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Association of the metabolic syndrome with age-related, nonatherosclerotic, chronic medical conditions

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Prevention of Nosocomial Pneumonia in the Intensive Care Unit: Beyond the Use of Bundles

Marin H. Kollef

Abstract

Background: The occurrence of nosocomial pneumonia (NP) in the hospital setting is especially problematic, as it is associated with a greater risk of in-hospital death, longer stays on mechanical ventilation and in the intensive care unit (ICU), more need for tracheostomy, and significantly higher medical care costs.

Methods: Review of the pertinent English-language literature.

Results: The adverse effect of NP on healthcare outcomes has increased pressure on clinicians and hospital systems to prevent this infection. This brief review provides an overview of the current approaches to the prevention of NP, focusing primarily on ventilator-associated pneumonia (VAP).

Conclusion: Clinicians working in ICUs should consider the following recommendations: (1) Develop a VAP prevention bundle based on evidence-based guidelines; (2) monitor the rates of VAP prior to and during implementation of the program; (3) make adjustments according to VAP occurrence; and (4) integrate VAP prevention with other quality improvement programs.

Pneumonia associated with the need for mechanical ventilation in the intensive care unit (ICU) setting is one of the most common infections managed by intensivists. The current classification of pneumonia in the ICU includes community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and nursing home-associated pneumonia (NHAP) (Table 1)[1–3]. Health care-associated pneumonia (HCAP) is the newest category of pneumonia and in many developed countries probably is the most common type necessitating ICU care. This is a distinct type of nosocomial pneumonia (NP), the others being HAP and VAP, that is present at the time of hospital or ICU admission where patients have specific underlying risk factors, including residence in a nursing home or long-term care facility; recent hospitalization or treatment with antibiotics; receipt of home or hospital-based intravenous therapy, wound care, or dialysis; and immunosuppression [2,3].

Patients with HCAP are more similar to patients with HAP and VAP and differ from patients with CAP because of the common presence of infection with multi-drug resistant (MDR) bacteria and the greater likelihood of co-morbidities, including cancer, chronic kidney disease, heart disease, chronic obstructive lung disease, immunosuppression, dementia, and impaired mobility [4–8]. From a prevention standpoint, HAP and VAP are most amenable to useful strategies applied in the hospital setting. However, the prevention of pneumonias developing outside of the hospital (CAP, HCAP) also can be accomplished, to some extent, through the use of specific hospital-based strategies [9,10]. The medical literature and available clinical evidence currently is most robust for VAP and less developed for HAP and HCAP. Therefore, this review focuses on the prevention of VAP, and the reader should assume that the recommendations also apply to HAP and HCAP unless stated otherwise. However, it is important to recognize that not all VAP prevention studies are similar in the rigor with which infection was defined. That is, some studies used microbiologic criteria to confirm infection, whereas others employed less-specific clinical criteria. Readers should take this into account when considering including specific interventions in their prevention bundles, especially costly interventions or those carrying a risk to the patient or environment.

Pathogenesis of Nosocomial Pneumonia

Under basal conditions, the lower respiratory tract is sterile. Thus, for pneumonia to develop, bacteria must be introduced into the lungs, typically by being aspirated from either the upper respiratory tract or the gastrointestinal tract.
Introduction generally is associated with impairment of host defenses, both locally and systemically. The pathogenesis of VAP thus is a dual process requiring colonization of the aerodigestive tract with potentially causative pathogens followed by aspiration of secretions contaminated with these pathogens that overcome lower respiratory tract defense mechanisms, resulting in infection.

A leading hypothesis regarding the pathogenesis of VAP, and NP in general, is that the oropharynx is overgrown by microorganisms, which subsequently are aspirated into the lungs and colonize the airway. This hypothesis is supported by the observation that whereas enteric gram-negative bacteria are absent from the oropharynx under basal conditions, they can be detected in that site in nearly 75% of critically ill patients [11]. A comparison of bacterial DNA samples on the tongues of critically ill patients with organisms recovered from bronchoalveolar lavage (BAL) samples supports this theory [12]. Upper airway colonization by enteric bacteria occurs in 45% to 100% of intubated patients. Besides being colonized by aspirated endogenous flora, the airways may be colonized by exogenous flora as a result of cross-contamination from other ICU patients through inadvertent transmission by healthcare workers.

A complementary hypothesis is that the upper gastrointestinal tract plays a critical role in the pathogenesis of VAP. According to this view, the stomach is a primary site of colonization that may subsequently infect the lung through bacterial overgrowth and retrograde movement, followed by aspiration of organisms from the oropharynx. The small decrease in the mortality rate seen in certain ICU patient populations after selective decontamination of the digestive tract (SDD) supports the idea that gut flora play a role in the pathogenesis of VAP and possibly HAP and HCAP. Chronic infection of biofilms on an endotracheal tube also may play a role [13].

**Prevention of Nosocomial Pneumonia**

**Pharmacologic approaches (Table 2)**

**Topical iseganan.** Iseganan is an antimicrobial peptide with activity against gram-positive and gram-negative bacteria and yeast. In a multicenter randomized trial, topical oropharyngeal administration of iseganan was not associated with a reduction in VAP [14].

**Orodigestive decontamination.** Orodigestive decontamination (ODD) is the use of a prophylactic antimicrobial

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**Table 1. Pneumonia Classification for Patients in the Intensive Care Setting**

<table>
<thead>
<tr>
<th>CAP</th>
<th>Infection present at hospital admission in patients who do not meet the criteria for HCAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCAP</td>
<td>Pneumonia present at hospital or ICU admission in patients with at least one of the following risk factors:</td>
</tr>
<tr>
<td></td>
<td>1. Hospitalization for ≥2 days in an acute-care facility within 180 days of infection</td>
</tr>
<tr>
<td></td>
<td>2. Residence in a nursing home or long-term care facility</td>
</tr>
<tr>
<td></td>
<td>3. Antibiotic therapy, chemotherapy, or wound care within 30 days of current infection</td>
</tr>
<tr>
<td></td>
<td>4. Hemodialysis at a hospital or clinic</td>
</tr>
<tr>
<td></td>
<td>5. Home infusion therapy or home wound care</td>
</tr>
<tr>
<td></td>
<td>6. Family member with infection caused by MDR bacteria</td>
</tr>
<tr>
<td></td>
<td>7. Significant immunosuppression (corticosteroids, HIV, organ transplant)</td>
</tr>
<tr>
<td>NHAP</td>
<td>Pneumonia occurring during residence in a nursing home or rehabilitation facility</td>
</tr>
<tr>
<td>HAP</td>
<td>Pneumonia occurring typically ≥48 h after hospital admission in a non-intubated patient</td>
</tr>
<tr>
<td>VAP</td>
<td>Pneumonia occurring typically ≥48 h after hospital admission and endotracheal intubation</td>
</tr>
</tbody>
</table>

CAP = community-acquired pneumonia; HCAP = healthcare-associated pneumonia; HIV = human immunodeficiency virus; MDR = multi-drug resistant; NHAP = nursing home-associated pneumonia; HAP = hospital-acquired pneumonia; VAP = ventilator-associated pneumonia; ICU = intensive care unit.

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**Table 2. Pharmacologic-Based Strategies for Prevention of Ventilator-Associated Pneumonia**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Recommendation</th>
<th>Evidence level</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical iseganan</td>
<td>No</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Orodigestive decontamination</td>
<td>No#</td>
<td>1</td>
<td>15,16</td>
</tr>
<tr>
<td>(topical/topical plus intravenous antibiotics)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral chlorhexidine</td>
<td>Yes</td>
<td>1</td>
<td>19–22</td>
</tr>
<tr>
<td>Aerosolized antibiotics</td>
<td>No recommendation</td>
<td>1</td>
<td>23,24</td>
</tr>
<tr>
<td>Intravenous antibiotics</td>
<td>No recommendation</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Specific stress ulcer prophylaxis regimen</td>
<td>No</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>Short-course antibiotic therapy</td>
<td>Yes</td>
<td>1</td>
<td>30–32</td>
</tr>
<tr>
<td>(when clinically applicable)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine antibiotic cycling/rotation/heterogeneity</td>
<td>No</td>
<td>2</td>
<td>33–35</td>
</tr>
<tr>
<td>Restricted (conservative) blood transfusion</td>
<td>Yes</td>
<td>2</td>
<td>36–38</td>
</tr>
<tr>
<td>Vaccines (influenza, pneumococcal)</td>
<td>Yes</td>
<td>1</td>
<td>40,41</td>
</tr>
</tbody>
</table>

*1 = Supported by randomized trials; 2 = supported by prospective or retrospective cohort studies; 3 = supported by case series.

*Based on current guidelines [19] and insufficient data on aerosolized and intravenous antibiotics used alone.

*Supported by case series.

*May be useful in specific clinical circumstances (as an adjunct to controlling an outbreak of a multi-drug resistant bacterial infection).

*General recommendation without specific evidence for ventilator-associated pneumonia.
regimen that includes nonabsorbable antibiotics applied to the oropharynx and gastrointestinal tract along with a short course of intravenous antibiotics. The technique has been studied for more than 25 years, and more than 10 meta-analyses have been written [15]. Despite a fairly consistent demonstration of modest decreases in the mortality rate and in blood stream infections, ODD is not in widespread use, primarily because of concerns about promoting antimicrobial resistance and uncertain cost-effectiveness. A randomized trial in more than 6,000 patients was published recently comparing ODD, oral decontamination with topical agents alone, and standard care [16]. Compared with standard care, ODD led to a 28-day mortality rate decrease from 27.5% to 26.9%. The 28-day mortality rate in the oral decontamination group was similar to that in the ODD group at 26.6%. Because antimicrobial resistance may take time to develop, however, its emergence may not be noticed during clinical trials, and this remains a major concern with the widespread implementation of ODD. Indeed, a follow-up of this study showed that increasing bacterial resistance emerged in the ICUs employing ODD [17,18]. Therefore, the routine use of ODD for the prevention of VAP cannot be recommended.

Oral chlorhexidine. Like the use of ODD, oral chlorhexidine administration has been associated with reductions in nosocomial infections, including VAP, primarily in patients undergoing cardiac surgery [19,20]. The overall magnitude of the effect on the prevention of VAP seems to be modest and probably is dependent on both the frequency of its administration and the concentration of chlorhexidine, as demonstrated in non-cardiac surgery populations [21,22].

Aerosolized antibiotics. The most recent American Thoracic Society/American Infectious Diseases Association guidelines for the management of NP concluded that aerosolized antibiotics have not been proved to have value in VAP treatment but can be considered as an adjunct for VAP caused by MDR pathogens that are not responsive to standard therapy [3]. Several small studies have been published in support of the use of inhaled antibiotics for both VAP and tracheobronchitis [23,24]. Although these trials are promising, current data are lacking to support the use of inhaled antibiotics as more than an adjunctive therapy in non-improving patients. There is no current role for aerosolized antibiotics for the prevention of VAP.

Intravenous antibiotics. Long courses of intravenous antibiotics can be associated with the emergence of antibiotic resistance, and therefore, their use should be limited to treatment indications. One study of cefuroxime administration for 24 h at the time of intubation in patients with closed head injury produced a significant reduction in early-onset VAP [25].

Specific stress ulcer prophylaxis. Stress ulcer prophylaxis (antacids, histamine type-2 receptor antagonists, proton-pump inhibitors) neutralizes gastric acid or reduces gastric acid secretion, facilitating gastric colonization with potentially pathogenic bacteria and yeast, which can be aspirated into the lungs and cause lower respiratory tract infections. Significant debate has ensued regarding the role of stress ulcer prophylaxis as a promoter of VAP [26]. Nevertheless, no convincing evidence exists to recommend one agent over another when stress ulcer prophylaxis is deemed necessary [27]. More recently, the use of proton-pump inhibitors has been associated also with the development of CAP, further linking alterations in upper gastrointestinal colonization to the development of pneumonia [28,29].

Short-course antibiotic therapy. Available evidence suggests that shorter courses of antibiotic therapy for VAP are clinically effective and associated with less emergence of antibiotic resistance [28–30]. When clinically acceptable, a seven- to eight-day course of antibiotic therapy should be considered adequate for patients demonstrating a clinical response to treatment (resolution of fever, reduced white blood cell count, improved oxygenation, and decreased respiratory secretions). Although this may not be a primary mode for the prevention of VAP, it can result in less emergence of antibiotic-resistant VAP [28].

Routine antibiotic cycling/rotation. In view of the available evidence, the routine use of antibiotic cycling or rotation cannot be recommended for the prevention of VAP [31–33].

Restricted use of blood transfusion. Transfusion of red blood cells has been associated with the development of nosocomial infections, including VAP [36–38]. Restricted use of transfusion therefore seems appropriate to minimize this risk [39].

Vaccines. Appropriate use of influenza and pneumococcal vaccines is recommended to reduce the incidence of respiratory failure related to these infections, which could secondarily increase the occurrence of VAP [40,41]. Clinicians should follow national recommendations regarding vaccination policies and chemoprophylaxis in order to minimize the impact of respiratory illness outbreaks in the community [42].

Non-Pharmacologic Approaches to Preventing Nosocomial Pneumonia (Table 3)

Use of non-invasive mask ventilation

The endotracheal tube plays an important role in the pathogenesis of VAP, which has led some authors to rename this nosocomial infection “endotracheal-tube associated pneumonia” [43]. Avoidance of endotracheal intubation by using mask ventilation reduces the occurrence of VAP and nosocomial sinusitis [44–46].

Avoid re-intubation

Re-intubation is associated with a higher risk of VAP by facilitating aspiration [47]. Appropriate interventions and surveillance should be in place to minimize unplanned extubations resulting in the need for re-intubation. Clinicians must balance the occurrence of re-intubations as part of the planned ventilator weaning process with the aim of minimizing the duration of mechanical ventilation, which also can help to prevent VAP.

Avoid patient transport

Unnecessary patient transport out of the ICU should be avoided, as such travel has been associated with VAP [48].
Orotracheal and orogastric intubation

Orotracheal and orogastric intubation have been associated with reduced incidences of VAP and nosocomial sinusitis [49,50]. Therefore, the oral route is preferred when intubation of the trachea and esophagus is necessary in a critically ill patient.

Early tracheostomy

One trial suggested that early tracheostomy could prevent VAP [51]. However, a more recent rigorously conducted study found no benefit [52].

Routine ventilator circuit changes

Manipulation and changing of ventilator circuits may promote aspiration and increase the occurrence of VAP [53,54]. Therefore, ventilator circuit changes should be made only when the circuit is damaged or visibly soiled. When significant condensate accumulates in a circuit, it should be removed to avoid aspiration and VAP [55].

Routine use of heat-moisture exchangers

Use of heat-moisture exchangers (HMEs) for humidification does not reduce the occurrence of VAP consistently compared with water humidification methods [56–58]. Therefore, deciding on their use is left to the treating physicians. Prolonged use of HMEs has not been associated with a higher risk of VAP [59,60].

Closed versus open endotracheal suctioning

According to clinical studies, closed and open endotracheal suctioning systems are linked to similar rates of VAP [61,62]. However, closed systems create less aerosolization of potentially infected airway secretions. Available evidence suggests that closed suctioning systems need to be changed only when malfunctioning or visibly soiled [63].

Subglottic suction drainage

Aspiration of subglottic secretions with a specially designed endotracheal tube has been associated with reductions in VAP [64–67]. However, subglottic suctioning can cause mucosal injury of the trachea and failure to aspirate secretions secondary to either increased viscosity or mucosal blockage of the suction port [68,69].

Shortening the duration of mechanical ventilation

The likelihood of VAP has been linked to the duration of mechanical ventilation [70]. Therefore, efforts to reduce the duration of mechanical ventilation by optimizing weaning attempts and utilizing sedation should be routine [71,72].

Adequate intensive care unit staffing

Inadequate staffing of ICUs has been associated with excess development of nosocomial infections and prolonged durations of mechanical ventilation [73,74]. Therefore, adequate staffing should be in place to ensure that protocols are followed to prevent VAP and other nosocomial infections, as well as to minimize patient exposure to mechanical ventilation.

Silver-coated endotracheal tube

Biofilm formation is an important pathogenic element in the development of VAP [75]. Recent clinical investigations suggest that a silver-coated endotracheal tube is safe and can reduce the incidence of VAP by almost 50% during the first ten days of mechanical ventilation [76,77]. Additionally, a retrospective analysis of the NASCENT study suggests that use of a silver-coated endotracheal tube may be associated with better outcomes for patients developing VAP [78].

Polyurethane cuffed endotracheal tubes

Endotracheal tube cuffs made of ultrathin polyurethane rather than polyvinyl chloride theoretically reduce channel
formation and minimize the volume of secretions micro-aspirated around the cuff. Limited data from some populations have demonstrated their efficacy [79,80]. Various shapes of the ultrathin polyurethane cuffs have been employed in the commercially available endotracheal tubes (cylindrical, tapering funnel-like design). Unfortunately, head-to-head studies of the efficacy of various cuff designs for the prevention of aspiration and VAP are not available. The development of endotracheal tubes that combine multiple prevention features (ultrathin polyurethane cuff with subglottic suctioning) may allow even greater reductions in VAP occurrence, although this has yet to be confirmed in clinical trials.

**Semierect positioning**

Supine positioning facilitates aspiration in the intubated patient and should be avoided if possible [81]. However, achieving head elevation to 45° may be difficult in many clinical situations. Under those circumstances, the head of the bed should be raised to the highest level applicable [82].

**Rotational beds**

Several small trials have shown that rotating beds can reduce the occurrence of VAP [83–85]. However, because of the cost of these beds and the populations studied, their use should be based on perceived benefit and available resources in particular cases.

**Chest physiotherapy**

In view of the available evidence, the routine use of chest physiotherapy cannot be recommended for the prevention of VAP [86–88].

**Protocols/bundles to Prevent Ventilator-Associated Pneumonia**

An increasing body of evidence suggests that the routine use of bundles or protocols aimed at preventing VAP can be successful [89–91]. The challenge is to ensure that compliance with the elements of the bundles and protocols is adhered to over time in order to sustain the early benefits. Additionally, clinicians must evaluate new technologies for inclusion in their established bundles. One example is the routine use of chlorhexidine baths for enhanced environmental control in order to reduce the occurrence of nosocomial infections. The data on the use of these baths to prevent VAP are mixed [92,93]; however, the overall reduction in ICU-acquired infections resulting from their use can justify the inclusion of such baths in a VAP prevention bundle.

**Prevention Protocols**

An education-based program at Barnes-Jewish Hospital directed toward respiratory care practitioners and ICU nurses was developed by a multidisciplinary task force to highlight correct practices for the prevention of VAP [90]. Each participant was required to take a test before reviewing a study module and an identical test after completion of the module. Following implementation of the module, the rate of VAP decreased to 5.7/1,000 ventilator days from 12.6/1,000 ventilator days [90]. The estimated cost savings secondary to the lower rate of VAP for the 12 mos following the intervention was estimated to exceed $400,000. This educational protocol was then implemented across the four largest hospitals in the local healthcare system [89]. The VAP rates for all four hospitals combined dropped by 46%, from 8.75/1,000 ventilator days in the year prior to the intervention to 4.74/1,000 ventilator days in the 18 mos following the intervention (p < 0.001). Statistically significant decreases in rates were observed at the pediatric hospital and at two of the three adult hospitals. No change in VAP rates was seen at the community hospital with the lowest rate of study module completion among respiratory therapists (56%). In addition to showing the effectiveness of a protocol for VAP prevention, these studies highlight the importance of compliance with the elements of the protocol to ensure its success. This same protocol also has been successful in the ICUs of a hospital in Thailand [91].

Lansford et al. developed a simple protocol for the prevention of VAP in trauma patients focusing on head-of-bed elevation, oral cleansing with chlorhexidine, a once-daily respiratory therapist-driven weaning attempt, and conversion of nasogastric to orogastric feeding tubes [50]. Implementation of the protocol was associated with a significant reduction in the rate of VAP (11 occurrences in 1,600 days of ventilator support [6.9/1,000 ventilator days] vs. two occurrences in 703 days of ventilation [2.8/1,000 ventilator days]). Elements of this protocol have proved effective in other surgical/trauma units as well [94]. However, compliance with infection control protocols often wanes over time and can be influenced significantly by staffing levels in the ICU [95,96]. Wahl et al. have shown that a computerized flow sheet employed in the ICU could improve compliance with care measures involved in the prevention of VAP, as well as other protocols [97].

Most recently, Boudadma et al. illustrated the benefits of a bundled approach to the prevention of VAP [98]. Their program was implemented in a 20-bed medical ICU of a teaching hospital in France and involved all healthcare workers. The French intervention included a multidisciplinary task force, an educational session, direct observations with performance feedback, technical improvements, and scheduled reminders. It focused on eight targeted measures based on well-recognized published guidelines, easily and precisely defined acts, and the bedside behavior of directly concerned healthcare workers. Compliance assessment consisted of five four-week periods (before the intervention and one, six, 12, and 24 mos thereafter). Hand hygiene and glove-and-gown use compliances were high (68% and 80%) initially and remained stable over time. Compliance with all other preventive measures was low initially but increased steadily over the two-year period of the study: backrest elevation (5–58%) and tracheal cuff pressure maintenance (40–89%), which improved after simple technical equipment implementation; orogastric tube use (52–96%); gastric overdistention avoidance (20–68%); good oral hygiene (47–90%); and elimination of nonessential tracheal suctioning (41–92%). The VAP prevalence rate decreased by 51% after implementation of the intervention (p < 0.001). This long-lasting program for preventing VAP increased compliance with preventive measures that are directly dependent on healthcare workers’ bedside performance. The use of a multidimensional framework appeared to be critical for the success of this program, as has been demonstrated for similar bundled approaches to VAP prevention [89,90].
Protocols, standardized order sets, checklists, and clinical practice teams all provide approaches for the prevention of VAP, as well as for the overall enhancement of critical care. Depending on local expertise and resources, an approach to quality care improvement in the ICU should be implemented and monitored over time (Table 4). The SMART approach for the prevention of nosocomial infections seems to be a concise framework for developing and implementing successful programs using available prevention strategies [99]. Evidence-based recommendations are available that reduce nosocomial ICU infection rates[100–102], especially when simple tactics are bundled. To increase the likelihood of success, the SMART approach, in which specific objectives or outcomes that are precisely defined and quantified (e.g., 25% reduction of VAP with protocol implementation), should be implemented. The outcome must be measurable, achievable, and, most important, clinically relevant. This will facilitate buy-in from stakeholders such as staff who have to carry out the protocols and bundles. Appointing a team to champion the intervention and collaboration with hospital administrators will help ensure the success of the interventions. Finally, the intervention must be time bound so that success or failure can be assessed objectively [98].

Summary Recommendations and Conclusion

Optimal management and prevention of nosocomial infections in the ICU setting is an important element of care for the critically ill patient. Clinicians need to develop systems within ICUs aimed at optimizing the care of patients in order to improve their clinical outcomes. In the future, emerging advances in the design of endotracheal tubes [103], use of probiotics [104], and development of new antibiotics should further our ability to prevent and treat NP. In the meantime, clinicians working in ICUs should consider the following recommendations:

1. Develop a VAP prevention bundle using evidence-based guidelines and the input of local experts in infection control and critical care;
2. Monitor the rates of VAP prior to and during the implementation of the prevention program to determine its success or failure;
3. Make adjustments to the prevention program according to VAP occurrence in terms of the bundle elements, strategies to enhance bundle compliance, and changes in patient mix, target pathogens, or changing definitions of VAP (e.g., U.S. Centers for Disease Control and Prevention Conference for Establishing a VAP Surveillance Definition, scheduled for Fall 2010);
4. Integrate VAP prevention with other quality improvement programs in the ICU to minimize redundancies and optimize the use of resources.

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References


PREVENTION OF NOSOCOMIAL PNEUMONIA


