stimulating factor has been found to amplify the immune response by regulating the number and function of neutrophils. Although it has not been studied in the context of preventing nosocomial pneumonia, granulocyte colony-stimulating factor should be administered to patients receiving ventilation who have neutropenic fever in an attempt to decrease the incidence of acquired infections, including ventilator-associated pneumonia.<sup>38,39</sup>

Routine prophylactic antibiotic therapy should also be administered to patients receiving ventilation who have neutropenic fever. Under these circumstances, the benefits of broad-spectrum antimicrobial therapy clearly outweigh any risk associated with the use of these agents until neutrophil recovery occurs.<sup>40</sup> The administration of prophylactic antibiotics

to patients with neutropenic fever has been shown to reduce the duration of febrile periods and decrease the incidence of infection-related events.<sup>40,41</sup>

### Vaccines

Various vaccination programs in adults and children have reduced the incidence of pneumonia caused by specific pathogens, including *H. influenzae* type b strains, *Strep. pneumoniae*, and influenza virus.<sup>42,43</sup> Vaccination against these pathogens may prevent some hospital-acquired infections as well. Indeed, the difference between nosocomial and community-acquired infections is becoming less clear, particularly in the era of managed care, when patients with acute and chronic illnesses often receive medical care outside the hospital. Therefore, pneumococcal vaccination and influenza vaccination (if indicated) should be considered before hospital discharge or included in the discharge planning for all patients at risk for subsequent respiratory infections, including ventilator-associated pneumonia.

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